Future's Mirror:
The Endocannabinoid System in Human Pathology

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"The future lies in the history."

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Standing Dead—
Let us cast aside the husk, walk away from that which was our name, and leave it as a dead thing. Standing Dead are we—as a tree rent by lightening: now bright and sudden, we who refuse to fall.

Cover design and artwork: Peggi Wolfe (Wolfepaw)

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Introductory Remarks

Mirror of ages. No more exquisite thing can be conceived than the intricate enmeshment of poetry and design, a delicate web drifting in tangled breeze, shimmering in reflection upon rippled waters, a silver question wavering and intricate, each thread ripe with patient purpose and beauty, ripe is she, this child of the ages. Within the present an image stretches, a hand and palm upturned to welcome and nourish, in kindness, so is the bounty time has cast but the dust of eons, as time crumbles, but the hollow sand within which the root of all perfect worlds is struck. So is her magic, but the virtue of the most delicate threads of patience.

The shores of time are rich with treasure.

This book is the child of chance and pain. Could it be? The rumor, the rumor of cure—for cancer? I heard a silly rumor. A rumor that *Cannabis* could influence illness and cure cancer…both. THC. The thin thread of words from the National Cancer Institute confirmed, with the shrug of a shoulder. I began to research. Only the history matters. Deeply, one must read and look here…then the science….then the history, then the science…and *then*, one sees. They have hidden, *time*. Here my friend, I will return her to you and you may know: She is rich with treasure.

From the National Cancer Institute.
"Antitumor activity
Studies in mice and rats have shown that cannabinoids may inhibit tumor growth by causing cell death, blocking cell growth, and blocking the development of blood vessels needed by tumors to grow. Laboratory and animal studies have shown that cannabinoids may be able to kill cancer cells while protecting normal cells.
A study in mice showed that cannabinoids may protect against inflammation of the colon and may have potential in reducing the risk of colon cancer, and possibly in its treatment.
A laboratory study of delta-9-THC in hepatocellular carcinoma (liver cancer) cells showed that it damaged or killed the cancer cells. The same study of delta-9-THC in mouse models of liver cancer showed that it had antitumor effects. Delta-9-THC has been shown to cause these effects by acting on molecules that may also be found in non-small cell lung cancer cells and breast cancer cells.
A laboratory study of cannabidiol (CBD) in estrogen receptor positive and estrogen receptor negative breast cancer cells showed that it caused cancer cell death while having little effect on normal breast cells. Studies in mouse models of metastatic breast cancer showed that cannabinoids may lessen the growth, number, and spread

of tumors.
A laboratory study of cannabidiol (CBD) in human glioma cells showed that when given along with chemotherapy, CBD may make chemotherapy more effective and increase cancer cell death without harming normal cells. Studies in mouse models of cancer showed that CBD together with delta-9-THC may make chemotherapy such as temozolomide more effective."

Source:
https://www.cancer.gov/about-cancer/treatment/cam/patient/cannabis-pdq#link/_13

Really? Perhaps…there's a bit more to it.

The endo-cannabinoid system in human pathology.

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"The future lies in the history."

Abstract:

Cannabis Sativa has been used for medicinal and other purposes for millennia. In the 1990s the CB_1 and CB_2 receptors and the *endogenous* ligands of the *endo*-cannabinoid system proper were discovered: Anandamide *N*-arachidonoylethanolamine (AEA) and 2-Arachidonoylglycerol (2-AG). External mediation of the bodily endo-cannabinoid system with exogenous phytochemical cannabinoids and other active compounds within Cannabis representative of the *full interactive proliferation of naturally occurring constituents* appears from manifest interdigitated cross-mediational systemic complexity and phylogenetic receptor analysis to imply the likelihood of potential synergistic therapeutic efficacy via evolutionary adaptations beginning from as far back as the Cambrian period or more. This approach utilizing the full proliferation of interactive compounds or some selected intra-active multi-constituent portion thereof, has been demonstrably curtailed by legal, political and systemic interference. This document will spell out the demonstrated functional potential and implied therapeutic utility of cannabinoids and cannabis extracts, support the aforementioned evolutionary hypothesis and demonstrated multifunctional medical utility with both phylogenetic and historical analysis, and then detail what appears to be the suppressed approach that may lead to the speedy and inexpensive treatment or cure of many dread diseases using Cannabis extracts, including but not limited to cancer. It is also clearly implied and well supported from historical and current medical perspectives that the raw drug itself is safe and effective in treating many conditions and should be available to dispense via prescription by all qualified medical professionals.

1. Introduction:

Cannabis is a genus of flowering plant belonging to the family Cannabaceae that has been used for medicinal and other purposes for many ages. The ability of Cannabis to alter conscious states has been known for some 12,000 years (Able, 1980; McPartland and Pruitt, 2002), and Cannabis has been cultivated for at least 6000 years (Atakan, 2012; Li, 1973). The three species often recognized, *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis,* may in fact be organized such that *Cannabis indica* and *Cannabis ruderalis* are understood to be subspecies of *Cannabis sativa* [Web ref. 1,2]. The historical written record indicates extracts of *Cannabis Sativa* have been

known to produce medicinal effects apart from their psychoactive properties as early as the third millennium BC, from which time Chinese texts describe therapeutic amelioration of pain and cramps (Mechoulam, 1986; Pacher et al. 2006). Chinese emperor Shen-nung (ca. 2000 B.C.) had recorded in the text *Pen-ts'ao Ching*, that cannabis positively affects rheumatism as if the condition were reversed, hence indicating possible anti-inflammatory actions (Hui-Lin, 1975; Burstein & Zurier, 2009). Recent archeological evidence of the usage of Cannabis can be found in the 2700-year-old grave of a Caucasoid shaman: ". . . tetrahydrocannabinol, the psychoactive component of cannabis, its oxidative degradation product, cannabinol, other metabolites, and its synthetic enzyme, tetrahydrocannabinolic acid synthase, as well as a novel genetic variant with two single nucleotide polymorphisms. The cannabis was presumably employed by this culture as a medicinal or psychoactive agent, or an aid to divination." (Russo et al. 2008). Oral ingestion of cannabis (in a dietary form known as Bhang) producing therapeutic anti-anxiety effects has been documented in ancient Indian texts from 3000 years past, and, the wide spread medical use of cannabis extracts in the United States and elsewhere continued until, in the year 1937 AD Cannabis was suddenly banned for medicinal use in the United States (Pacher et al. 2006).

Cannabinoids are generally defined as: "The chemical compounds that are the active principles in marijuana." [Gale Encyclopedia of Medicine, 2008]. There are 5 presently recognized *endo*-cannabinoids which act upon the same system as phytochemical and synthetic cannabinoids, but are endogenous: Arachidonoylethanolamine (anandamide), 2-arachidonoylglycerol (2-AG), 2-arachidonyl glyceryl ether (noladin ether), virodhamine and N-arachidonoyl-dopamine (NADA). [Web ref. 6]. The basics of endo-cannabinoid signaling reveal a diverse and complex process of interwoven dynamic effects, which are often characterized by retrograde signaling. Retrograde endocannabinoid signaling regulates neuronal activity by way of synthesis and release of enocannabinoid compounds in depolarized post synaptic elements, inducing subsequent substance mobility toward the presynaptic endocannabinoid receptors to which said endocannabinoids bind, thereby influencing future neuronal activity and neurotransmitter release from the presynaptic end of the system (Lovinger, 2008). One familiar example is that of *depolarization-induced suppression of inhibition* in GABA-mediated neuronal activity. Endocannabinoids are released from the postsynaptic neuron after its depolarization, and bind to CB_1 receptors in the presynaptic neuron causing a reduction in subsequent GABA release [Web ref. 3]. CB_1 and CB_2 receptors both modulate the release of chemical messengers, CB_1 in the main from neurons, CB_2 from immune cells (Pertwee, 2006).

The basic endocannabinoids, phytochemical cannabinoids and receptors were discovered as follows (Russo, 2011, p. 1345):
cannabidiol (CBD) (Mechoulam and Shvo, 1963);
tetrahydrocannabinol (THC) (Gaoni and Mechoulam, 1964a);
cannabigerol (CBG) (Gaoni and Mechoulam, 1964b);
cannabichromene (CBC) (Gaoni and Mechoulam,1966);
cannabidivarin (CBDV) (Vollner et al., 1969)
tetrahydrocannabivarin (THCV) (Gill et al., 1970)
CB1 (Devane et al., 1988);
anandamide (arachidonoylethanolamide, AEA) (Devane et al., 1992);

2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995).

Subclasses of cannabinoids include [Web ref. 4]:

- Cannabigerols (CBG)
- Cannabichromenes (CBC)
- Cannabidiols (CBD)
- Tetrahydrocannabinols (THC)
- Cannabinol (CBN)
- Cannabinodiol (CBDL)
- Cannabicyclol (CBL)
- Cannabielsoin (CBE)
- Cannabitriol (CBT)
- Cannabivarin (CBV)
- Tetrahydrocannabivarin (THCV)
- Cannabidivarin (CBDV)
- Cannabichromevarin (CBCV)
- Cannabigerovarin (CBGV)
- Cannabigerol Monoethyl Ether (CBGM)

Both CB_1 and CB_2 receptors are *G-protein-coupled receptors* (GPCRs) (Pertwee et al. 2010). Interestingly, both can be found in the human placenta, where they have been shown to have a part in the regulation of serotonin (5-HT) transporter activity (Atakan, 2012; Kenney et al. 1999). CB_1 and CB_2 receptors both work to inhibit the activity of adenylyl cyclase through their Gi/Go_α subunits (Shoemaker, et al. 2005; Demuth and Molleman, 2006). [Web ref. 6].

CB_1:
The central nervous system has more CB_1 receptors than any other single receptor, and the CB_1 receptor is the most highly expressed GPCR in the brain (Pagotto, 2006; Callen et al. 2012). High levels of expression are found in: the olfactory bulb, neocortex, pyriform cortex, hippocampus and amygdala, the basal ganglia, thalamic and hypothalamic nuclei, and subcortical regions such as the septal region, cerebellar cortex, and brainstem nuclei including the periaqueductal grey, and

also the spine (Pagotto, 2006; Pacher et al. 2006) [Web ref. 5]. CB_1 receptors mediate dopaminergic, gamma-aminobutyric acid (GABA), glutamatergic, serotoninergic, noradrenalin and acetylcholine neurotransmitter systems. Receptor heteromers and resultant systemic combinative effects across different neuronal types create highly complex systemic expressions. Some involve heteromers with the dopamine D_2 receptor, where as in other heteromers two types may be influenced, such as dopamine D_2 and adenosine A_{2A} receptors (Atakan, 2012). CB_1 receptors are expressed to a lesser extent in the pituitary gland, immune cells and reproductive tissues, although they are located in the main at central and peripheral nerve terminals where they mediate the inhibition of transmitter release (Pertwee, 2006).

CB_2:
CB_2 receptors are expressed most often on immune T-cells, macrophages, B-cells, and hematopoietic cells. They are involved in the epidermal and related processes of keratinocytes, and play a role in antinociception, meaning the relief of pain. They are expressed in microglial cells in the brain. Also, CB_2 receptors are targets for therapies in other areas of their anatomical expression, including but not limited to: endothelial and smooth muscle cells, fibroblasts, cardiomyocytes, and the peripheral or central nervous systems (Pacher & Mechoulam, 2011) [Web ref. 6]. The CB_2 receptor is heavily expressed also, in the gastrointestinal system where it modulates inflammatory response (Izzo, 2004; Wright et al. 2008). CB_2 receptors are implicated in a variety of modulatory functions, including immune suppression, induction of apoptosis, and induction of cell migration (Basu, 2011). [Web ref. 6].

CB_1 and CB_2 systems can form heteromers with each other. From (Atakan, 2012):

"Most recently it has been shown that CB_2Rs form heteromers with CB_1Rs in the brain and the agonist coactivation of CB_1Rs and CB_2Rs results in negative crosstalk in AKT1 phosphorylation and neurite outgrowth (Callén *et al*. 2012). The authors point out that there is a bidirectional cross antagonism which involves the antagonists of either receptor to block the other. It is suggested that these data illuminate the mechanism by which CB_2Rs can negatively modulate CB_1R function."

The system is highly complex, and not yet well understood. The various multitude of systemic interactions involve not only the recognized 60–113 or so cannabinoids, a number which varies with each source, but one must also admit the likely possibility of more as of yet undiscovered active agents from this intra-dynamic storehouse of phytochemical pharmacopeia, the undiscovered actions and interactions between the plethora of phytochemical constituencies and the bodily system extending to include "entourage effects" with other naturally occurring active components such as but not limited to: terpenoids, flavonoids, and others (Radwan et al. 2009; Andre et al;. 2016; De Petrocellis et al. 2011; Russo, 2011; Aizpurua-Olaizola, 2016). [Web ref. 7]. Please note: Cannabis has over 400 chemicals within its constituency (Atakan, 2012).

Those many and various compounds *interact* to create many potent medical effects. In *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects* (Russo, 2011 p. 1345), we read: "Support derives from studies in which cannabis extracts demonstrated effects

two to four times greater than THC (Carlini *et al*., 1974); unidentified THC antagonists and synergists were claimed (Fairbairn and Pickens, 1981), anticonvulsant activity was observed beyond the cannabinoid fraction (Wilkinson *et al*., 2003), and extracts of THC and CBD modulated effects in hippocampal neurones distinctly from pure compounds (Ryan *et al*., 2006)."

At this point some readers may have noticed that it is claimed by many governmental authorities such as that of the United States Federal Government, that Cannabis has *no medical value whatsoever*. Indeed, it is classified along with heroin as a dangerous addictive drug. A Schedule 1 drug that has the "high potential for abuse and no accepted medical treatment use." [Web ref. 8] Is this true? Are cannabis and its constituents dangerous and addictive like heroin? Does cannabis in fact, have *no medical value whatsoever?* Are these true statements, or are they not? Let us look to empirical studies, many of which are themselves government funded to ascertain the correct answer. Does this drug have valid medical usages, or does it not?

References for this section found in **References, List One**.

2. Detailed clinical applicability of Cannabinoids and secondary phytochemical constituents, or: What's it good for?

In this section we will condense, greatly simplify and reduce what it is to be strictly remembered is a deeply abbreviated sampling of the highly substantial and overwhelming volume of literature available in support of these many points. I will list subject matter of significant importance with quotations so as to assure the reader each of these many points is accurate and uninfluenced by interpretation.

Subject matter of significant importance:

It is entirely possible that phytochemical cannabinoids might aid in withdrawal and secession of alcohol use in cases of alcoholism as in the paper: *Cannabis as a substitute for alcohol and other drugs* (Reiman, 2009), where we read: "The substitution of one psychoactive substance for another with the goal of reducing negative outcomes can be included within the framework of harm reduction," and also, that organic harm due to alcohol abuse might well be reduced with inclusion of non-psychoactive cannabinoid CBD which is articulated in the paper, *Cannabidiol, Antioxidants, and Diuretics in Reversing Binge Ethanol-Induced Neurotoxicity* (Hamelink et al. 2005), where we read: "We demonstrate here that CBD, a nonpyschoactive component of marijuana, substantially limits neuronal damage to hippocampal and entorhinal cortical brain regions when administered concurrently with alcohol."

Allergic conditions may benefit from therapeutic approaches based around exogenous phytochemical cannabinoids as they affect the endocannabinoid system as demonstrated in rodent models with delayed-type hypersensitivity (DTH) reactions and antigen-induced T-cell cytokine expression, as in the paper *Cannabidiol attenuates delayed-type hypersensitivity reactions via suppressing T-cell and macrophage reactivity* (Liu et al. 2010), where we read: "CBD curbs DTH reactions via suppressing the infiltration and functional activity of T cells and macrophages in the inflammatory site, suggesting a therapeutic potential for CBD for the treatment of type IV hypersensitivity" THC demonstrates efficacy in a murine model of allergen-induced airway inflammation. In *Beneficial effects of cannabinoids (CB) in a murine model of allergen-induced airway inflammation: role of CB1/CB2 receptors* (Braun, 2011), we read: "THC treatment of C57BL/6 wildtype mice dramatically reduced airway inflammation as determined by significantly reduced total cell counts in bronchoalveolar lavage (BAL). . . ." [through] "receptor-independent signalling . . . "

Asthma sufferers may benefit. In *Acute effects of smoked marijuana and oral delta-9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects* (Gong et al. 1984), we read: "both smoked marijuana and oral THC caused significant bronchodilation of at least 2 hours' duration." In the paper *Cannabinoids as novel anti-inflammatory drugs* (Nagarkatti et al. 2009), we read: ". . . use of exogenous cannabinoids in vivo can constitute a potent treatment modality against inflammatory disorders" We also note positive effects in *Bronchodilator effect of delta1-tetrahydrocannabinol* (Hartley et al. 1978) where we read: "1 delta1-trans-tetrahydrocannabinol, (delta1-THC) produces bronchodilatation in asthmatic patients." We note commercial applications

of THC delivery in the product press release: *New Synthetic Delta-9-THC Inhaler Offers Safe, Rapid Delivery.*

Autism patients may benefit by symptomatic reduction associated with THC. See: *Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child* (Kurz and Lindengasse, 2010). CB2 receptor mediation is a potential target related to altered immune response of peripheral blood mononuclear cells as in: *Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders* (Siniscalco, et al. 2013). Evidence exists from credible sources concerning the effective functional use of cannabinoids with Autistic conditions: see *Associate Professor Emeritus of Psychiatry at Harvard Medical School: A Novel Approach to the Symptomatic Treatment of Autism by Lester Grinspoon M.D. (2010)*.

Beta-Caryophyllene is a dietary constituent of cannabis with beneficial properties. In the paper, *Beta-caryophyllene is a dietary cannabinoid* (Gertsch et al. 2008), we read: "These results identify (*E*)-BCP as a functional nonpsychoactive CB2 receptor ligand in foodstuff and as a macrocyclic antiinflammatory cannabinoid in *Cannabis*." In support, in *Anti-inflammatory cannabinoids in diet: Towards a better understanding of CB2 receptor action?* (Gertsch, 2008), we read: "Our recent finding that beta-caryophyllene, a ubiquitous lipohilic plant natural product, selectively binds to the CB2 receptor and acts as a full agonist is unexpected. Maybe even more unexpected is that oral administration of this dietary compound exerts potent anti-inflammatory effects…" To add further support to the role of dietary cannabinoids, dietary cannabis constuituancies of other sorts, and Beta-Caryophyllene in particular, in *Endocannabinoids, and Related Analogs in Inflammation* (Burstein and Zurier, 2013), we read: ". . . phytocannabinoids such as tetrahydrocannabinol and cannabidiol, synthetic analogs such as ajulemic acid and nabilone, the endogenous cannabinoids anandamide and related compounds, namely, the elmiric acids, and finally, noncannabinoid components of *Cannabis* that show anti-inflammatory action." And as to further organ effects and benefits we read in *β-Caryophyllene inhibits dextran sulfate sodium-induced colitis in mice through CB2 receptor activation and PPARγ pathway* (Bento et al. 2011): "These results demonstrate that the anti-inflammatory effect of BCP involves CB2 and the PPARγ pathway and suggest BCP as a possible therapy for the treatment of inflammatory bowel disease." —Other compounds associated with cannabis have potent efficacy in ameliorating inflammatory bowel disease as well. In *Cannabinoids cool the intestine* (Kunos and Pacher, 2004), we read: "Cannabinoids inhibit motility and secretion in the intestine. They are now assigned the additional task of curbing excessive inflammation, suggesting that drugs targeting the endogenous cannabinoid system could be exploited for inflammatory bowel disease." In *Cannabidiol Reduces Intestinal Inflammation through the Control of Neuroimmune Axis* (Filippis et al. 2011), it is stated: "Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases."

Bipolar disorder patients could benefit. In *Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential* (Ashton et al. 2005), we read: "Cannabis use is common in patients with this disorder and anecdotal reports suggest that some patients take it to

alleviate symptoms of both mania and depression. We undertook a literature review of cannabis use by patients with bipolar disorder and of the neuropharmacological properties of cannabinoids suggesting possible therapeutic effects in this condition. . . . specific plant extracts containing THC, CBD, or a mixture of the two in known concentrations, are available and can be delivered sublingually. Controlled trials of these cannabinoids as adjunctive medication in bipolar disorder are now indicated." In *Opposite relationships between cannabis use and neurocognitive functioning in bipolar disorder and schizophrenia* (Ringen et al. 2009), we read: "The findings suggest that cannabis use may be related to improved neurocognition in bipolar disorder. . . " And in *Genetic association between bipolar disorder and 524A>C (Leu133Ile) polymorphism of CNR2 gene, encoding for CB2 cannabinoid receptor* (Minocci et al. 2011), we read: ". . . our results suggest that CB2 cannabinoid receptor may play a role in BD."

Brain Trauma can be ameliorated. In *Cannabinoids and brain injury: therapeutic implications* (Mechoulam et al. 2002), we read: "Mounting in vitro and in vivo data suggest that the endocannabinoids anandamide and 2-arachidonoyl glycerol, as well as some plant and synthetic cannabinoids, have neuroprotective effects following brain injury." And also from *Cannabinoids as neuroprotective agents in traumatic brain injury* (Biegon, 2004), we read: "Cannabinoids of all classes have the ability to protect neurons from a variety of insults that are believed to underlie delayed neuronal death after traumatic brain injury (TBI), including excitotoxicity, calcium influx, free radical formation and neuroinflammation." Also from *Cannabinoids as Therapeutic Agents for Ablating Neuroinflammatory Disease* (Cabral and Griffin-Thomas, 2008), we read: "Thus, the cannabinoid-cannabinoid receptor system may prove therapeutically manageable in ablating neuropathogenic disorders such as Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, HIV encephalitis, closed head injury, and granulomatous amebic encephalitis." Then from *Pre- and post-conditioning treatment with an ultra-low dose of Δ9-tetrahydrocannabinol (THC) protects against pentylenetetrazole (PTZ)-induced cognitive damage* (Assaf et al. 2011), we read: "Our results suggest that a pre- or post-conditioning treatment with extremely low doses of THC, several days before or after brain injury, may provide safe and effective long-term neuroprotection."

Cholesterol and Alzheimer's (see sections below for more) may be ameliorated with dietary hemp seed. From *The effects of hempseed meal intake and linoleic acid on Drosophila models of neurodegenerative diseases and hypercholesterolemia* (Lee et al. 2011), we read: ". . . our results indicate that HSM and linoleic acid exert inhibitory effects on both Aβ42 cytotoxicity and cholesterol uptake, and are potential candidates for the treatment of Alzheimer's disease and cardiovascular disease." Also, in *Cholesterol-induced stimulation of platelet aggregation is prevented by a hempseed-enriched diet* (Prociuk et al. 2008), we read: "The results of this study demonstrate that when hempseed is added to a cholesterol-enriched diet, cholesterol-induced platelet aggregation returns to control levels.

Cystic Fibrosis could be treated. In *Cannabinoids and Cystic Fibrosis: A Novel Approach to Etiology and Therapy* (Fride, 2002), we read: "Thus it is suggested that potential benefits from THC treatment, in addition to appetite stimulation, will include antiemetic, bronchodilating, anti-inflammatory, anti-diarrheal and hypoalgesic effects." In *The endocannabinoid-CB receptor*

system: Importance for development and in pediatric disease (Fride, 2004), we read: "We suggest cannabinoid treatment for children or young adults with cystic fibrosis in order to achieve an improvement of their health condition including improved food intake and reduced inflammatory exacerbations."

Dermatitis appears to be treatable with cannabinoid therapies. *Hemp seed, and hemp seed oil should be added to the diet to stave off a variety of conditions*. In *Efficacy of dietary hempseed oil in patients with atopic dermatitis* (Callaway et al. 2005), we read: "Dietary hempseed oil caused significant changes in plasma fatty acid profiles and improved clinical symptoms of atopic dermatitis." Receptor activity in association with active phytochemical constituent cannabinoids is also clearly indicated in the amelioration of pathology. In *Attenuation of allergic contact dermatitis through the endocannabinoid system* (Karsak et al. 2007), it states: "Cannabinoid receptor antagonists exacerbated allergic inflammation, whereas receptor agonists attenuated inflammation. These results demonstrate a protective role of the endocannabinoid system in contact allergy in the skin and suggest a target for therapeutic intervention." In *Anti-inflammatory activity of topical THC in DNFB-mediated mouse allergic contact dermatitis independent of CB1 and CB2 receptors* (Gaffal et al. 2013), we read: "Topically applied THC can effectively attenuate contact allergic inflammation by decreasing keratinocyte-derived pro-inflammatory mediators that orchestrate myeloid immune cell infiltration independent of CB1/2 receptors. This has important implications for the future development of strategies to harness cannabinoids for the treatment of inflammatory skin diseases."

Dystonia may be treatable with cannabinoids alone or as adjuncts to existing therapies. In *Tetrahydrocannabinol potentiates reserpine-induced hypokinesia* (Moss et al. 1981), we read: "Insofar as reserpine has been used with some clinical efficacy in hyperkinetic movement disorders such as Huntington's disease and tardive dyskinesia, it may be that potentiation of reserpine's hypokinetic effect by a drug such as THC could greatly increase the clinical value of reserpine or related drugs in the treatment of these disorders." In support of the direct interventional utility of cannabinoids such as CBD in dystonia, in the study *Open label evaluation of cannabidiol in dystonic movement disorders* (Consroe et al. 1986), we read: "Dose-related improvement in dystonia was observed in all patients and ranged from 20 to 50%. Side-effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation." Concerning blepharospasm, in *Cannabinoid agonists in the treatment of blepharospasm--a case report study* (Gauter et al. 2004), it is stated, "Dronabinol for several weeks improved the patients' social life and attenuated pain perception remarkably. This case study demonstrates that the therapy with a cannabinoid agonist may provide a novel tool in the treatment of blepharospasm and maybe of other multifactorial related movement disorders." Also, in *Cannabis sativa and dystonia secondary to Wilson's disease*, we read: "A patient with generalized dystonia due to Wilson's disease obtained marked improvement in response to smoking cannabis."

Fibromyalgia may be treated with Cannabis derived phytochemicals including cannabinoids. In *Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey* (Weber et al. 2009), we read: "The present survey demonstrates its ameliorating potential for the treatment of chronic pain in central

neuropathy and fibromyalgia. A supplemental delta 9-THC treatment as part of a broader pain management plan therefore may represent a promising coanalgesic therapeutic option. . . . *Opioid doses were reduced* and patients perceived THC therapy as effective with tolerable side effects." [emphasis added]. Let the reader closely note not only general treatment efficacy, but also the *interactive effects between opioids and THC, allowing opioid dosage reduction*. An informative piece of text is available within the article, *Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation* (Burstein and Zurier, 2009): "Possibly the very earliest literature reference on *Cannabis* describes its use as an anti-inflammatory agent. The Chinese emperor Shen-nung (ca. 2000 B.C.), in a work called *Pen-ts'ao Ching*, noted many of the effects of *Cannabis* in humans. Among other properties, it was claimed that cannabis "undoes rheumatism", suggesting possible anti-inflammatory effects (122). The reports described in this review of the current literature provide support for the claims made by the ancient Chinese healers. These more recent publications include relief from chronic neuropathic pain, fibromyalgia, rheumatoid arthritis, and postoperative pain. In addition, a large body of preclinical data on all classes of cannabinoids, including the endogenous examples, point to a variety of therapeutic targets for cannabinoids and important roles for the endocannabinoids in the physiology of inflammation." And in *Cannabis Use in Patients with Fibromyalgia: Effect on Symptoms Relief and Health-Related Quality of Life* (Fiz et al. 2011), we read, "After 2 hours of cannabis use, VAS scores showed a statistically significant (p<0.001) reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of well being. The mental health component summary score of the SF-36 was significantly higher (p<0.05) in cannabis users than in non-users. . . . The use of cannabis was associated with beneficial effects on some FM symptoms."

GERD may be treated with cannabinoids. In *Cannabinoids for gastrointestinal diseases: potential therapeutic applications*, it is stated (DiCarlo and Izzo, 2003): "A pharmacological modulation of the endogenous cannabinoid system could provide new therapeutics for the treatment of a number of gastrointestinal diseases, including nausea and vomiting, gastric ulcers, irritable bowel syndrome, Crohn's disease, secretory diarrhoea, paralytic ileus and gastroesophageal reflux disease." In *Beyond acid suppression: new pharmacologic approaches for treatment of GERD,* we read (Kuo and Holloway, 2010): "Cannibinoid agonists, such as Delta(9)-THC, have also been demonstrated to reduce TLESRs and reflux events respectively."

Herpes may be treatable using cannabinoids. In *The effect of delta-9-tetrahydrocannabinol on herpes simplex virus replication*, we read (Blevins and Dumic, 1980): "Both herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) failed, in an identical fashion to replicate and produce extensive c.p.e. in human cell monolayer cultures which were exposed (8 h before infection, at infection, or 8 h p.i.) to various concentrations of delta-9-tetrahydrocannabinol. Similar results were obtained with a plaque assay utilizing confluent monkey cells." In *Suppressive effect of delta-9-tetrahydrocannabinol on herpes simplex virus infectivity in vitro* (Lancz et al. 1991), it is stated: "Delta-9-Tetrahydrocannabinol (THC) was found to reduce the infectivity of herpes simplex virus and was without effect against adenovirus type 2 or poliovirus." In *Delta-9 tetrahydrocannabinol (THC) inhibits lytic replication of gamma oncogenic herpesviruses in vitro* (Medveczky et al. 2004), it is stated that, "THC specifically targets viral and/or cellular mechanisms required for replication and possibly shared by these gamma

herpesviruses, and the endocannabinoid system is possibly involved in regulating gamma herpesvirus latency and lytic replication. The immediate early gene ORF 50 promoter activity was specifically inhibited by THC." And also, in *Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia* (Phan et al. 2010), we read, "Postherpetic neuralgia is a frequent adverse event in herpes zoster patients and difficult to treat. Conventional analgetic therapy often fails to reduce the burning pain transmitted by unmyelinated nerve fibers. These nerves express cannabinoid receptors which exert a role in modulation of nociceptive symptoms. . . . Topical cannabinoid receptor agonists are an effective and well-tolerated adjuvant therapy option in postherpetic neuralgia."

MRSA is a modern scourge which could be positively affected as well. In *Antibacterial cannabinoids from Cannabis sativa: a structure-activity study* (Appendino et al. 2008), we read: "Marijuana (Cannabis sativa) has long been known to contain antibacterial cannabinoids, whose potential to address antibiotic resistance has not yet been investigated. All five major cannabinoids (cannabidiol (1b), cannabichromene (2), cannabigerol (3b), Delta (9)-tetrahydrocannabinol (4b), and cannabinol (5)) showed potent activity against a variety of methicillin-resistant Staphylococcus aureus (MRSA) strains of current clinical relevance." In *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects* (Russo, 2011), we read: "Particular focus will be placed on phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant Staphylococcus aureus)."

ALS (Lou Gehrig's Syndrome) [also see PD section for significant further relevant information.]:

In Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid (Raman et al. 2004), we read: "Here we report that treatment with Delta(9)-tetrahydrocannabinol (Delta(9)-THC) was effective if administered either before or after onset of signs in the ALS mouse model (hSOD(G93A) transgenic mice). Administration at the onset of tremors delayed motor impairment and prolonged survival in Delta(9)-THC treated mice when compared to vehicle controls." In *Marijuana in the management of amyotrophic lateral sclerosis* (Carter and Rosen, 2001), we read: " . . . marijuana has now been shown to have strong antioxidative and neuroprotective effects, which may prolong neuronal cell survival. In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS." It is possible CBD might delay disease onset. In *Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival* (Weydt et al. 2005), it is stated: "CBN was delivered via subcutaneously implanted osmotic mini-pumps (5 mg/kg/day) over a period of up to 12 weeks. We found that this treatment significantly delays disease onset by more than two weeks." In the report *Cannabinoids and neuroprotection in motor-related disorders* (De Lago and Fernández-Ruiz, 2007), it is stated that: "This should serve to encourage that the present promising evidence obtained mainly at the preclinical level might progress to a real exploitation of neuroprotective benefits of potential cannabinoid-based medicines." In *Cannabis and amyotrophic lateral sclerosis: hypothetical and practical applications, and a call for clinical trials* (Carter at al. 2010), we read: "Based on the currently available scientific data, it is reasonable to think that cannabis might significantly slow the progression of ALS, potentially extending life

expectancy and substantially reducing the overall burden of the disease."

Alzheimer's Disease:

CBD and THC demonstrate efficacy in ameliorating pathology in cases of Alzheimer's. The CBI and CB2 receptors are involved. In *Prevention of Alzheimer's Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation* (Ramirez et al. 2005), we read: "Our results indicate that cannabinoid receptors are important in the pathology of AD and that cannabinoids succeed in preventing the neurodegenerative process occurring in the disease." The report *Cannabidiol in vivo blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression* (Esposito et al. 2007) states: "The results of the present study confirm *in vivo* anti-inflammatory actions of CBD, emphasizing the importance of this compound as a novel promising pharmacological tool capable of attenuating Aβ evoked neuroinflammatory responses." The medical article, *Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells* (Iuvone et al. 2004), contains this text: "Our results indicate that cannabidiol exerts a combination of neuroprotective, anti-oxidative and anti-apoptotic effects against beta-amyloid peptide toxicity, and that inhibition of caspase 3 appearance from its inactive precursor, pro-caspase 3, by cannabidiol is involved in the signalling pathway for this neuroprotection." The report *Cannabidiol Reduces Aβ-Induced Neuroinflammation and Promotes Hippocampal Neurogenesis through PPARγ Involvement* (Esposito et al. 2011) contains the statements: "Peroxisome proliferator-activated receptor-γ (PPARγ) has been reported to be involved in the etiology of pathological features of Alzheimer's disease (AD). Cannabidiol (CBD), a Cannabis derivative devoid of psychomimetic effects, has attracted much attention because of its promising neuroprotective properties in rat AD models, even though the mechanism responsible for such actions remains unknown. . . . Moreover, due to its interaction at PPARγ, CBD was observed to stimulate hippocampal neurogenesis." Within the report: *Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimers' disease* (Martin-Moreno et al. 2011), we read: "In summary, CBD is able to modulate microglial cell function *in vitro* and induce beneficial effects in an *in vivo* model of AD. Given that CBD lacks psychoactivity it may represent a novel therapeutic approach for this neurologic disease." In *Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress* (Booz, 2011), we read: "This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain." In *Safety and efficacy of dronabinol in the treatment of agitation in patients with Alzheimer's disease with anorexia: A retrospective chart review* (Patel et al. 2003), it is stated that: "Dronabinol treatment for agitation in AD patients with anorexia was effective in 31 out of 48 of patients who were refractory to other medications. No adverse events were reported." In *Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease* (Volicer et al. 1997), we read: "These results indicate that dronabinol is a promising novel therapeutic agent which may be useful not only for treatment of anorexia but also to improve disturbed behavior in patients with Alzheimer's disease." In *A*

molecular link between the active component of marijuana and Alzheimer's disease pathology (Eubanks et al. 2006), the statement is found: "Here, we demonstrate that the active component of marijuana, Delta9-tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of Alzheimer's disease." The study, *Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement* (Esposito et al. 2006), states that: "We have previously shown that cannabidiol, the main non-psychotropic component from Cannabis sativa, possess a variegate combination of anti-oxidant and anti-apoptotic effects that protect PC12 cells from Abeta toxicity. . . . The here reported data increases our knowledge about the possible neuroprotective mechanism of cannabidiol, highlighting the importance of this compound to inhibit beta-amyloid induced neurodegeneration, in view of its low toxicity in humans." The text of *The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells* (Esposito et al. 2006), states that: "Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. A massive accumulation of beta-amyloid (Abeta) peptide aggregates has been proposed as pivotal event in AD. . . . These results provide new molecular insight regarding the neuroprotective effect of cannabidiol and suggest its possible role in the pharmacological management of AD, especially in view of its low toxicity in humans." The paper, *Alzheimer's disease; taking the edge off with cannabinoids?* (Campbell and Gowran, 2007) states that: "Δ9-tetrahydrocannabinol can also inhibit acetylcholinesterase activity and limit amyloidogenesis which may improve cholinergic transmission and delay disease progression."

Arthritis:

As noted above in a quotation from the paper *Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation* (Burstein and Zurier, 2009): "Possibly the very earliest literature reference on *Cannabis* describes its use as an anti-inflammatory agent. The Chinese emperor Shen-nung (ca. 2000 B.C.), in a work called *Pen-ts'ao Ching*, noted many of the effects of *Cannabis* in humans. Among other properties, it was claimed that cannabis "undoes rheumatism", suggesting possible anti-inflammatory effects (122)." Next, in the study, *ANTI-EDEMA AND ANALGESIC PROPERTIES OF Δ9-TETRAHYDROCANNABINOL (THC)* (Sofia et al. 1973), it is stated that: "Δ9-Tetrahydrocannabinol (THC) is an orally effective anti-edema and analgesic agent. . . . Furthermore, THC is an effective inhibitor of developing adjuvant-induced arthritis and suppresses further development of time established disease. The analgesic activity for THC is substantially greater than that for aspirin. The compound has no antipyretic activity at a dose producing profound anti-edema effects." The work, *Immunoactive cannabinoids: Therapeutic prospects for marijuana constituents* (Straus, 2000), contains the following statements: "CBD is a potential lead to new classes of agents that would interfere with inflammatory pathways. . . . It is conceivable that marijuana contains a series of cannabinoids that, in the aggregate, could alleviate arthritis as implied in the present report (2), yet remain well tolerated." Then, in the study, *The Cannabinergic System as a Target for Anti-inflammatory Therapies* (Lu et al. 2006), we read: "Several of these compounds were tested for their effects on immune function, and the results suggest therapeutic opportunities for a variety of inflammatory diseases such as multiple sclerosis,

rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, allergic asthma, and autoimmune diabetes through modulation of the endocannabinoid system." Furthermore, in *Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress* (Booz, 2011), we find: "cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain." Next, in the study, *Cannabinoids as novel anti-inflammatory drugs* (Nagarkatti et al. 2009): the text states: "It is becoming increasingly clear that cannabinoid receptors and their endogenous ligands play a crucial role in the regulation of the immune system. Exogenous cannabinoids have been shown to suppress T-cell-mediated immune responses by primarily inducing apoptosis and suppressing inflammatory cytokines and chemokines. Such observations indicate that targeting cannabinoid receptor–ligand interactions may constitute a novel window of opportunity to treat inflammatory and autoimmune disorders." Then, in *Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression* (Rieder et al. 2010), it is stated that: ". . . activation of CB2 provides a novel therapeutic modality against inflammatory and autoimmune diseases as well as malignancies of the immune system, without exerting the untoward psychotropic effects." In the study, *Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis* (Blake et al. 2005), we find: "In the first ever controlled trial of a CBM in RA, a significant analgesic effect was observed and disease activity was significantly suppressed following Sativex treatment." In the study, *The antinociceptive effect of Delta9-tetrahydrocannabinol in the arthritic rat involves the CB(2) cannabinoid receptor* (Cox et al. 2007), the text states: "Our results indicate that the cannabinoid CB(2) receptor plays a critical role in cannabinoid-mediated antinociception, particularly in models of chronic inflammatory pain." In *Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis* (Richardson et al. 2008), we read: "Pre-clinical and clinical studies have demonstrated that cannabis-based drugs have therapeutic potential in inflammatory diseases, including rheumatoid arthritis (RA) and multiple sclerosis. . . . Our data predict that the cannabinoid receptor system present in the synovium may be an important therapeutic target for the treatment of pain and inflammation associated with OA and RA." In the paper *Synergy between Δ^9-tetrahydrocannabinol and morphine in the arthritic rat* (Cox et al. 2007), taking careful note of the relation between opioids (morphine) and THC in terms of tolerance and analgesic efficacy we read: "The isobolographic analysis indicated a synergistic interaction between Delta(9)-THC and morphine in both the non-arthritic and the arthritic rats. Since Freund's adjuvant-induced alteration in endogenous opioid tone has been previously shown, our data indicate that such changes did not preclude the use of Delta(9)-THC and morphine in combination. As with acute preclinical pain models in which the Delta(9)-THC/morphine combination results in less tolerance development, the implication of the study for chronic pain conditions is discussed." In the study, *Involvement of the endocannabinoid system in osteoarthritis pain* (La Porta et al. 2014), we read: The ubiquitous distribution of cannabinoid receptors, together with the physiological role of the endocannabinoid system in the regulation of pain, inflammation and even joint function further support the therapeutic interest of cannabinoids for osteoarthritis. However, limited clinical evidence has been provided to support

this therapeutic use of cannabinoids, despite the promising preclinical data. This review summarizes the promising results that have been recently obtained in support of the therapeutic value of cannabinoids for osteoarthritis management."

Atherosclerosis:

Atherosclerosis may be treatable with cannabis. In *Does Cannabis Hold the Key to Treating Cardiometabolic Disease?* (Szmitko and Verma, 2006) we read: "Studies have demonstrated that modulation of the endocannabinoid system holds great therapeutic promise for the treatment of obesity, dyslipidemia, insulin resistance and atherosclerosis." In the text of *Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice* (Steffens et al. 2005), we find the statement: "Thus, THC or cannabinoids with activity at the CB2 receptor may be valuable targets for treating atherosclerosis." In the study *Cannabinoid receptors in atherosclerosis* (Steffens and Mach, 2006) we read: "The immunomodulatory capacity of cannabinoids is now well established and suggests a broad therapeutic potential of cannabinoids for a variety of conditions, including atherosclerosis." Next, in *Towards a therapeutic use of selective CB2 cannabinoid receptor ligands for atherosclerosis* (Steffens and Mach, 2006), we find: "Cannabinoids, such as Delta9-tetrahydrocannabinol (THC), which is the major psychoactive compound of marijuana, modulate immune functions and might therefore be of therapeutic use for the treatment of inflammatory diseases. The authors have demonstrated recently that oral treatment with low dose THC inhibits atherosclerosis progression in mice through pleiotropic immunomodulatory effects on inflammatory cells. . . " In the report *Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption* (Rajesh et al. 2007), the statement can be found: "Since a disruption of the endothelial function and integrity by HG is a crucial early event underlying the development of various diabetic complications, our results suggest that CBD, which has recently been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans, may have significant therapeutic benefits against diabetic complications and atherosclerosis." Then in *Cannabinoids and cardiovascular disease: the outlook for clinical treatments* (Ashton and Smith, 2007), we read: "Both CB1 and CB2 receptors have been implicated in a number of cardiovascular processes, including vasodilation, cardiac protection, modulation of the baroreceptor reflex in the control of systolic blood pressure, and inhibition of endothelial inflammation and the progress of atherosclerosis in a murine model." Next, in *Cannabinoid receptors in acute and chronic complications of atherosclerosis* (Mach et al. 2008), we read: "It is tempting to suggest that pharmacological modulation of the endocannabinoid system is a potential novel therapeutic strategy in the treatment of atherosclerosis." More evidence is found in *Pleiotropic effects of the CB2 cannabinoid receptor activation on human monocyte migration: implications for atherosclerosis and inflammatory diseases* (Pacher and Ungvári, 2008) where we read: "In conclusion, these new findings, coupled with recent evidence demonstrating that CB2 receptor activation also attenuates TNF-α-induced endothelial cell activation, transendothelial migration of monocytes and monocyte/neutrophil-endothelial adhesion (3, 4, 21, 23), and decreases TNF-α-induced proliferation and migration of human coronary vascular smooth muscle cells by (22)

modulating distinct signaling pathways, provide important new mechanistic insights on the possible pleiotropic effects of CB2 activation in atherosclerosis and other inflammatory disorders." Hemp seed must be added to the diet. In *Cholesterol-induced stimulation of platelet aggregation is prevented by a hempseed-enriched diet* (Prociuk et al. 2008), we read: "The results of this study demonstrate that when hempseed is added to a cholesterol-enriched diet, cholesterol-induced platelet aggregation returns to control levels." In the study, *The emerging role of the endocannabinoid system in cardiovascular disease* (Pacher and Steffens, 2009), the statement is found: "In contrast, activation of CB2 receptors in immune cells exerts various immunomodulatory effects, and the CB2 receptors in endothelial and inflammatory cells appear to limit the endothelial inflammatory response, chemotaxis, and inflammatory cell adhesion and activation in atherosclerosis and reperfusion injury. Here, we will overview the cardiovascular actions of endocannabinoids and the growing body of evidence implicating the dysregulation of the ECS in a variety of cardiovascular diseases.
"

The Cancers

Breast cancer

Breast cancer may be treatable with Cannabis and cannabinoids. In *Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma* (Ligresti et al. 2006), we read; "In conclusion, our data indicate that cannabidiol, and possibly Cannabis extracts enriched in this natural cannabinoid, represent a promising nonpsychoactive antineoplastic strategy. In particular, for a highly malignant human breast carcinoma cell line, we have shown here that cannabidiol and a cannabidiol-rich extract counteract cell growth both in vivo and in vitro as well as tumor metastasis in vivo." In the work *Δ9-Tetrahydrocannabinol Inhibits Cell Cycle Progression in Human Breast Cancer Cells through Cdc2 Regulation* (Caffarel et al. 2006), we find the statements: "Here, we show that Δ9-tetrahydrocannabinol (THC), through activation of CB2 cannabinoid receptors, reduces human breast cancer cell proliferation by blocking the progression of the cell cycle and by inducing apoptosis. . . . Taken together, these data might set the bases for a cannabinoid therapy for the management of breast cancer." In *Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells* (McAllister et al. 2007), we read: "In conclusion, CBD represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumor aggressiveness." In *Delta(9)-tetrahydrocannabinol Inhibits 17,-Estradiol-induced Proliferation and Fails to Activate Androgen and Estrogen Receptors in MCF7 Human Breast Cancer Cells* (Von Bueren et al. 2008) we read: "THC fails to act as an estrogen or androgen and appears to reduce 17,-estradiol-induced proliferation of breast cancer cell lines by a mechanism which is independent of AR and probably does not involve ER either. These results support the notion that THC controls cell proliferation through activation of cannabinoid receptors, independently of AR and ER, and thus might also be used in patients with hormonesensitive tumors." In, *JunD is involved in the antiproliferative effect of Delta9-tetrahydrocannabinol on human breast cancer cells* (Caffarel et al. 2008), we read: "It has been recently shown that cannabinoids, the active components of marijuana and their derivatives, inhibit cell cycle progression of human breast cancer cells. Here we studied the mechanism of Delta(9)-

tetrahydrocannabinol (THC) antiproliferative action in these cells, and show that it involves the modulation of JunD, a member of the AP-1 transcription factor family." Further, in *Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis* (McAllister et al. 2011), it is stated: "Using immune competent mice, we then show that treatment with CBD significantly reduces primary tumor mass as well as the size and number of lung metastatic foci in two models of metastasis. Our data demonstrate the efficacy of CBD in pre-clinical models of breast cancer. The results have the potential to lead to the development of novel non-toxic compounds for the treatment of breast cancer metastasis, and the information gained from these experiments broaden our knowledge of both Id-1 and cannabinoid biology as it pertains to cancer progression." Next, in *Cannabinoids in the treatment of cancer* (Alexander et al. 2009), we find: "Cannabinoids, the active components of the hemp plant Cannabis sativa, along with their endogenous counterparts and synthetic derivatives, have elicited anti-cancer effects in many different in vitro and in vivo models of cancer. While the various cannabinoids have been examined in a variety of cancer models, recent studies have focused on the role of cannabinoid receptor agonists (both CB(1) and CB(2)) in the treatment of estrogen receptor-negative breast cancer." Also, in *Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition* (Caffarel et al. 2010), we read: "Our results show that both Δ9-tetrahydrocannabinol, the most abundant and potent cannabinoid in marijuana, and JWH-133, a non-psychotropic CB2 receptor-selective agonist, reduce tumor growth, tumor number, and the amount/severity of lung metastases in MMTV-neu mice." Next, in *Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy* (Shrivastava et al. 2011), we read: "Our study revealed an intricate interplay between apoptosis and autophagy in CBD-treated breast cancer cells and highlighted the value of continued investigation into the potential use of CBD as an antineoplastic agent." In *Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis*, we read (McAllister et al. 2011): "Our data demonstrate the efficacy of CBD in pre-clinical models of breast cancer."

Cervical cancer

Cervical cancer may be treated with cannabinoids. In the work, *Arachidonyl ethanolamide induces apoptosis of uterine cervix cancer cells via aberrantly expressed vanilloid receptor-1* (Contassot et al. 2004), we read: "Delta(9)-Tetrahydrocannabinol, the active agent of Cannabis sativa, exhibits well-documented antitumor properties." In *Inhibition of Cancer Cell Invasion by Cannabinoids via Increased Expression of Tissue Inhibitor of Matrix Metalloproteinases-1* (Ramer and Hinz, 2008) we read: "Matrigel-coated and uncoated Boyden chambers were used to quantify invasiveness and migration, respectively, of human cervical cancer (HeLa) cells that had been treated with cannabinoids (the stable anandamide analog R(+)-methanandamide [MA] and the phytocannabinoid Δ 9 -tetrahydrocannabinol [THC]) . . . Increased expression of TIMP-1 mediates an anti-invasive effect of cannabinoids. Cannabinoids may therefore offer a therapeutic option in the treatment of highly invasive cancers." In *Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1* (Ramer et al. 2010), it is stated: "Altogether, these findings provide a novel mechanism underlying the anti-invasive action of cannabidiol and imply its use as a therapeutic option for the treatment of highly invasive cancers."

Cholangiocarcinoma

Cholangiocarcinoma may be treated with cannabinoids. In, *Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects* (Izzo and Camilleri, 2008) we read: "Cannabinoids have the potential for therapeutic application in gut and liver diseases. Two exciting therapeutic applications in the area of reversing hepatic fibrosis as well as antineoplastic effects may have a significant impact in these diseases. This review critically appraises the experimental and clinical evidence supporting the clinical application of cannabinoid receptor-based drugs in gastrointestinal, liver and pancreatic diseases." In *The dual effects of delta(9)-tetrahydrocannabinol on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration* (Leelawat et al. 2010), it is stated: "Consequently, THC is potentially used to retard cholangiocarcinoma cell growth and metastasis."

Colorectal cancer

Colorectal cancer may be treated with cannabinoids. In *The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase 2* (Patsos et al. 2005), we read: "These findings suggest anandamide may be a useful chemopreventive/therapeutic agent for colorectal cancer as it targets cells that are high expressors of COX-2, and may also be used in the eradication of tumour cells that have become resistant to apoptosis." In *Cannabinoids and cancer: potential for colorectal cancer therapy* (Patsos et al. 2005), it is stated: "Cannabinoids are a class of compounds that are currently used in the treatment of chemotherapy-induced nausea and vomiting, and in the stimulation of appetite. However, there is accumulating evidence that they could also be useful for the inhibition of tumour cell growth by modulating key survival signalling pathways." In *Cannabinoid Receptor Activation Induces Apoptosis through Tumor Necrosis Factor α–Mediated Ceramide De novo Synthesis in Colon Cancer Cells* (Cianchi et al. 2008), it is stated: "In the present study, we report that both CB1 and CB2 cannabinoid receptor activation induces apoptosis in colon cancer cells, and this is mediated by the *de novo* synthesis of ceramide. Interestingly, we show for the first time that signaling through CB1/CB2 receptor increases ceramide production via a mechanism that involves TNF-α." In *The cannabinoid δ9-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells* (Greenhough et al. 2007), we read: "Reduction of BAD protein expression by RNA interference rescued colorectal cancer cells from THC-induced apoptosis. These data suggest an important role for CB1 receptors and BAD in the regulation of apoptosis in colorectal cancer cells. The use of THC, or selective targeting of the CB1 receptor, may represent a novel strategy for colorectal cancer therapy." In the work *Cannabinoid receptor-independent cytotoxic effects of cannabinoids in human colorectal carcinoma cells: synergism with 5-fluorouracil* (Gustafsson et al. 2009), it is stated: "Cannabinoids (CBs) have been found to exert antiproliferative effects upon a variety of cancer cells, including colorectal carcinoma cells. The aim of this preclinical study was to investigate the effect of synthetic and endogenous CBs. . . . It is concluded that the CB system may provide new targets for the development of drugs to treat colorectal cancer." In *Cannabinoids in intestinal inflammation and cancer* (Izzo and Camilleri, 2009), it is stated: "Emerging evidence suggests that

cannabinoids may exert beneficial effects in intestinal inflammation and cancer." The work, *Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from Cannabis sativa* (Ruhaak et al. 2011), states: "Anti-inflammatory activity (i.e., inhibition of COX-2) is proposed to play an important role in the development of colon cancer, which makes this subject interesting to study further. In the present work, the six cannabinoids tetrahydrocannabinol (Δ^9-THC), tetrahydrocannabinolic acid (Δ^9-THC-A), cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerol (CBG) and cannabigerolic acid (CBGA), isolated from Cannabis sativa, were evaluated for their effects on prostaglandin production. For this purpose an in vitro enzyme based COX-1/COX-2 inhibition assay and a cell based prostaglandin production radioimmunoassay were used. Cannabinoids inhibited cyclooxygenase enzyme activity with IC_{50} values ranging from $1.7 \cdot 10^{-3}$ to $2.0 \cdot 10^{-4}$ M." In the paper *Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent* (Sreevalsan et al. 2011), we read: "The effects of cannabidiol (CBD) and the synthetic cannabinoid WIN-55,212 (WIN) on LNCaP (prostate) and SW480 (colon) cancer cell proliferation were determined by cell counting; apoptosis was determined by cleavage of poly(ADP)ribose polymerase (PARP) and caspase-3 (Western blots); and phosphatase mRNAs were determined by real-time PCR. The role of phosphatases and cannabinoid receptors in mediating CBD- and WIN-induced apoptosis was determined by inhibition and receptor knockdown. Conclusion: Cannabinoid receptor agonists induce phosphatases and phosphatase-dependent apoptosis in cancer cell lines; however, the role of the CB receptor in mediating this response is ligand-dependent."

Glioma (brain cancer)

Glioma may be treated with Cannabinoids. Please do read!

In *Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines* (Massi et al. 2004), we read: "in conclusion, the nonpsychoactive CBD was able to produce a significant antitumor activity both in vitro and in vivo, thus suggesting a possible application of CBD as an antineoplastic agent." In *Delta9-tetrahydrocannabinol induces apoptosis in C6 glioma cells* (Sánchez et al. 1998), it is stated: "delta9-Tetrahydrocannabinol (THC), the major active component of marijuana, induced apoptosis in C6.9 glioma cells, as determined by DNA fragmentation and loss of plasma membrane asymmetry. Results thus show that THC-induced apoptosis in glioma C6.9 cells may rely on a CBI receptor-independent stimulation of sphingomyelin breakdown." In the work, *Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas* (Blázquez et al. 2004), the text states: "Moreover, intratumoral administration of the cannabinoid Δ9-tetrahydrocannabinol to two patients with glioblastoma multiforme (grade IV astrocytoma) decreased VEGF levels and VEGFR-2 activation in the tumors. Because blockade of the VEGF pathway constitutes one of the most promising antitumoral approaches currently available, the present findings provide a novel pharmacological target for cannabinoid-based therapies." In *Anti-tumoral action of cannabinoids: Involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation* (Galve-Roperh et al. 2000), we read: "Δ^9-Tetrahydrocannabinol, the main active component of marijuana, induces apoptosis of transformed neural cells in culture. Here, we show that intratumoral administration of Δ^9-tetrahydrocannabinol and the synthetic cannabinoid agonist WIN-55,212-2 induced a

considerable regression of malignant gliomas in Wistar rats and in mice deficient in recombination activating gene 2. . . . Experiments with two subclones of C6 glioma cells in culture showed that cannabinoids signal apoptosis by a pathway involving cannabinoid receptors, sustained ceramide accumulation and Raf1/extracellular signal-regulated kinase activation. These results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas." In *The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells* (Massii et al. 2006), we read: "Recently, we have shown that the non-psychoactive cannabinoid compound cannabidiol (CBD) induces apoptosis of glioma cells in vitro and tumor regression in vivo. The present study investigated a possible involvement of caspase activation and reactive oxygen species (ROS) induction in the apoptotic effect of CBD. Thus, we found a different sensitivity to the anti-proliferative effect of CBD in human glioma cells and non-transformed cells that appears closely related to a selective ability of CBD in inducing ROS production and caspase activation in tumor cells." In *A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme* (Guzmán et al. 2006), it is stated: "Δ9-Tetrahydrocannabinol inhibited tumour-cell proliferation *in vitro* and decreased tumour-cell Ki67 immunostaining when administered to two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids." In *Inhibition of tumor angiogenesis by cannabinoids* (Blázquez et al. 2003), we read: "Cannabinoids, the active components of marijuana and their derivatives, induce tumor regression in rodents (8). . . . . Inhibition of tumor angiogenesis may allow new strategies for the design of cannabinoid-based antitumoral therapies." In the work entitled, *Hypothesis: cannabinoid therapy for the treatment of gliomas?* (Velasco et al. 2004), we read: "Remarkably, cannabinoids kill glioma cells selectively and can protect non-transformed glial cells from death. These and other findings reviewed here might set the basis for a potential use of cannabinoids in the management of gliomas." In *Cannabinoids and gliomas* (Velasco et al. 2007), it states: "The good safety profile of THC, together with its possible growth-inhibiting action on tumor cells, justifies the setting up of future trials aimed at evaluating the potential antitumoral activity of cannabinoids." In *Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism* (Vaccani et al. 2005), we read: "These results reinforce the evidence of antitumoral properties of CBD, demonstrating its ability to limit tumor invasion, although the mechanism of its pharmacological effects remains to be clarified." In *Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells* (McAllister, et al. 2005) the text states (please note the synthetic drug's performance): "Evidence of selective efficacy with WIN 55,212-2 was also observed but the selectivity was less profound, and the synthetic agonist produced a greater disruption of normal cell morphology compared to Delta(9)-THC." In, *Effects on cell viability* (Guzmán, 2005) we read: "It is therefore very likely that cannabinoids regulate cell survival and cell death pathways differently in tumour and non-tumour cells. Regarding immune cells, cannabinoids affect proliferation and survival in a complex and still obscure manner that depends on the experimental setting. The findings reviewed here might set the basis for the use of cannabinoids in the treatment of cancer and neurodegenerative diseases." In *A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme* (Guzmán et al. 2006), we read: "Here we report the first clinical study aimed at assessing cannabinoid antitumoral action, specifically a pilot phase I trial in which nine patients with

recurrent glioblastoma multiforme were administered THC intratumoraly. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids." In *The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells* (Massi et al. 2006), it states: "Recently, we have shown that the non-psychoactive cannabinoid compound cannabidiol (CBD) induces apoptosis of glioma cells in vitro and tumor regression in vivo. The present study investigated a possible involvement of caspase activation and reactive oxygen species (ROS) induction in the apoptotic effect of CBD. CBD produced a gradual, time-dependent activation of caspase-3, which preceded the appearance of apoptotic death." In *Cannabinoids Induce Glioma Stem-like Cell Differentiation and Inhibit Gliomagenesis* (Aguado et al. 2007), we read: "Overall, our results demonstrate that cannabinoids target glioma stem-like cells, promote their differentiation, and inhibit gliomagenesis, thus giving further support to their potential use in the management of malignant gliomas." In *Targeting astrocytomas and invading immune cells with cannabinoids: a promising therapeutic avenue* (Cudaback and Stella, 2007), we read: "In this study, we review in vitro and in vivo evidence supporting the use of cannabinoids for treatment of brain tumors. We further propose the continued intense investigation of cannabinoid efficacies as novel anti-cancer agents, especially in models recapitulating such properties within the unique environment of the brain." In *Cannabinoids and gliomas* (Velasco et al. 2007), it states: "Of interest, cannabinoids seem to be selective antitumoral compounds, as they kill glioma cells, but not their non-transformed astroglial counterparts. On the basis of these preclinical findings, a pilot clinical study of Delta(9)-tetrahydrocannabinol (THC) in patients with recurrent glioblastoma multiforme has been recently run. The good safety profile of THC, together with its possible growth-inhibiting action on tumor cells, justifies the setting up of future trials aimed at evaluating the potential antitumoral activity of cannabinoids." In *Cannabinoids as potential new therapy for the treatment of gliomas* (Parolaro and Massi, 2008) we read: "Moreover, cannabinoids appear to be selective antitumoral agents as they kill glioma cells without affecting the viability of nontransformed counterparts. A pilot clinical trial on patients with glioblastoma multiforme demonstrated their good safety profile together and remarkable antitumor effects, and may set the basis for further studies aimed at better evaluating the potential anticancer activity of cannabinoids." In *Cannabinoids Inhibit Glioma Cell Invasion by Down-regulating Matrix Metalloproteinase-2 Expression* (Blázquez et al. 2008), it states: "Manipulation of MMP-2 expression by RNA interference and cDNA overexpression experiments proved that down-regulation of this MMP plays a critical role in THC-mediated inhibition of cell invasion. Cannabinoid-induced inhibition of MMP-2 expression and cell invasion was prevented by blocking ceramide biosynthesis and by knocking-down the expression of the stress protein p8. As MMP-2 up-regulation is associated with high progression and poor prognosis of gliomas and many other tumors, MMP-2 down-regulation constitutes a new hallmark of cannabinoid antitumoral activity." In *Delta 9-tetrahydrocannabinol inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells* (Galanti et al. 2008), we read: "Delta(9)-THC is shown to significantly affect viability of GBM cells via a mechanism that appears to elicit G(1) arrest due to downregulation of E2F1 and Cyclin A. Hence, it is suggested that Delta(9)-THC and other cannabinoids be implemented in future clinical evaluation as a therapeutic modality for brain tumors." In *Down-regulation of tissue inhibitor of metalloproteinases-1 in gliomas: a new marker of cannabinoid antitumoral activity?* (Blázquez et

al. 2008), it states: “Here we evaluated the effects of cannabinoids on the expression of tissue inhibitors of metalloproteinases (TIMPs), which play critical roles in the acquisition of migrating and invasive capacities by tumor cells. Local administration of Delta(9)-tetrahydrocannabinol (THC), the major active ingredient of cannabis, down-regulated TIMP-1 expression in mice bearing subcutaneous gliomas, as determined by Western blot and immunofluorescence analyses. This cannabinoid-induced inhibition of TIMP-1 expression in gliomas (i) was mimicked by JWH-133, a selective CB(2) cannabinoid receptor agonist that is devoid of psychoactive side effects, (ii) was abrogated by fumonisin B1, a selective inhibitor of ceramide synthesis de novo, and (iii) was also evident in two patients with recurrent glioblastoma multiforme (grade IV astrocytoma). THC also depressed TIMP-1 expression in cultures of various human glioma cell lines as well as in primary tumor cells obtained from a glioblastoma multiforme patient.” In *5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid* (Massi et al. 2008), we read: “in conclusion, the present investigation indicates that CBD exerts its antitumoral effects through modulation of the LOX pathway and of the endocannabinoid system, suggesting a possible interaction of these routes in the control of tumor growth.” In *Anticancer mechanisms of cannabinoids* (Velasco et al. 2016), we read: “In addition to the well-known palliative effects of cannabinoids on some cancer-associated symptoms, a large body of evidence shows that these molecules can decrease tumour growth in animal models of cancer. They do so by modulating key cell signalling pathways involved in the control of cancer cell proliferation and survival. In addition, cannabinoids inhibit angiogenesis and decrease metastasis in various tumour types in laboratory animals. In this review, we discuss the current understanding of cannabinoids as antitumour agents, focusing on recent discoveries about their molecular mechanisms of action, including resistance mechanisms and opportunities for their use in combination therapy.” In *Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells* (Salazar et al. 2009), we read: “These findings describe a mechanism by which THC can promote the autophagic death of human and mouse cancer cells and provide evidence that cannabinoid administration may be an effective therapeutic strategy for targeting human cancers.” In *TRB3 links ER stress to autophagy in cannabinoid antitumoral action* (Salazar et al. 2009), we read: “Δ9-tetrahydrocannabinol (THC), the main active component of marijuana, is being investigated as a potential anti-tumoral agent. We find that THC stimulates an endoplasmic reticulum (ER) stress-related signaling pathway, which activates autophagy via inhibition of the Akt/mTORC1 axis.” In *Cannabidiol Enhances the Inhibitory Effects of Δ9 -Tetrahydrocannabinol on Human Glioblastoma Cell Proliferation and Survival*, closely *noting the interactive effects* (Marcul et al. 2010), we read: “Our results suggest that the addition of cannabidiol to Δ9 -THC may improve the overall effectiveness of Δ9 -THC in the treatment of glioblastoma in cancer patients.” In *The Expression Level of CB1 and CB2 Receptors Determines Their Efficacy at Inducing Apoptosis in Astrocytomas* (Cudaback et al. 2010), we read: “the treatment of tumors with high concentrations of cannabinoids should not be overlooked. In fact, stereotaxic injection of high concentrations of cannabinoids will eradicate a significant portion of C6 astrocytomas inoculated into rodent brains without affecting healthy surrounding tissue or inducing overt adverse effects. . . Since stereotaxic injection of chemotherapeutic compounds directly into human brain tumor masses constitutes a routine approach for neurosurgeons, high concentrations of cannabinoids can easily be delivered by this technique. . . Thus, our results suggest that high concentrations of cannabinoids constitute the

preferred regimen for neurosurgeons to use when treating malignant astrocytomas with this class of compounds." In *Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas--possible role of Cannabis inhalation* (Foroughi et al. 2011), we read: "Neither patient received any conventional adjuvant treatment. The tumors regressed over the same period of time that cannabis was consumed via inhalation, raising the possibility that the cannabis played a role in the tumor regression." In *Molecular Mechanisms Involved in the Antitumor Activity of Cannabinoids on Gliomas: Role for Oxidative Stress* (Massi et al. 2010), we read: "Of interest, cannabinoids have displayed great potency in reducing the growth of glioma tumors, one of the most aggressive CNS tumors, either *in vitro* or in animal experimental models curbing the growth of xenografts generated by subcutaneous or intrathecal injection of glioma cells in immune-deficient mice. Cannabinoids appear to be selective antitumoral agents as they kill glioma cells without affecting the viability of non-transformed cells. This review will summarize the anti-cancer properties that cannabinoids exert on gliomas and discuss their potential action mechanisms that appear complex, involving modulation of multiple key cell signaling pathways and induction of oxidative stress in glioma cells." In *A combined preclinical therapy of cannabinoids and temozolomide against glioma* (Torres et al. 2011), it is stated: "Altogether, our findings support that the combined administration of TMZ and cannabinoids could be therapeutically exploited for the management of GBM." In *Stimulation of the midkine/ALK axis renders glioma cells resistant to cannabinoid antitumoral action* (Lorente et al. 2011), we read: "Δ(9)-Tetrahydrocannabinol (THC), the major active ingredient of marijuana, and other cannabinoids inhibit tumor growth in animal models of cancer, including glioma, an effect that relies, at least in part, on the stimulation of autophagy-mediated apoptosis in tumor cells."

Leukemia

Leukemia may be treated with cannabinoids. *In Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in the regulation of p22phox and Nox4 expression* (McKallip et al. 2006), we read: "Together, the results from this study reveal that cannabidiol, acting through CB2 and regulation of Nox4 and p22(phox) expression, may be a novel and highly selective treatment for leukemia." In the study *Effects of cannabinoids on L1210 murine leukemia. 1. Inhibition of DNA synthesis* (Tucker and Friedman, 1977), it is stated: "Delta-9-tetrahydrocannabinol and delta8-tetrahydrocannabinol inhibited RNA and protein synthesis in a fashion analagous to the inhibition of DNA synthesis." In *Gamma-irradiation enhances apoptosis induced by cannabidiol, a non-psychotropic cannabinoid, in cultured HL-60 myeloblastic leukemia cells* (Gallily et al. 2003), we read: "Two non-psychotropic cannabinoids, cannabidiol (CBD) and cannabidiol-dimethylheptyl (CBD-DMH), induced apoptosis in a human acute myeloid leukemia (AML) HL-60 cell line. . . . Prior exposure of the cells to gamma-irradiation (800 cGy) markedly enhanced apoptosis, reaching values of 93 and 95%, respectively. Human monocytes from normal individuals were resistant to either cannabinoids or gamma-irradiation. Caspase-3 activation was observed after the cannabinoid treatment, and may represent a mechanism for the apoptosis." In the work, *Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease* (McKallip et al. 2002), we read: "Exposure of murine tumors EL-4, LSA, and P815 to delta-9-tetrahydrocannabinol (THC) in vitro led to a significant reduction in cell viability and an increase in apoptosis." In the study *Cannabis-induced*

cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway (Powles et al. 2005), it is stated: "We have shown that THC is a potent inducer of apoptosis, even at 1 × IC50 (inhibitory concentration 50%) concentrations and as early as 6 hours after exposure to the drug. These effects were seen in leukemic cell lines (CEM, HEL-92, and HL60) as well as in peripheral blood mononuclear cells." In *Enhancing the in vitro cytotoxic activity of Delta9-tetrahydrocannabinol in leukemic cells through a combinatorial approach* (Liu et al. 2008), we read: "Delta(9)-Tetrahydrocannabinol (THC) is the active metabolite of cannabis, which has demonstrable cytotoxic activity in vitro. In support of our previously published data, we have investigated the interactions between THC and anti-leukemia therapies and studied the role of the signalling pathways in mediating these effects. Results showed clear synergistic interactions between THC and the cytotoxic agents in leukemic cells. " In *Cannabidiol induced a contrasting pro-apoptotic effect between freshly isolated and precultured human monocytes* (Wu et al. 2010), the text states: "It has been documented that cannabidiol (CBD) induced apoptosis in a variety of transformed cells, including lymphocytic and monocytic leukemias. In contrast, a differential sensitivity between normal lymphocytes and monocytes to CBD-mediated apoptosis has been reported." In *Cannabidiol-Induced Apoptosis in Human Leukemia Cells: A Novel Role of Cannabidiol in the Regulation of p22phox and Nox4 Expression* (McKallip et al. 2006), we read: "Together, the results from this study reveal that cannabidiol, acting through CB2 and regulation of Nox4 and p22*phox* expression, may be a novel and highly selective treatment for leukemia." In *Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease* (McKallip et al. 2002), we read: "Together, the current data demonstrate that CB2 cannabinoid receptors expressed on malignancies of the immune system may serve as potential targets for the induction of apoptosis. Also, because CB2 agonists lack psychotropic effects, they may serve as novel anticancer agents to selectively target and kill tumors of immune origin." The study *Cannabinoids induce incomplete maturation of cultured human leukemia cells* (Murison et al. 1987), states: "the THC-treated cells failed to exhibit other monocyte markers such as attachment to the surface of tissue culture dishes or morphological maturation beyond the promonocyte stage." In the report, *Δ9-Tetrahydrocannabinol-Induced Apoptosis in Jurkat Leukemia T Cells Is Regulated by Translocation of Bad to Mitochondria* (Jia et al. 2006), we read: "Plant-derived cannabinoids, including Δ9-tetrahydrocannabinol (THC), induce apoptosis in leukemic cells, although the precise mechanism remains unclear. . . . Together, these data suggested that Raf-1/MEK/ERK/RSK-mediated Bad translocation played a critical role in THC-induced apoptosis in Jurkat cells."

Liver Cancer

Liver cancer may benefit from Cannabinoid therapy. In *Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma* (Xu et al. 2006), we read: "Our results indicate that CB1 and CB2 have potential as prognostic indicators and suggest possible beneficial effects of cannabinoids on prognosis of patients with HCC." In the study, *Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects* (Izzo and Camilleri, 2008), it is stated: "Cannabinoids have the potential for therapeutic application in gut and liver diseases. Two exciting therapeutic applications in the area

of reversing hepatic fibrosis as well as antineoplastic effects may have a significant impact in these diseases. . . . . other cannabinoid modulators are likely to have an impact on human disease in the future, including hepatic fibrosis and neoplasia." In *Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy* (Vara et al. 2011), we read: "In vivo studies revealed that Δ(9)-THC and JWH-015 reduced the growth of HCC subcutaneous xenografts, an effect that was not evident when autophagy was genetically or pharmacologically inhibited in those tumors. Moreover, cannabinoids were also able to inhibit tumor growth and ascites in an orthotopic model of HCC xenograft."

Lung Cancer

As has been long known lung cancer may benefit from treatment with cannabinoids. *In Antineoplastic activity of cannabinoids*, a study from 1975 (Munson et al. 1975) we read: "Lewis lung adenocarcinoma growth was retarded by the oral administration of delta-9-tetrahydrocannabinol, delta-8-tetrahydrocannabinol, and cannabinol (CBN) . . . However, delta-9-THC administered daily for 10 days significantly inhibited Friend leukemia virus-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for actinomycin D. Experiments with bone marrow and isolated Lewis lung cells incubated in vitro with delta-8-THC and delta-9-THC showed a dose-dependent (10 -4 10 -7) inhibition (80-20%, respectively) of tritiated thymidine and 14C -uridine uptake into these cells. CBD was active only in high concentrations (10 -4) . . . . That these compounds readily cross the blood-brain barrier and do not possess many of the toxic manifestations of presently used cytotoxic agents, makes them an appealing group of drugs to study." In *Anticancer activity of cannabinoids*, a study from 1975 (Munson et al. 1975), we read: "Lewis lung adenocarcinoma growth was retarded by the oral administration of delta-9-tetrahydrocannabinol, delta-8-tetrahydrocannabinol, and cannabinol (CBN), but not cannabidiol (CBD). Animals treated for 10 consecutive days with delta-9-THC, beginning the day after tumor implantation, demonstrated a dose-dependent action of retarded tumor growth. . . . Delta-9-THC, delta-8-THC, and CBN increased the mean survival time (36% at 100 mg/kg, 25% at 200 mg/kg, and 27% at 50 mg/kg;, respectively)." In *Inhibition of Cancer Cell Invasion by Cannabinoids via Increased Expression of Tissue Inhibitor of Matrix Metalloproteinases-1* (Ramer and Hinz, 2008), we read: "The role of TIMP-1 in the anti-invasive action of cannabinoids was analyzed by transfecting HeLa, human cervical carcinoma (C33A), or human lung carcinoma cells (A549) cells with siRNA targeting TIMP-1. . . . Increased expression of TIMP-1 mediates an anti-invasive effect of cannabinoids. Cannabinoids may therefore offer a therapeutic option in the treatment of highly invasive cancers." In the work *Decrease of plasminogen activator inhibitor-1 may contribute to the anti-invasive action of cannabidiol on human lung cancer cells* (Ramer et al. 2010), we read: "Our data provide evidence for a hitherto unknown mechanism underlying the anti-invasive action of cannabidiol on human lung cancer cells." In *Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1* (Ramer et al. 2010), it is stated: "Altogether, these findings provide a novel mechanism underlying the anti-invasive action of cannabidiol and imply its use as a therapeutic option for the treatment of highly invasive cancers." In *Cannabinoid Receptors, CB1 and CB2, as Novel Targets for Inhibition of Non-Small Cell Lung Cancer Growth and Metastasis* (Preet et al. 2011), we read: "Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths worldwide; however, only limited

therapeutic treatments are available. Hence, we investigated the role of cannabinoid receptors, CB1 and CB2, as novel therapeutic targets against NSCLC. . . . . These results suggest that CB1 and CB2 could be used as novel therapeutic targets against NSCLC." In *Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1* (Ramer et al. 2012), it is stated: "Overall, our data indicate that cannabinoids induce ICAM-1, thereby conferring TIMP-1 induction and subsequent decreased cancer cell invasiveness." In *Δ^9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo* (Preet et al. 2008), we read: "Tumor samples from THC-treated animals revealed antiproliferative and antiangiogenic effects of THC. Our study suggests that cannabinoids like THC should be explored as novel therapeutic molecules in controlling the growth and metastasis of certain lung cancers."

Lymphoma

Lymphoma may be treated with cannabinoids. In *Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease* (McKallip et al. 2002), we read: "Together, the current data demonstrate that CB2 cannabinoid receptors expressed on malignancies of the immune system may serve as potential targets for the induction of apoptosis. Also, because CB2 agonists lack psychotropic effects, they may serve as novel anticancer agents to selectively target and kill tumors of immune origin." *In Cannabinoid receptor ligands mediate growth inhibition and cell death in mantle cell lymphoma* (Flygare et al. 2005), we read: "Our data suggest that cannabinoid receptors may be considered as potential therapeutic targets in MCL." In the paper *Expression of cannabinoid receptors type 1 and type 2 in non-Hodgkin lymphoma: growth inhibition by receptor activation* (Gustafsson et al. 2008), it is stated: "Together, our results suggest that therapies using cannabinoid receptor ligands will have efficiency in reducing tumor burden in malignant lymphoma overexpressing CB1 and CB2."

Melanoma

Cannabinoids may be used to treat Melanoma. In *Cannabinoid receptors as novel targets for the treatment of melanoma* (Blázquez et al. 2006), we read: "Cannabinoid antimelanoma activity was independent of the immune status of the animal, could be achieved without overt psychoactive effects and was selective for melanoma cells vs. normal melanocytes. Cannabinoid antiproliferative action on melanoma cells was due, at least in part, to cell cycle arrest at the G1-S transition via inhibition of the prosurvival protein Akt and hypophosphorylation of the pRb retinoblastoma protein tumor suppressor. These findings may contribute to the design of new chemotherapeutic strategies for the management of melanoma." In the work *Dronabinol for supportive therapy in patients with malignant melanoma and liver metastases* (Zutt et al. 2006), it is stated: "Loss of appetite and nausea due to liver metastases of malignant melanoma can be treated in individual cases supportively with Dronabinol." In *Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression* (Rieder et al. 2010), we read: "In this review, we will focus on apoptotic mechanisms of immunosuppression mediated by cannabinoids on different immune cell populations and discuss how activation of CB2 provides a novel therapeutic modality against inflammatory and autoimmune diseases as well as malignancies of the immune

system, without exerting the untoward psychotropic effects."

Neuroblastoma

Cannabinoids may be used to treat Neuroblastoma. In the article *Inhibition of neuroblastoma adenylate cyclase by cannabinoid and nantradol compounds* (Howlett, 1984), we read: "These data demonstrate that cannabinoid and nantradol compounds decrease cyclic AMP accumulation in neuronally derived cells, and that this results from an inhibition of basal and hormone-stimulated adenylate cyclase activity." In *Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membranes* (Howlett and Fleming, 1984), we read: "Adenylate cyclase in plasma membranes was inhibited by micromolar concentrations of delta 8-tetrahydrocannabinol and delta 9-tetrahydrocannabinol and by levonantradol and desacetyllevonantradol. . . . . The inhibition of adenylate cyclase was specific for psychoactive cannabinoids, since cannabinol and cannabidiol produced minimal or no response." In *Interaction of delta-9-tetrahydrocannabinol with rat B103 neuroblastoma cells* (Cabral et al. 1987), it states: "The effect of delta-9-tetrahydrocannabinol (delta-9-THC) on the growth kinetics and morphology of rat B103 neuroblastoma cells was assessed. . . . . These results suggest that delta-9-THC interacts with cellular membranes, thereby altering neuroblastoma cell growth and behavior." In the paper *Tau protein after delta-9-tetrahydrocannabinol in a human neuroblastoma cell line* (Lew, 1996), we read: "A human neuroblastoma cell line, SH-SY5Y, was used to determine the effects of delta-9-tetrahydrocannabinol (THC) on microtubule-associated tau protein. 2. After 48-hr treatment, THC (10(-9) M) decreased 50 kD tau protein in the cytoplasmic (supernatant) fraction, and in the membrane (pellet) fraction the drug (10(-7) M) also decreased 50 kD tau protein. 3. This reduction in tau protein was accompanied by a 27% reduction ($P < 0.05$) in the membrane (pellet) total protein after (10(-7) M) THC and a 28% increase ($P < 0.02$) in cytoplasmic (supernatant) total protein after 10(-9) M THC." In *Stimulation of anandamide biosynthesis in N-18TG2 neuroblastoma cells by delta 9-tetrahydrocannabinol (THC)* (Burstein and Hunter, 1995), it is stated: "A concentration-related stimulation of anandamide (arachidonylethanolamide) synthesis by delta 9-tetrahydrocannabinol (THC) was observed in N-18TG2 neuroblastoma cells." In *Anandamide induces apoptosis in human cells via vanilloid receptors. Evidence for a protective role of cannabinoid receptors* (Maccarrone et al. 2000), we read: "The endocannabinoid anandamide (AEA) is shown to induce apoptotic bodies formation and DNA fragmentation, hallmarks of programmed cell death, in human neuroblastoma CHP100 and lymphoma U937 cells." In *Increasing Antiproliferative Properties of Endocannabinoids in N1E-115 Neuroblastoma Cells through Inhibition of Their Metabolism* (Hamtiaux et al. 2011), we read: "The antitumoral properties of endocannabinoids received a particular attention these last few years. Indeed, these endogenous molecules have been reported to exert cytostatic, apoptotic and antiangiogenic effects in different tumor cell lines and tumor xenografts. Therefore, we investigated the cytotoxicity of three *N*-acylethanolamines – *N*-arachidonoylethanolamine (anandamide, AEA), *N*-palmitoylethanolamine (PEA) and *N*-oleoylethanolamine (OEA) - which were all able to time- and dose-dependently reduce the viability of murine N1E-115 neuroblastoma cells."

Oral Cancer

Oral cancer patients may benefit from treatment with cannabinoids. In *Peripheral Cannabinoids Attenuate Carcinoma Induced Nociception in Mice* (Guerrero et al. 2008), we read: "These findings support the suggestion that cannabinoids are capable of producing antinociception in carcinoma-induced pain." In *Cannabinoids attenuate cancer pain and proliferation in a mouse model* (Saghafi et al. 2011), we read: "The systemic administration of cannabinoid receptor agonists may have important therapeutic implications wherein cannabinoid receptor agonists may reduce morbidity and mortality of oral cancer." In the work *Cannabinoids Inhibit Cellular Respiration of Human Oral Cancer Cells* (Whyte et al. 2010), it is stated: "The primary cannabinoids, Δ9-tetrahydrocannabinol (Δ9-THC) and Δ8-tetrahydrocannabinol (Δ8-THC) are known to disturb the mitochondrial function and possess antitumor activities. These observations prompted us to investigate their effects on the mitochondrial O2 consumption in human oral cancer cells (Tu183). . . . A rapid decline in the rate of respiration was observed when Δ9-THC or Δ8-THC was added to the cells. The inhibition was concentration-dependent, and Δ9-THC was the more potent of the two compounds. Anandamide (an endocannabinoid) was ineffective; suggesting the effects of Δ9-THC and Δ8-THC were not mediated by the cannabinoidreceptors. Inhibition of O2 consumption by cyanide confirmed the oxidations occurred in the mitochondrial respiratory chain. . . . These results show the cannabinoids are potent inhibitors of Tu183 cellular respiration and are toxic to this highly malignant tumor."

Pancreatic cancer

Pancreatic cancer may be treated with cannabinoids. The paper, *Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress–Related Genes* (Carracedo et al. 2006), states: "Pancreatic adenocarcinomas are among the most malignant forms of cancer and, therefore, it is of especial interest to set new strategies aimed at improving the prognostic of this deadly disease. . . Knockdown experiments using selective small interfering RNAs showed the involvement of p8 via its downstream endoplasmic reticulum stress–related targets activating transcription factor 4 (ATF-4) and TRB3 in Δ9-tetrahydrocannabinol–induced apoptosis. Cannabinoids also reduced the growth of tumor cells in two animal models of pancreatic cancer. In addition, cannabinoid treatment inhibited the spreading of pancreatic tumor cells. . . . In conclusion, results presented here show that cannabinoids lead to apoptosis of pancreatic tumor cells via a CB2 receptor and *de novo* synthesized ceramide-dependent up-regulation of p8 and the endoplasmic reticulum stress–related genes *ATF-4* and *TRB3*. In *Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects* (Izzo and Camilleri, 2008), we read: "This review critically appraises the experimental and clinical evidence supporting the clinical application of cannabinoid receptor-based drugs in gastrointestinal, liver and pancreatic diseases. . . . cannabinoid modulators are likely to have an impact on human disease in the future, including hepatic fibrosis and neoplasia." In the paper *Cannabinoids in pancreatic cancer: Correlation with survival and pain* (Michalski et al. 2008), we read: "Cannabinoids exert antiproliferative properties in a variety of malignant tumors, including pancreatic ductal adenocarcinoma (PDAC) . . . Therefore, changes in the levels of endocannabinoid metabolizing enzymes and cannabinoid receptors on pancreatic cancer cells may affect prognosis and pain status

of PDAC patients. . . . natural cannabinoids had been used by many societies until their prohibition at the beginning of the last century due to their addictive potential. However, the potential for addiction and psychotropic side effects seems to be by far overestimated, especially for patients with malignant tumors, for whom pain control, stable weight and quality of life are the main measures of medical therapy. . . Cannabinoids have just recently been shown to exert growth inhibitory properties in pancreatic cancer. Taken together, our observation could—together with other reports—build the basis for a clinical testing of cannabinoids in the treatment of pancreatic cancer. Furthermore, our data strengthen the perception that cannabinoids may be useful in treating pancreatic cancer-associated pain." In *TRB3 links ER stress to autophagy in cannabinoid antitumoral action* (Salazar et al. 2009), we read: "We find that THC stimulates an endoplasmic reticulum (ER) stress-related signaling pathway, which activates autophagy via inhibition of the Akt/mTORC1 axis. We also show that autophagy is upstream of apoptosis in cannabinoid-induced cancer cell death and that activation of this pathway is necessary for the anti-tumoral action of cannabinoids in vivo." In *Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism* (Donadelli et al. 2011), we read: "These findings support a key role of the ROS-dependent activation of an autophagic program in the synergistic growth inhibition induced by GEM/cannabinoid combination in human pancreatic cancer cells."

Prostate cancer

Prostate cancer is treatable with cannabinoids. In *Delta9-tetrahydrocannabinol induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism* (Ruiz et al. 1999), we read: "The effect of delta9-tetrahydrocannabinol (THC), the major psycho-active component of marijuana, in human prostate cancer cells PC-3 was investigated. THC caused apoptosis in a dose-dependent manner." In *Expression of functionally active cannabinoid receptor CB1 in the human prostate gland* (Ruiz-Llorente et al. 2003), we read: "Although cannabinoids have functional and morphologic effects in the prostate gland, the expression of cannabinoid receptors in this tissue has never been investigated. The aim of this study was to analyze the expression of cannabinoid receptors in the human prostate gland and their regulatory effects on adenylyl cyclase activity. . . . The cannabinoid receptor expressed in the prostate negatively regulates adenylyl cyclase activity through a pertussis toxin-sensitive protein." In *Cannabinoid Receptor Agonist-induced Apoptosis of Human Prostate Cancer Cells LNCaP Proceeds through Sustained Activation of ERK1/2 Leading to G_1 Cell Cycle Arrest* (Sarfaraz et al. 2006), we read: "Based on these data we suggest that cannabinoid receptor agonists should be considered as novel agents for the management of prostate cancer." In *Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production* (Mimeault et al. 2003), we read: "The potent anti-proliferative and cytotoxic effects of ANA on metastatic prostatic cancer cells might provide basis for the design of new therapeutic agents for effective treatment of recurrent and invasive prostatic cancers." In *Endocannabinoids in endocrine and related tumours* (Bifulco et al. 2008), we read: "Accumulated evidence indicates that CBs could be an important target for the treatment of cancer due to their ability to regulate signalling pathways critical for cell growth and survival. Several studies have produced exciting new leads in the search for anticancer treatments with cannabinoid-related drugs." In the work,

Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2 (Olea-Herrero et al. 2009), we read: "We have previously shown that cannabinoids induce growth inhibition and apoptosis in prostate cancer PC-3 cells, which express high levels of cannabinoid receptor types 1 and 2 ($CB_1$and CB_2). . . . . This study defines the involvement of CB_2-mediated signalling in the *in vivo* and *in vitro*growth inhibition of prostate cancer cells and suggests that CB_2 agonists have potential therapeutic interest and deserve to be explored in the management of prostate cancer." In *The endocannabinoid system and cancer: therapeutic implication* (Guindon and Hohmann, 2011), we read: "In this regard, cannabis-like compounds offer therapeutic potential for the treatment of breast, prostate and bone cancer in patients." In *The endocannabinoid system in prostate cancer* (Díaz-Laviada, 2011), we read: "Moreover, several cannabinoids exert antitumoral properties against prostate cancer, reducing xenograft prostate tumor growth, prostate cancer cell proliferation and cell migration." In *Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent* (Sreevalsan et al. 2011), it is stated: "We hypothesized that the anticancer activity of cannabinoids was linked to induction of phosphatases. . . . CBD and WIN inhibited LNCaP and SW480 cell growth . . . Cannabinoid receptor agonists induce phosphatases and phosphatase-dependent apoptosis in cancer cell lines." In *Cannabinoid receptor type 1 (CB1) activation inhibits small GTPase RhoA activity and regulates motility of prostate carcinoma cells* (Nithipatikom et al. 2012), we read: "The CB1 and its endogenous and synthetic agonists are emerging as therapeutic targets in several cancers due to their ability to suppress carcinoma cell invasion and migration. . . . These results indicate the unique CB1 signaling and support the model that EC, through their autocrine activation of CB1 and subsequent repression of RhoA activity, suppress migration in prostate carcinoma cells." In *The cannabinoid R+ methanandamide induces IL-6 secretion by prostate cancer PC3 cells* (Olea-Herrero et al. 2009), we read: " Our findings also suggest that CB2 agonists may offer a novel approach in the treatment of prostate cancer by decreasing cancer epithelial cell proliferation." In the work *Receptors and Prolactin Receptors by Endocannabinoids Leads to Inhibition of Human Breast and Prostate Cancer Cell Proliferation* (Melck et al. 2000), we read: "These findings suggest that endogenous cannabinoids and CB1 receptor agonists are potential negative effectors of PRL- and NGF induced biological responses, at least in some cancer cells."

Squamous cell carcinoma

Squamous cell carcinoma may be treated with cannabinoids. In the work, *A Population-based Case-Control Study of Marijuana Use and Head and Neck Squamous Cell Carcinoma* (Liang et al. 2009), we read: "Our study suggests that moderate marijuana use is associated with reduced risk of HNSCC." In *Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors* (Casanova et al. 2003), we read: "In any event, the present report, together with the implication of CB2- or CB2-like receptors in the control of peripheral pain (40–42) and inflammation (41), opens the attractive possibility of finding cannabinoid-based therapeutic strategies for diseases of the skin and other tissues." In the paper *Peripheral Cannabinoids Attenuate Carcinoma Induced Nociception in Mice* (Guerrero et al. 2008), we read: "These findings support the suggestion that cannabinoids are capable of producing antinociception in carcinoma-induced pain." In *Cannabinoids as therapeutic agents in cancer: current status and*

future implications (Chakravarti et al. 2014), we read: "Δ9-THC induced apoptosis in oral squamous cell carcinoma (OSCC), a malignant form of oral cancer."

Thyroid cancer

Thyroid cancer may be treated with Cannabinoids. In *Inhibitory effects of cannabinoid CB1 receptor stimulation on tumor growth and metastatic spreading: actions on signals involved in angiogenesis and metastasis* (Portella et al. 2003), we read: "Our findings indicate that CB1 receptor agonists might be used therapeutically to retard tumor growth in vivo by inhibiting at once tumor growth, angiogenesis, and metastasis." In *A new strategy to block tumor growth by inhibiting endocannabinoid inactivation* (Bifulco et al. 2004), it is stated: "These findings indicate that endocannabinoids tonically control tumor growth in vivo by both CB1-mediated and non-CB1-mediated mechanisms and that, irrespective of the molecular mechanism of their anti-proliferative action, inhibitors of their inactivation might be used for the development of novel anti-cancer drugs." In the work *Endocannabinoids in endocrine and related tumours* (Bifulco et al. 2008), we read: "recent evidence indicates that endocannabinoids influence the intracellular events controlling the proliferation of numerous types of endocrine and related cancer cells, thereby leading to both in vitro and in vivo antitumour effects. In particular, they are able to inhibit cell growth, invasion and metastasis of thyroid, breast and prostate tumours. The chief events of endocannabinoids in cancer cell proliferation are reported highlighting the correspondent signalling involved in tumour processes: regulation of adenylyl cyclase, cyclic AMP-protein kinase-A pathway and MEK-extracellular signal-regulated kinase signalling cascade." In *Cannabinoid 2 receptor induction by IL-12 and its potential as a therapeutic target for the treatment of anaplastic thyroid carcinoma* (Shi et al. 2008), we read: "Given that cannabinoids have shown antitumor effects in many types of cancer models, CB2 may be a viable therapeutic target for the treatment of anaplastic thyroid carcinoma.

Cancer—General information

A point to to consider: The reader may now be somewhat convinced that there is considerable multi-target mechanism-specific applicability of phytochemical cannabinoids and other constituents of cannabis in the amelioration of pathologies such as cancer and other diseases through a great number of highly interdigitated systemic mediations. Please continue on, and again observe the scope, level of degree of said *intra*-connectivity between this plant and human health and pathology, which possibly appears even from this incomplete and early vantage point to be part of a single coevolutionary environmental systemic dynamic of some kind, hence the stress on the prefix "intra-." It appears even now, that this level of interwoven systemic mediation and multilayered systemic cross-relational complexity could imply some sort of long-term adaptation to explain the observed complexity and cross-mediatory dynamics, checks and balances of these therapeutic compounds. The specifics of phylogenetic receptor evolution will be dealt with in a later section.

In *Targeting CB2-GPR55 Receptor Heteromers Modulates Cancer Cell Signaling* (Moreno et al. 2014), we read: "These findings unveil the existence of previously unknown signaling platforms that help explain the complex behavior of cannabinoids and may constitute new targets for therapeutic intervention in oncology." In *Endocannabinoids in the immune system and cancer* (Parolaro et al. 2002), it is stated: "The experimental evidence reviewed in this article argues in favor of the therapeutic potential of these compounds in immune disorders and cancer." In *Therapeutic potential of cannabinoids in CNS disease* (Croxford, 2003), we read: ". . . delta(9)-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity. Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that occur with existing therapeutic agents. . . . This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment." In *Cannabinoid receptor systems: therapeutic targets for tumour intervention* (Jones and Howl, 2003), we read: "Much of our understanding of the signalling mechanisms activated by cannabinoids is derived from studies of receptors expressed by tumour cells; hence, this review provides a succinct summary of the molecular pharmacology of cannabinoid receptors and their roles in tumour cell biology. Moreover, there is now a genuine expectation that the manipulation of cannabinoid receptor systems may have therapeutic potential for a diverse range of human diseases. Thus, this review also summarises the demonstrated antitumour actions of cannabinoids and indicates possible avenues for the future development of cannabinoids as antitumour agents." In *Changes in the Endocannabinoid System May Give Insight into new and Effective Treatments for Cancer* (Alpini & DeMorrow, 2009), we read: "Marijuana and its derivatives have been used in medicine for centuries, however, it was not until the isolation of the psychoactive component of Cannabis sativa (Δ9-tetrahydrocannabinol; Δ9-THC) and the subsequent discovery of the endogenous cannabinoid signaling system that research into the therapeutic value of this system reemerged. Ongoing research is determining that regulation of the endocannabinoid system may be effective in the treatment of pain (Calignano *et al.*, 1998; Manzanares *et al.*, 1999), glaucoma (Voth and Schwartz, 1997), and neurodegenerative disorders such as Parkinson's disease (Piomelli *et al.*, 2000) and multiple sclerosis (Baker *et al.*, 2000). In addition, cannabinoids might be effective anti-tumoral agents because of their ability to inhibit the growth of various types of cancer cell lines in culture (De Petrocellis *et al.*, 1998; Ruiz *et al.*, 1999; Sanchez *et al.*, 1998, 2001) and in laboratory animals (Galve-Roperh *et al.*, 2000)." In *Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents* (Pisanti et al. 2009), it is stated: "Emerging evidence suggests that agonists of cannabinoid receptors expressed by tumour cells may offer a novel strategy to treat cancer." In *Cannabinoid receptor ligands as potential anticancer agents--high hopes for new therapies?* (Oesch and Gertsch, 2009), we read: "Probably the most interesting question is whether cannabinoids could be useful in chemoprevention or in combination with established chemotherapeutic agents." In *Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain*, carefully noting *combinative* phytochemical effects and interaction with opioids (Johnson et al. 2010), we read: "This study compared the efficacy of a tetrahydrocannabinol:cannabidiol (THC:CBD) extract, a nonopioid analgesic endocannabinoid

system modulator, and a THC extract, with placebo, in relieving pain in patients with advanced cancer. In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59). The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC:CBD compared with placebo (improvement of -1.37 vs. -0.69), whereas the THC group showed a nonsignificant change (-1.01 vs. -0.69). Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). . . . This study shows that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids." In *Targeting the endocannabinoid system for the treatment of cancer--a practical view* (Fowler et al. 2010), we read: "It is concluded that cannabinoids (or agents modulating the endogenous cannabinoid system) are an attractive target for drug development in the cancer area. . . " In *Cannabis-derived substances in cancer therapy--an emerging anti-inflammatory role for the cannabinoids*, noting multiple effects of therapeutic systemic mediation (Liu et al. 2010), we read: "Recently, interest in developing cannabinoids as therapies has increased following reports that they possess anti-tumour properties. Research into cannabinoids as anti-cancer agents is in its infancy, and has mainly focussed on the pro-apoptotic effects of this class of agent. Impressive anti-cancer activities have been reported; actions that are mediated in large part by disruptions to ubiquitous signalling pathways such as ERK and PI3-K. However, recent developments have highlighted a putative role for cannabinoids as anti-inflammatory agents. Chronic inflammation has been associated with neoplasia for sometime, and as a consequence, reducing inflammation as a way of impacting cancer presents a new role for these compounds." In *Antitumorigenic effects of cannabinoids beyond apoptosis, noting multiple effects of therapeutic systemic mediation* (Freimuth et al. 2010) we read: "Over past years, the antitumorigenic effects of cannabinoids have emerged as an exciting field in cancer research. Apart from their proapoptotic and antiproliferative action, recent research has shown that cannabinoids may likewise affect tumor cell angiogenesis, migration, invasion, adhesion, and metastasization." In *Anticancer mechanisms of cannabinoids* (Velasco et al. 2016), it states: "In addition to the well-known palliative effects of cannabinoids on some cancer-associated symptoms, a large body of evidence shows that these molecules can decrease tumour growth in animal models of cancer. . . . Those observations have already contributed to the foundation for the development of the first clinical studies that will analyze the safety and potential clinical benefit of cannabinoids as anticancer agents." In the paper *The endocannabinoid system and cancer: therapeutic implication* (Guindon and Hohmann, 2011), we read: "The endocannabinoid system is implicated in a variety of physiological and pathological conditions (inflammation, immunomodulation, analgesia, cancer and others). The main active ingredient of cannabis, Δ(9) -tetrahydrocannabinol (Δ(9) -THC), produces its effects through activation of CB(1) and CB(2) receptors. CB(1) receptors are expressed at high levels in the central nervous system (CNS), whereas CB(2) receptors are concentrated predominantly, although not exclusively, in cells of the immune system. . . . . Identification of safe and effective treatments to manage and improve cancer therapy is critical to improve quality of life and reduce unnecessary suffering in cancer patients. In this regard, cannabis-like compounds offer therapeutic potential for the treatment of breast, prostate and bone cancer in patients. Further basic research on anti-cancer

properties of cannabinoids as well as clinical trials of cannabinoid therapeutic efficacy in breast, prostate and bone cancer is therefore warranted." In *Cannabinoids, endocannabinoids, and cancer* (Hermanson and Marnett, 2011), we read: "Modulation of the endocannabinoid system by pharmacological agents in various cancer types reveals that it can mediate antiproliferative and apoptotic effects by both cannabinoid receptor-dependent and -independent pathways. Selective agonists and antagonists of the cannabinoid receptors, inhibitors of endocannabinoid hydrolysis, and cannabinoid analogs have been utilized to probe the pathways involved in the effects of the endocannabinoid system on cancer cell apoptosis, proliferation, migration, adhesion, and invasion. The antiproliferative and apoptotic effects produced by some of these pharmacological probes reveal that the endocannabinoid system is a promising new target for the development of novel chemotherapeutics to treat cancer."

Colitis

Colitis may be treatable with cannabiniods. In *Agonists of cannabinoid receptor 1 and 2 inhibit experimental colitis induced by oil of mustard and by dextran sulfate sodium*, (Kimball et al. 2006) we read: "These findings validate the OM colitis model with respect to the DSS model and provide strong support to the emerging idea that cannabinoid receptor activation mediates protective mechanisms in experimental colitis." In the paper, *Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors* (Storr et al. 2008), is stated: "Mice were treated with trinitrobenzene-sulfonic acid in presence and absence of the fatty acid amide hydrolase (FAAH) blocker URB597, the EC membrane transport inhibitor VDM11, and combinations of both. Inflammation was significantly reduced in the presence of URB597, VDM11, or both as evaluated by macroscopic damage score, myeloperoxidase levels, and colon length. These effects were abolished in CB(1)- and CB(2)-receptor-gene-deficient mice. . . . In conclusion, drugs targeting EC degradation offer therapeutic potential in the treatment of inflammatory bowel diseases." In *Activation of cannabinoid (CB)1 receptors results in attenuation of experimental colitis* (Storr et al. 2009), we read: "Our aim was to examine the role of CB2 receptors in experimental colitis . . . We show that activation of the CB2 receptor protects against experimental colitis in mice. Increased expression of CB2 receptor mRNA and aggravation of colitis by AM630 suggests a role for this receptor in normally limiting the development of colitis. These results support the idea that the CB2 receptor may be a possible novel therapeutic target in inflammatory bowel disease." In *Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis* (Borrelli et al. 2009), we read: "In conclusion, cannabidiol, a likely safe compound, prevents experimental colitis in mice." In *The Cannabinoid 1 Receptor (CNR1) 1359 G/A Polymorphism Modulates Susceptibility to Ulcerative Colitis and the Phenotype in Crohn's Disease* (Storr et al. 2010), the text states: "The endocannabinoid system may influence the manifestation of inflammatory bowel diseases, suggesting endocannabinoids as potential target for future therapies." In *The effects of Δ9-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis* (Jamontt et al. 2010), we read: "In this model of colitis, THC and CBD not only reduced inflammation but also lowered the occurrence of functional disturbances. Moreover the combination of CBD and THC could be beneficial therapeutically, via additive or potentiating effects." In *Cannabidiol Reduces Intestinal*

Inflammation through the Control of Neuroimmune Axis (De Filippis et al. 2011), we read: "Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases." In *Alternative targets within the endocannabinoid system for future treatment of gastrointestinal diseases* (Schicho and Storr, 2011), we read: "Many beneficial effects of herbal and synthetic cannabinoids on gut motility and inflammation have been demonstrated, suggesting a vast potential for these compounds in the treatment of gastrointestinal disorders. . . . Drugs that inhibit endocannabinoid degradation and raise the level of endocannabinoids are becoming increasingly promising alternative therapeutic tools to manipulate the ECS."

Depression:

Those who suffer from depression could benefit from treatment with cannabinoids. In *Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects* (Jiang et al. 2005), we read: "The hippocampal dentate gyrus in the adult mammalian brain contains neural stem/progenitor cells (NS/PCs) capable of generating new neurons, i.e., neurogenesis. Most drugs of abuse examined to date decrease adult hippocampal neurogenesis, but the effects of cannabis (marijuana or cannabinoids) on hippocampal neurogenesis remain unknown. . . . X-irradiation of the hippocampus blocked both the neurogenic and behavioral effects of chronic HU210 treatment, suggesting that chronic HU210 treatment produces anxiolytic- and antidepressant-like effects likely via promotion of hippocampal neurogenesis." In *Decreased depression in marijuana users* (Denson and Earleywine, 2006), we read: "Despite comparable ranges of scores on all depression subscales, those who used once per week or less had less depressed mood, more positive affect, and fewer somatic complaints than non-users. Daily users reported less depressed mood and more positive affect than non-users." In *Do patients use marijuana as an antidepressant?* (Gruber et al. 1996), we read: "We review this literature and present five cases in which the evidence seems particularly clear that marijuana produced a direct antidepressant effect. If true, these observations argue that many patients may use marijuana to "self-treat" depressive symptoms." In *Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex* (Bambico et al. 2007), we read: "These results demonstrate that CB1R agonists possess antidepressant-like properties and modulate 5-HT neuronal activity via the mPFCv." In *Treating depression with cannabinoids* (Blaas, 2008), we read: "The presented observations suggest that dronabinol has an antidepressive potential that can readily be used in medical practice." In *Antidepressant-like effect of Δ9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L* (El-Alfy et al. 2010), we read: "Results of this study show that Δ9-THC and other cannabinoids exert antidepressant-like actions, and thus may contribute to the overall mood-elevating properties of cannabis." In *Pharmacological exploitation of the endocannabinoid system: new perspectives for the treatment of depression and anxiety disorders?* (Saito et al. 2010), we read: Animal experiments suggest that drugs promoting endocannabinoid action may represent a novel strategy for the treatment of depression and anxiety disorders." In *Endocannabinoid system dysfunction in mood and related disorders* (Ashton and Moore, 2011), we read: "However, efficacy trials of cannabinoids in psychiatric disorders are limited but offer some encouragement. . . . Research is needed to elucidate the role of the EC system in psychiatric disorders and for clinical trials with

THC, CBD and synthetic cannabinoids to assess their therapeutic potential." In *Cannabinoids and emotionality: a neuroanatomical perspective* (McLaughlin and Gobbi, 2012), we read: "The endocannabinoid system has recently emerged as a promising therapeutic target for the treatment of stress-related emotional disorders. A growing literature base has collectively demonstrated that facilitation of endocannabinoid signaling promotes antidepressant- and anxiolytic-like responses in preclinical animal models, while disruption of this system profoundly affects emotion, cognition, and neuroendocrine functioning. . . . Accordingly, local pharmacological augmentation of endocannabinoid signaling within discrete corticolimbic subregions may serve as a promising therapeutic strategy for the treatment of these debilitating disorders."

Diabetes

Diabetes may be treated with cannabinoids. In *Cannabidiol Preserves Retinal Neurons and Reduces Vascular Permeability in Experimental Diabetes* (Liou et al. 2004), we read: "CBD preserves retinal neurons and reduces vascularpermeability in experimental diabetes. These results suggest that CBD could be a valuable new therapy for the treatment/prevention of diabetes' retinal complications." *In Cannabidiol Arrests Onset of Autoimmune Diabetes in NOD Mice* (Weiss et al. 2008), we read: "Our data strengthen our previous assumption that CBD, known to be safe in man, can possibly be used as a therapeutic agent for treatment of type 1 diabetes." In *Neuroprotective and Blood-Retinal Barrier-Preserving Effects of Cannabidiol in Experimental Diabetes* (El-Remessy et al. 2006), we read: "CBD treatment significantly reduced oxidative stress; decreased the levels of tumor necrosis factor-α, vascular endothelial growth factor, and intercellular adhesion molecule-1; and prevented retinal cell death and vascular hyperpermeability in the diabetic retina." In *Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption* (Rajesh et al. 2007), we read: "A nonpsychoactive cannabinoid cannabidiol (CBD) has been shown to exert potent anti-inflammatory and antioxidant effects and has recently been reported to lower the incidence of diabetes in nonobese diabetic mice and to preserve the blood-retinal barrier in experimental diabetes. . . . our results suggest that CBD, which has recently been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans, may have significant therapeutic benefits against diabetic complications and atherosclerosis." In *Mediation of Cannabidiol anti-inflammation in the Retina by Equilibrative Nucleoside Transporter and A2A Adenosine Receptor* (Liou et al. 2008), we read: "Cannabidiol (CBD), a non-psychotropic, non-toxic compound has been shown to block diabetes- and endotoxin-induced retinal damage. . . . These results suggest that the activated A2AAR in the retinal microglial cells plays a major role in anti-inflammation in the retina, and that CBD anti-inflammatory effects are linked to adenosine uptake inhibition." *In Presence of functional cannabinoid receptors in human endocrine pancreas* (Bermúdez-Silva et al. 2008), we read: "Together, these results suggest a role for endogenous endocannabinoid signalling in regulation of endocrine secretion in the human pancreas." In *Cannabidiol As a Putative Novel Therapy for Diabetic Retinopathy: A Postulated Mechanism of Action as an Entry Point for Biomarker-Guided Clinical Development* (Liou et al. 2009), we read: "This review is focused on cannabidiol, a non-psychoactive native cannabinoid, as an emerging and novel therapeutic modality based on systematic studies in animal models of inflammatory retinal

diseases including diabetic retinopathy - one of the retinal diseases associated with vascular neuroinflammation. We present the postulated and preclinically documented novel mechanisms that may underlie cannabidiol mode of action in diabetic retinopathy."

In *Cannabinoids as novel anti-inflammatory drugs* (Nagarkatti et al. 2009)*, we read: "*Manipulation of endocannabinoids and/or use of exogenous cannabinoids *in vivo* can constitute a potent treatment modality against inflammatory disorders. This review will focus on the potential use of cannabinoids as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components. . . . Insulin-dependent Type 1 diabetes mellitus (T1DM) is an autoimmune disease resulting in destruction of insulin-producing pancreatic β cells, a process that is assumed to be mediated mainly by CD4 Th1 and CD8 T lymphocytes [125]. In rodents, T1D is induced by administration of multiple low doses of streptozotocin (MLDSTZ). This model is used for studying autoimmune processes associated with pancreatic β-cell pathogenesis. A study performed by Li *et al.* indicated that Δ9-THC could exert a transient attenuation of MLDSTZ-induced autoimmune diabetes. Δ9-THC treated (150 mg/kg) CD-1 mice exhibited reduced hyperglycemia and a significant decrease in the loss of pancreatic insulin. MLDSTZ-induced insulitis was also significantly attenuated by decreases in CD3+ inflammatory cells in the pancreatic islets and in mRNA expression for IL-12, IFN-γ and TNF-α. It was suggested that in this model, the autoimmune component was most effectively modulated by Δ9-THC treatment [126]. Similarly, CBD treatment has been shown to significantly inhibit and delay destructive insulitis and inflammatory Th1-associated cytokine production in nonobese diabetes-prone (NOD) female mice. CBD-treated mice exhibited significant reduction of plasma levels of the proinflammatory cytokines IFN-γ and TNF-α, whereas production of the Th2-associated cytokines IL-4 and IL-10 was increased when compared with untreated control mice, thus shifting the immune response from Th1 to Th2 dominance [127]. A recent study indicated that treatment of 11–14-week-old female NOD mice, either in a latent diabetes stage (after 14 weeks) or with initial symptoms of diabetes (appearing up to 14 weeks) with CBD for 4 weeks, could lead to sustained inhibition of insulitis [128]. CBD treatment inhibited specific destruction of the islets and reduced the infiltrates by mononuclear cells into the islets, thus preventing diabetes. Furthermore, cannabinoids have also been demonstrated to possess additional beneficial effects in animal models of diabetes. It has been reported that rats treated with CBD for periods of 1–4 weeks experienced significant protection from diabetic retinopathy [129]. Cannabinoids have also been shown to alleviate neuropathic pain associated with the disease. Mice injected with a cannabis receptor agonist experienced a reduction in diabetic-related tactile allodynia compared with nontreated controls [130]. Thus, cannabinoids can be considered useful for controlling T1D due to their anti-inflammatory properties."

In *Biological effects of THC and a lipophilic cannabis extract on normal and insulin resistant 3T3-L1 adipocytes* (Gallant et al. 2009), we read: "Insulin-induced glucose uptake increased, while the rate of adipogenesis decreased with increasing THC concentration." In *Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress* (Comelli et al. 2009), we read: "Neuropathy is the most common complication of diabetes and it is still considered to be relatively refractory to most of the analgesics. The aim of the present study was to explore the antinociceptive effect of a controlled cannabis extract (eCBD) in attenuating diabetic

neuropathic pain. Repeated treatment with cannabis extract significantly relieved mechanical allodynia and restored the physiological thermal pain perception in streptozotocin (STZ)-induced diabetic rats without affecting hyperglycemia. In addition, the results showed that eCBD increased the reduced glutathione (GSH) content in the liver leading to a restoration of the defence mechanism and significantly decreased the liver lipid peroxidation suggesting that eCBD provides protection against oxidative damage in STZ-induced diabetes that also strongly contributes to the development of neuropathy. Finally, the nerve growth factor content in the sciatic nerve of diabetic rats was restored to normal following the repeated treatment with eCBD, suggesting that the extract was able to prevent the nerve damage caused by the reduced support of this neurotrophin. These findings highlighted the beneficial effects of cannabis extract treatment in attenuating diabetic neuropathic pain, possibly through a strong antioxidant activity and a specific action upon nerve growth factor." In *Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain* (Toth et al. 2010), we read: "The prevention of microglial accumulation and activation in the dorsal spinal cord was associated with limited development of a neuropathic pain state. Cannabinoids demonstrated antinociceptive effects in this mouse model of DPN. These results suggest that such interventions may also benefit humans with DPN, and their early introduction may also modify the development of the NeP state." In *Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression* (Rieder et al. 2010), we read: "Studies from our laboratory have focused on mechanisms of apoptosis induction by natural and synthetic cannabinoids through activation of CB2 receptors. In this review, we will focus on apoptotic mechanisms of immunosuppression mediated by cannabinoids on different immune cell populations and discuss how activation of CB2 provides a novel therapeutic modality against inflammatory and autoimmune diseases as well as malignancies of the immune system, without exerting the untoward psychotropic effects." In *Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy* (Rajesh et al. 2010), we read: "Collectively, these results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications, and perhaps other cardiovascular disorders, by attenuating oxidative/nitrative stress, inflammation, cell death and fibrosis." In *Diabetic retinopathy: Role of inflammation and potential therapies for anti-inflammation* (Liou, 2010), we read: "This review is focused on the therapeutic effects of cannabidiol (CBD), a non-psychoactive native cannabinoid, as an emerging and novel therapeutic modality in ophthalmology based on systematic studies in animal models of inflammatory retinal diseases including diabetic retinopathy - a retinal disease associated with vascular-neuroinflammation. Special emphasis is placed on novel mechanisms which may shed light on the pharmacological activity associated with CBD preclinically. These include a self-defence system against inflammation and neurodegeneration mediated by inhibition of equilibrative nucleoside transporter and activation of adenosine receptor by treatment with CBD." In *Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress* (Booz, 2011), we read: "This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic

pain." In *Cannabidiol Dampens Streptozotocin-Induced Retinal Inflammation by Targeting of Microglial Activation* (Liou et al. 2011), we read: "These data reveal a previously unrecognized role for CBD inattenuating diabetes-induced retinal inflammation by interfering with inflammatory signaling that occurs in activated microglia. Moreover, these data present new thoughts as to how compounds similar to CBD may suppress retinal complications associated with diabetes." In *The endocannabinoid system and plant-derived cannabinoids in diabetes and diabetic complications* (Horváth et al. 2012), we read: "The modulation of the activity of this system holds tremendous therapeutic potential in a wide range of diseases, ranging from cancer, pain, neurodegenerative, and cardiovascular diseases to obesity and metabolic syndrome, diabetes, and diabetic complications. This review focuses on the role of the endocannabinoid system in primary diabetes and its effects on various diabetic complications, such as diabetic cardiovascular dysfunction, nephropathy, retinopathy, and neuropathy, particularly highlighting the mechanisms beyond the metabolic consequences of the activation of the endocannabinoid system. The therapeutic potential of targeting the endocannabinoid system and certain plant-derived cannabinoids, such as cannabidiol and Δ9-tetrahydrocannabivarin, which are devoid of psychotropic effects and possess potent anti-inflammatory and/or antioxidant properties, in diabetes and diabetic complications is also discussed."

Epilepsy/ Seizures

The connection between epileptic conditions and amelioration of symptomatology with cannabis has clear modern precedent within medical literature. Epilepsy and seizures can be treated with cannabinoids, as has been shown in western medical circles, demonstrably since 1947-1949. In the 1949 document Reprinted from *Federation Proceedings, Federation of American Society for Experimental Biology, vol. 8, lY49, p. 284*. In the article *Anti-epileptic Action of Marijuana-Active Substances* (Davis and Ramsey, 1949), we read: "The demonstration of anticonvulsant activity of the tetra-hydrocannabinol (THC) congeners by laboratory tests (Loewe and Goodman, Federation Proc. 6:352, 1947) prompted clinical trial in five institutionalized epileptic children. All of them had severe symptomatic grand ma1 epilepsy with mental retardation; three had cerebral palsy in addition. . . . Two isomeric 3 (1,2-dimethyl heptyl) homologs of THC were tested, Numbers 122 and 125A, with ataxia potencies fifty and eight times, respectively, that of natural marijuana principles. Number 122 was given to two patients for three weeks and to three patients for seven weeks. Three responded at least as well as to previous therapy; the fourth became almost completely and the fifth entirely seizure free. . . . Other psychic disturbances or toxic reactions were not manifested during the periods of treatment." In *Anticonvulsant action of cannabis in the rat: role of brain monoamines, noting the natural compound* (Ghosh and Bhattacharya, 1978), we read: "The role of brain monoamines in the anticonvulsant action of Cannabis indica resin (CI), against maximal electroshock-induced seizures in albino rats, was investigated by using pharmacologic agents that influence brain monoamine activity. Delta-9-tetrahydrocannabinol content of cannabis resin was estimated to be 17%. The anticonvulsant action of CI (200 mg/kg, i.p.) was significantly inhibited after pretreatment with drugs that reduce brain serotonin activity but not by drugs that reduce brain catecholamine activity. Similarly, the anticonvulsant action of a subanticonvulsant dose (50 mg/kg, i.p.) of CI was potentiated by serotonin precursors but not by

catecholamine precursors. Potentiation of the anticonvulsant action of CI by nialamide or by imipramine was inhibited after pretreatment with 5,6-dihydroxytryptamine. The results suggest that the anticonvulsant action of CI in the rat is serotonin- and not catecholamine-mediated." In *The cannabinoids as potential antiepileptics* (Karler and Turkanis, 1981), we read: "The anticonvulsant nature of cannabidiol suggests that it has a therapeutic potential in at least three of the four major types of epilepsy: grand mal, cortical focal, and complex partial seizures." In *Hypnotic and antiepileptic effects of cannabidiol* (Carlini and Cunha, 1981), we read: "Fifteen patients suffering from secondary generalized epilepsy refractory to known antiepileptic drugs received either 200 to 300 mg cannabidiol daily or placebo for as long as 4.5 months. Seven out of the eight epileptics receiving cannabidiol had improvement of their disease state, whereas only one placebo patient improved." In Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice (Consroe et al. 1982), we read: "The differential effects of CBD suggest that the cannabinoid acts to inhibit seizure spread in the CNS by an action on GABA, but not glycine, mechanisms." In *On the application of cannabis in paediatrics and epileptology* (Lorenz, 2004), we read: "THC effected reduced spasticity, improved dystonia, increased initiative (with low dose), increased interest in the surroundings, and anticonvulsive action." In Cannabinoids: Defending the Epileptic Brain (Wallace, 2004), we read: "Here, by using the rat pilocarpine model of epilepsy, we show that the marijuana extract 9-tetrahydrocannabinol (10 mg/kg) as well as the cannabimimetic, 4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1-i,j]quinolin-6-one [R(+)WIN55,212 (5 mg/kg)], completely abolished spontaneous epileptic seizures. In *Development of pharmacoresistance to benzodiazepines but not cannabinoids in the hippocampal neuronal culture model of status epilepticus* (Deshpande et al. 2007), we read: Thus, the use of cannabinoids in the treatment of SE may offer a unique approach to controlling SE without the development of pharmacoresistance observed with conventional treatments." In *The phytocannabinoid Δ9-tetrahydrocannabivarin modulates inhibitory neurotransmission in the cerebellum, we read* (Ma et al. 2008): The phytocannabinoid Δ9-tetrahydrocannabivarin (Δ9-THCV) has been reported to exhibit a diverse pharmacology; here, we investigate functional effects of Δ9-THCV, extracted from *Cannabis sativa*, using electrophysiological techniques to define its mechanism of action in the CNS. . . . our preliminary studies suggest that Δ9-THCV may be anti-convulsant in a developmental model of epilepsy (Weston *et al*., 2006; see Pertwee, 2008). Our data support recent proposals that phytocannabinoids may represent important, but neglected, therapeutic agents (Mechoulam, 2005). It will be of interest in future studies to investigate how different phytocannabinoids may similarly modulate disease states in the CNS." In *The cannabinoid anticonvulsant effect on pentylenetetrazole-induced seizure is potentiated by ultra-low dose naltrexone in mice* (Bahremand et al. 2008), carefully noting interactive effects with other compounds (noting the interesting responsive systemic reactive up-mediation of opioids in low doses of naltrexone) we read: "Cannabinoid compounds are anticonvulsant since they have inhibitory effects at micromolar doses, which are mediated by activated receptors coupling to G(i/o) proteins. Surprisingly, both the analgesic and anticonvulsant effects of opioids are enhanced by ultra-low doses (nanomolar to picomolar) of the opioid antagonist naltrexone and as opioid and cannabinoid systems interact, it has been shown that ultra-low dose naltrexone also enhances cannabinoid-induced antinociception. . . . . The present data indicate that the interaction between opioid and cannabinoid systems extends to ultra-low dose levels and ultra-low doses of opioid receptor antagonist in

conjunction with very low doses of cannabinoids may provide a potent strategy to modulate seizure susceptibility." In *Cannabidiol Displays Antiepileptiform and Antiseizure Properties In Vitro and In Vivo* (Jones et al. 2010), we read: "Thus, we demonstrate the potential of CBD as a novel antiepileptic drug in the unmet clinical need associated with generalized seizures." In *Δ^9-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats* (Hill et al. 2010), we read: "These data demonstrate that Δ^9-THCV exerts antiepileptiform and anticonvulsant properties, actions that are consistent with a CB1 receptor-mediated mechanism and suggest possible therapeutic application in the treatment of pathophysiologic hyperexcitability states." In *The case for assessing cannabidiol in epilepsy* (Cilio et al. 2014), we read: "Over the past few years, considerable attention has focused on cannabidiol (CBD), the major nonpsychotropic compound of Cannabis sativa. Basic research studies have provided strong evidence for safety and anticonvulsant properties of CBD. However, the lack of pure, pharmacologically active compounds and *legal restrictions have prevented clinical research and confined data on efficacy and safety to anecdotal reports*. [Editor's emphasis].

Heart Protection:

The heart may benefit from cannabinoids: In *Delta-9-tetrahydrocannabinol protects cardiac cells from hypoxia via CB2 receptor activation and nitric oxide production* (Shmist et al. 2006), we read: "Delta-9-tetrahydrocannabinol protects cardiac cells from hypoxia via CB2 receptor activation and nitric oxide production . . . Taken together, our findings suggest that THC protects cardiac cells against hypoxia via CB2 receptor activation by induction of NO production." In *Does cannabis hold the key to treating cardiometabolic disease?* (Szmitko and Verma, 2006), we read: "By uncovering the cellular interactions of the cannabinoid ^{9}-tetrahydrocannabinol (^{9}-THC)—the major active component of marijuana—researchers have identified new molecular pathways for treating cardiometabolic disease. Studies have demonstrated that modulation of the endocannabinoid system holds great therapeutic promise for the treatment of obesity, dyslipidemia, insulin resistance and atherosclerosis . . . By contrast, CB_2 receptors are located primarily on blood cells and immune tissues, and stimulation of these receptors with ^{9}-THC results in an immunosuppressive phenotype via the modulation of immune-cell cytokine production.[5] This molecular system might have a role in the development of obesity, the metabolic syndrome and atherosclerosis, and its modulation might form the basis of new therapeutic strategies for these pathophysiologically linked conditions." In *Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury* (Durst et al. 2007), we read: "Our study shows that CBD induces a substantial in vivo cardioprotective effect from ischemia that is not observed ex vivo. Inasmuch as CBD has previously been administered to humans without causing side effects, it may represent a promising novel treatment for myocardial ischemia." In *Cannabinoid receptors in acute and chronic complications of atherosclerosis* (Mach et al. 2008), we read: "Thus, CB2 receptors are protective in myocardial ischaemia/reperfusion and implicated in the modulation of chemotaxis, which is crucial for the recruitment of leukocytes during inflammation. Delta-9-Tetrahydrocannabinol (THC)-mediated activation has been shown to inhibit atherosclerotic plaque progression in a CB2 dependent manner." In *Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice* (Steffens et al. 2005), we read: "Our data demonstrate that oral treatment with a low dose of THC inhibits atherosclerosis

progression in the apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC or cannabinoids with activity at the CB2 receptor may be valuable targets for treating atherosclerosis." In *Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion* (Walsh et al. 2010), we read: "This study demonstrates that CBD is cardioprotective in the acute phase of I/R by both reducing ventricular arrhythmias and attenuating infarct size." In *The cardiac and haemostatic effects of dietary hempseed* (Rodriguez-Leyva and Pierce, 2010), we read: ". . . hempseed no longer contains psychotropic action and instead may provide significant health benefits." In *The Potential for Clinical Use of Cannabinoids in Treatment of Cardiovascular Diseases* (Durst and Lotan, 2011), we read: ". . . these studies provide evidence for the safety of cannabinoid compounds in humans. CBD, for example, which was shown to reduce infarct size, is currently being tested in inflammatory bowel disease, psychosis, and diabetes. The evidence of a potential role for cannabinoid in various cardiovascular pathologies, together with the safety data gleaned from various human intervention studies, indicate that now is the time to show efficacy across species and continue toward human trials." In *Cannabidiol as an anti-arrhythmic, the role of the CB1 receptors* (Hepburn et al. 2011), we read: "Cannabidiol (CBD) has been shown to be anti-arrhythmic (Walsh *et al*, 2010) and tissue sparing (Durst *et al*, 2007) in an in vivo rat model of coronary artery occlusion (CAO), although the receptors through which this occurs have yet to be identified. . . . The observed synergism which persists when CB1 receptors are blocked prior to CBD administration, suggests cross-talk between CB1 and other CB receptors in the heart during ischaemia."

HIV/AIDS

HIV/AIDS may be treated with cannabinoids, both to augment weight gain and also, to reduce disease load. In *Cannabinoid administration attenuates the progression of simian immunodeficiency virus* (Molina et al. 2011), we read: "Δ(9)-Tetrahydrocannabinol (Δ(9)-THC), the primary psychoactive component in marijuana, is FDA approved to ameliorate AIDS-associated wasting. Because cannabinoid receptors are expressed on cells of the immune system, chronic Δ(9)-THC use may impact HIV disease progression. . . . However, chronic Δ(9)-THC administration decreased early mortality from SIV infection ($p = 0.039$), and this was associated with attenuation of plasma and CSF viral load and retention of body mass ($p = NS$). In vitro, Δ(9)-THC (10 μm) decreased SIV (10 TCID(50)) viral replication in MT4-R5 cells. These results indicate that chronic Δ(9)-THC does not increase viral load or aggravate morbidity and may actually ameliorate SIV disease progression. We speculate that reduced levels of SIV, retention of body mass, and attenuation of inflammation are likely mechanisms for Δ(9)-THC-mediated modulation of disease progression that warrant further study." In *Cannabinoid Inhibition of Macrophage Migration to the Trans-Activating (Tat) Protein of HIV-1 Is Linked to the CB2 Cannabinoid Receptor* (Raborn and Cabral, 2010), we read: "Macrophages and macrophage-like cells are important targets of HIV-1 infection at peripheral sites and in the central nervous system. After infection, these cells secrete a plethora of toxic factors, including the viral regulatory trans-activating protein (Tat). This protein is highly immunogenic and also serves as a potent chemoattractant for monocytes. . . . Collectively, the pharmacological and biochemical

knockdown data indicate that cannabinoid-mediated modulation of macrophage migration to the HIV-1 Tat protein is linked to the CB2 cannabinoid receptor. Furthermore, these results suggest that the CB2 cannabinoid receptor has potential to serve as a therapeutic target for ablation of HIV-1-associated untoward inflammatory response." In *Chronic cannabinoid administration lowers viral replication in lymph nodes of SIV infected Rhesus macaques* (Walker et al. 2010), we read: "The primary psychoactive component of marijuana, Δ9-tetrahydrocannabinol (Δ9-THC), is used to mitigate AIDS-associated wasting. Cannabinoid receptors are expressed on cells of the immune system suggesting that chronic Δ9-THC administration may impact on human immunodeficiency virus progression. Ongoing studies indicate that Δ9-THC -treated, simian immunodeficiency virus (SIV)-infected rhesus macaques have increased survival and lower plasma viral loads. We hypothesized that chronic Δ9-THC treatment decreases viral replication by anti-inflammatory effects at lymphoid tissues. . . .Chronic Δ9-THC treatment resulted in lower plasma viral load (5.28 vs 6.11 log copies of gagRNA/ml plasma), lymph node proviral DNA (1.57 vs 1.99 log copies/10,000 cells) and viral gagRNA (1.14 vs 2.08 log copies/total RNA), irrespective of disease stage. Lymph node content of IL-1b, IL-6, IL-8, and MCP-1 positively correlated with levels of plasma viral load across all animals ($p<0.05$). No effect of Δ9-THC was found on cytokine expression. These results suggest that chronic Δ9-THC treatment enhances control of viral replication but does not appear to be mediated by decreased inflammation." In *The endocannabinoid system in gp120-mediated insults and HIV-associated dementia* (Bari et al. 2010), we read: "Endocannabinoids (eCBs) include a group of lipid mediators that act as endogenous agonists at cannabinoid (CB(1), CB(2)) and vanilloid (TRPV1) receptors. In the last two decades a number of eCBs-metabolizing enzymes have been discovered that, together with eCBs and congeners, target receptors and proteins responsible for their transport and intracellular trafficking form the so-called "endocannabinoid system" (ECS). Within the central nervous system ECS elements participate in neuroprotection against neuroinflammatory/neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis. More recently, a role for eCBs has been documented also in human immunodeficiency virus-1 (HIV-1) envelope glycoprotein gp120-mediated insults, and in HIV-associated dementia (HAD)." In the study *Cannabinoid neuroimmune modulation of SIV disease, taking close and carful note of the interdigitation of combined mechanisms in play* (Molina et al. 2011), we read: "Δ-9-tetrahydrocannabinol (Δ-9-THC), the primary psychoactive component in marijuana, is FDA-approved to ameliorate AIDS-associated wasting. Because cannabinoid receptors are expressed on cells of the immune system, it is possible that chronic Δ-9-THC use may impact HIV disease progression. Until recently, longitudinal, controlled, systems-approach studies on the effects of cannabinoids on disease progression were lacking. Data from our controlled studies in non-human primates show chronic Δ-9-THC administration prior to and during simian immunodeficiency virus (SIV) infection ameliorates disease progression, attenuates viral load and tissue inflammation, significantly reducing morbidity and mortality of SIV-infected macaques. Identification of possible mechanisms responsible for this modulation of disease progression is complicated due to the multiplicity of cannabinoid-mediated effects, tissue specific responses to the viral infection, multiple cellular mechanisms involved in inflammatory responses, coordinated neuroendocrine and localized responses to infection, and kinetics of viral replication. Emerging results from our studies reveal that the overall mechanisms mediating the protective effects of cannabinoids involve novel epigenomic regulatory mechanisms in need of systematic

investigation." In *Cannabinoids inhibit migration of microglial-like cells to the HIV protein Tat* (Fraga et al. 2011), we read: "Microglia are a population of macrophage-like cells in the central nervous system (CNS) which, upon infection by the human immunodeficiency virus (HIV), secrete a plethora of inflammatory factors, including the virus-specified trans-activating protein Tat. Tat has been implicated in HIV neuropathogenesis since it elicits chemokines, cytokines, and a chemotactic response from microglia. It also harbors a β-chemokine receptor binding motif, articulating a mode by which it acts as a migration stimulus. Since select cannabinoids have anti-inflammatory properties, cross the blood-brain barrier, and target specific receptors, they have potential to serve as agents for dampening untoward neuroimmune responses. . . Delta-9-tetrahydrocannabinol (THC) and CP55940 exerted a concentration-related reduction in the migration of BV-2 cells towards Tat. A similar inhibitory response was obtained when the endogenous cannabinoid 2-arachidonoylglycerol (2-AG) was used."

Parkinson's Disease

Parkinson's may be treated with cannabinoids. In *Cannabinoids and neuroprotection in basal ganglia disorders* (Sagredo et al. 2007), we read: "cannabinoids may provide neuroprotection in different neurodegenerative disorders including Parkinson's disease and Huntington's chorea, two chronic diseases that are originated as a consequence of the degeneration of specific nuclei of basal ganglia, resulting in a deterioration of the control of movement. Both diseases have been still scarcely explored at the clinical level for a possible application of cannabinoids to delay the progressive degeneration of the basal ganglia. However, the preclinical evidence seems to be solid and promising. . . . . Considering the relevance of these preclinical data and the lack of efficient neuroprotective strategies in both disorders, we urge the development of further studies that allow that the promising expectatives generated for these molecules progress from the present preclinical evidence till a real clinical application." In *Cannabinoids and neuroprotection in motor-related disorders* (De Lago and Fernández-Ruiz, 2007), we read: "Neuroprotective properties of cannabinoids have been extensively studied in the last years in different neurodegenerative pathologies. This potential is based on the antioxidant, anti-inflammatory and anti-excitotoxic properties exhibited by these compounds that allow them to afford neuroprotection in different neurodegenerative disorders like Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS) and others. . . . Lastly, neuroprotective effects of cannabinoids exerted by the activation of CB1 but also CB2 receptors have been also identified in amyotrophic lateral sclerosis (ALS), another degenerative disease characterized by the selective death of spinal motoneurons. In the present review, we will collect the latest advances in the knowledge of the cellular and molecular mechanisms through which cannabinoids might arrest/delay the degeneration of specific neuronal subpopulations in these motor-related disorders. This should serve to encourage that the present promising evidence obtained mainly at the preclinical level might progress to a real exploitation of neuroprotective benefits of potential cannabinoid-based medicines." In *Cannabinoids and Parkinson's disease* (García-Arencibia et al. 2009), we read: "Cannabinoid-based medicines have been proposed as clinically promising therapies in Parkinson's disease (PD), given the prominent modulatory function played by the cannabinoid signaling system in the basal ganglia. . . . However, the potential of cannabinoid-based medicines in PD have been still scarcely studied at the clinical level despite the existence of solid and promising preclinical evidence.

Considering the relevance of these preclinical data, the need for finding treatments for motor symptoms that may be alternative to classic dopaminergic replacement therapy, and the lack of efficient neuroprotective strategies in PD, we believe it is of major interest to develop further studies that allow the promising expectations generated for these molecules to progress from the present preclinical evidence towards a real clinical application." In *The endocannabinoid system as a target for the treatment of motor dysfunction* (Fernández-Ruiz, 2009), we read: "There is evidence that cannabinoid-based medicines that are selective for different targets in the cannabinoid signalling system (e.g. receptors, inactivation mechanism, enzymes) might be beneficial in basal ganglia disorders, namely Parkinson's disease (PD) and Huntington's disease (HD)." In *Role of CB2 receptors in neuroprotective effects of cannabinoids* (Fernández-Ruiz et al. 2008), we read: ". . . experimental models of these disorders, the activation of CB2 receptors has been related to a delayed progression of neurodegenerative events, in particular, those related to the toxic influence of microglial cells on neuronal homeostasis. The present article will review the evidence supporting that CB2 receptors might represent a key element in the endogenous response against different types of cytotoxic events, and that this receptor type may be a clinically promising target for the control of brain damage in neurodegenerative disorders." In *Cannabinoids as Therapeutic Agents for Ablating Neuroinflammatory Disease* (Cabral and Griffin-Thomas, 2008), we read: "Thus, the cannabinoid-cannabinoid receptor system may prove therapeutically manageable in ablating neuropathogenic disorders such as Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, HIV encephalitis, closed head injury, and granulomatous amebic encephalitis." In *Cannabinoids and neurodegenerative diseases* (Romero and Orgado, 2009), we read: ". . . antioxidative, antiglutamatergic and antiinflammatory effects are now recognized as derived from cannabinoid action and are known to be of common interest for many neurodegenerative processes. Thus, these characteristics make cannabinoids attractive candidates for the development of novel therapeutic strategies."

References for this section found in **References, List Two**.

Thanks to *Granny Storm Crow's MMJ Reference List- January 2012* for many leads in finding papers used to assemble the above section:
http://www.medicinalgenomics.com/wp-content/uploads/2013/01/700-cannabis-studies-2012.pdf

3. Phylogenetic analysis of the CB receptors.

The evolutionary intra-connectivity within our singular bio-system is manifest throughout the system. Evolution has shaped and crafted a great and intricate tapestry of homology and adaptation. Highly detailed empirically supported mathematical models derived from Time-Dependent Density Functional Theory indicate that life may well have evolved from photosynthetic prebiotic kernel systems in the Isua Greenstone Belt in Greenland some 3.7–3.85 billion years past (Tamulis et al., 2016). This common ancestry has branched into many individuated examples of evolutionary specificity, which can be observed to share fundamental commonalities, and homologies (Panksepp, 1998; 2012). So great is the commonality of evolutionary genetic origin that fruit flies and mice may tell us of human Parkinson's "Pink 1" genetic mutations influencing mitochondrial functioning, and primitive Aplysia have revealed the foundational epigenetic basis of memory, which persists and may be recalled by stimulus when neuronal connectivity has been disrupted (Chen et al., 2014; Morais et al., 2009; Clark et al., 2006; Yun et al., 2014). Neuronal activity affects gene expression (Panksepp, 1998 p. 93; Watanabe et al., 1994; Zhu et al., 1995). Epigenetic memory extends across generations in mice, C-Elegans and humans (Greer et al., 2014; Dias & Ressler, 2014; Yehuda et al., 2015). Through demonstration of extensive resultant primary-source inter-specie systemic commonality across divergent evolutionary presentation, it is possible to deduce automatic reflexive unconscious responses, archetypal and phylogenetic representations, adaptations and unconsciously instantiated human learning, may be somatically and epigenetically sourced (Norman, 2015, 2015*a, b, c*). The obvious commonality between emotive/affective bio-systemic expression amongst other animals and man has long been noted [see Darwin, 1872: *The Expression of Emotions in Man and Animals*]. Brain circuits mediating *panic* in the guinea pig, rat, primate, chicken and cat are highly conserved, and share origins near where physical pain may be generated by electrical stimulation of the midbrain PAG (Panksepp, 1998, p. 267-268, Panksepp et al., 1980; De Lanerolle & Lang, 1988; Jurgens & Ploog, 1988; Robinson, 1967). Play, or "Ludic" circuitry is demonstrated in humans and rats, the latter exhibiting something closely akin to laughter, and basic empathy (Panksepp, 1998 pp. 280-299; Panksepp & Panksepp, 2013). Rage system circuitry running from the medial amygdaloid areas downward via the stria terminalis to the medial hypothalamus then the midbrain PAG, and rage system neurochemistry, are conserved to a great degree across mammals (Panksepp, 1998 pp. 190-196; Miczek, 1987; Miczek et al., 1994). Fear circuitry stimulated from the lateral and central amygdala, anterior and medial hypothalamus and midbrain PAG is also commonly attributed across divergent mammalian organisms (Panksepp, 1998 pp. 207-214; Panksepp, 1990; Davis et al., 1994). Nearly identical chemistry is evidenced across species, such as seen in the similarly structured reptilian peptide vasotocin, the piscine peptide mesotocin, and human vasopressin and oxytocin, which produce sexual response in amphibians, fish and humans respectively (Panksepp, 1998, pp. 230-231). Not surprisingly, the CB receptors have also been forged in evolution's patient furnace.

What follows is mainly derived from the study (McPartland and Pruitt, 2002), and the citations therein, which this author [R.N.] advises should be read closely. The CB_1 and CB_2 receptors are truly ancient as is revealed in phylogenetic analysis. These receptors occur in mammals, birds, amphibians, fish, sea urchins, mollusks, leeches, and in the primitive fresh-water polyp *Hydra*

vulgaris. The first "primordial" receptor dates from 600 million years ago or earlier, approximately coinciding with the time of the Cambrian explosion revealing a fundamental system that predates the separation of vertebrates and invertebrates. The related Vanilloid G-protein coupled receptors [(VR) receptors] which regulate pain perception appear to predate the CB receptors, implying that anandamide served as the initial endogenous ligand to an evolutionarily primary VR receptor system. *It is to be closely noted* that the analysis we are about to derive, although supported by that supposition, is *not* dependent upon it. It is hypothesized and demonstrated in (McPartland and Pruitt, 2002), we believe rightly, that the CB receptors then acquired a mutation through lack of selective constraints (Baker 1997) permitting the receptors by way of evolutionary process to then couple also with 2-AG. Indeed, the system must and will adapt and evolve to its greatest advantage.

If amino acid correlations are compared between the two genes which encode the CB_1 and CB_2 receptors, the gene CNR1 (nucleotide sequence 1755 base pairs) and the gene CNR2 (nucleotide sequence 1776 base pairs), they are identical at only 44% of their translated amino acid residues (ibid. p. 75; Munro at al. 1993). These two ancient and related yet divergent receptors, CB_1 and CB_2, can be located as *homologs* in other species. A *homolog* is a similar structure, behavior, or other trait shared by different species. In (McPartland and Pruitt, 2002), (p.75) we read: "In the field of phylogenetics, homologs are divided into two groups: Orthologs are homologous genes found in different organisms, derived by descent from a common ancestor. Paralogs are homologous genes found in a given organism, derived by a gene duplication event." CNR1 orthologs have been cloned from 62 species of mammals. Sequenced CNR1 orthologs from earlier vertebrates are abundant, including: *Taeniopygia guttata* the zebra finch; *Taricha granulosa* the newt salamander, and *Fugu rubripes* the puffer fish (ibid, p.76). CNR2 orthologs are evident in rodents such as *Rattus norvegicus* and *Mus musculus*. Invertebrates such as the leech *Hirudo medicinalis* demonstrate a CB_1 gene fragment. Non-mollecular methods show that the sea urchins *Strongylocentrotus purpuratus* and *Paracentrotus lividus*, the leech *Theromyzon tessulatum*, the mollusk *Mytilus edulis*, and the very most primitive of all animals with a nerve network, the cnidarian *Hydra vulgaris* show evidence of these receptors (ibid. p. 76; Salzet et al. 2000). Other life forms such as the fruit fly *Drosophila melanogaster* and the nematode worm *Caenorhabditis elegans* appear to have amino acid substitutions at particular residues which imply the genes have been *lost or mutated* into pseudogenes. Similar results extend to various insects, such as *Apis mellifera, D. melanogaster, Gerris marginatus, Spodoptera frugiperda,* and *Zophobas atratus* (Di Marzo et al. 2000; McPartland and Pruitt, 2002).

It is plain at this juncture that the CNR1 and CNR2 genes (and hence CB_1 and CB_2 receptors) are shared as homologous orthologs across many life forms and species, and in other contrary examples such as many insects or C-Elegans, the genes which appear to *once have been present*, have been lost or suffered "crippling" amino acid substitutions. Clearly, these receptors and the genes which encode them are shared between many divergent species, and once were likely shared by more. How fully are the sequences conserved, and how far back can these processes be seen to extend? How deeply intertwined is the ever diverging evolutionary expression we see before us?

In order to answer those questions most clearly, we may first examine the phylogenetic evidence of initial CB receptor expression, homologous connectivity of orthologs and subsequent divergence, after which we will go back further still and consider the parent VR receptor, the initial split between plants and animals, hence the likely primeval source and then, proposed subsequent mechanisms of evolutionary expression.

The degree of sequence divergence is correlated with time. The rhesus monkey's (*Macaca mulatta*) CNR1 sequence is identical to our human CNR1 sequence, however, the partial sequence for CNR1 from the leech (*H. medicinalis*) has only 58 percent in common. Humans and leeches diverged over a half billion years in the past, some 600 million years ago, in contrast to the scant 10 million years for the divergence between humans and monkeys.

A gene tree of available CB orthologs (McPartland and Pruitt, 2002, p. 87) was assembled and patterned based on the percentage of identical sequences measured between CNR1, its paralogs and orthologs (Feng and Doolittle 1996). The CB gene tree is based in the primary ancestral CB gene. The first bifurcation in the tree represents the divergance between CNR1 and CNR2 sequences in a duplication event which began separate paralogous lineages, the CNR1 orthologs and CNR2 orthologs (McPartland and Pruitt, 2002, p. 85). The basic amino acid percentages found are as follows.

Homologues of human CB1 receptors, with percent identity calculated with BLAST 2.0 algorithm. (McPartland and Pruitt, 2002, p. 86):

Percent identity with human CB1 gene sequence

Monkey (*Macaca mulatta*) CB1 100% of 472 amino acids
Rat (*Rattus norvegicus*) CB1 97% of 473 amino acids
Mouse (*Mus musculus*) CB1 97% of 473 amino acids
Finch (*Taeniopygia guttata*) CB1 91% of 473 amino acids
Newt (*Taricha granulosa*) CB1 83% of 473 amino acids
Puffer fish (*Fugu rubripes*) CB1A 72% of 468 amino acids
Puffer fish (*Fugu rubripes*) CB11B 59% of 470 amino acids
Leech (*Hirudo medicinalis*) 58% of 153 amino acids
Human CB2 47% of 360 amino acids

The puffer fish paralogs are the product of a second gene duplication event not evidenced in humans (ibid. p. 86).

Below find species expressing CB receptors marked with an "x" to the right, those not expressing CB receptors due to "crippling" amino acid substitutions marked with a "0," in order of major taxonomic clades (ibid. p. 87).

Species expressing CB receptors: (x)
Species not expressing CB receptors: (0)

Human (vertebrate) CNR1 x
Monkey (vertebrate) CB1 x
Rat (vertebrate) CB1 x
Mouse (vertebrate) CB1 x
Finch (vertebrate) CB1 x
Newt (vertebrate) CB1 x
Fugu fish (vertebrate) CB1A x
Fugu fish (vertebrate) CB1B x
Strongylocentrotus (echinoderm) x
Paracentrotus (echinoderm) x
Hirudo (annelid) x
Mytilus (mollusc) x

Caenorhabditis (nematode) 0
Drosophila, Apis (arthropods) 0

Hydra (cnidarian) x

Saccharomyces (fungus) 0
Arabidopsis, Cannabis (plants) 0
Archaeoglobus, Methanococcus (archaean) 0
Bacillus, Escherichia, Xylella (bacteria) 0

Human (vertebrate) CNR2 x
Rat (vertebrate) CB2 x
Mouse (vertebrate) CB2 x

Clearly, this receptor is ancient as can be deduced by way of its genetic variance across species and even more so as made evident by the startling lack of sequence commonality between the genes encoding CB_1 and CB_2 receptors, indicative of a very ancient bifurcation, indeed! It appears a process of receptor adaptivity is taking place, and to see the diverse distribution of the receptor, which was also once part of those species in which it is not currently represented, implies that this dynamic adaptivity extends in all likelihood backward to a common ancestor and process from which life, and so the CB receptors themselves have sprung. In (McPartland et al. 2001) we learn that 2-AG has been derived from the neural structures of *A. mellifera* and *D. melanogaster*, although both lack CB receptors. Soderstrom et al. (1997) found green algae produces substances which bind to CB receptors; Tomato, soybean, and barley lipoxygenase enzymes can metabolize anandamide (van Zadelhoff, Veldink, and Vliegenhart 1998); pine trees produce an analog of 2-AG which shows cannabinoid activity (Nakane et al. 2000) (McPartland and Pruitt, 2002, p. 79). A common ancestry and process beneath the proliferation of life is implied. If we can deduce this process-commonality, perhaps, we may be able to understand the particular evolutionary reason for the "magic" we see, where one plant holds the singular and seemingly miraculous ability to positively affect so many pathologies. Perhaps this magic is not magic at all, but the sensible and

necessary result of a discernible process. If so, we may then begin to advance toward the hopeful goal of treatment and cure, utilizing the very product and processes of evolution itself.

Analysis of the data suggest the ancient CB gene demonstrates a duplication event which created conditions for the emergence of the present day CNR1 and CNR2. Said event necessarily took place before the divergence of vertebrates and invertebrates, as orthologs of CB_1 are found in vertebrates (fish, amphibians, birds, and mammals) and invertebrates (the leech) (ibid. p. 88). CNR1/CNR2 divergence (47% identity) exceeds that of the divergence (58% identity) between the leech CB_1 gene and CNR1, indicating the duplication event's age exceeds the age of leech CB_1 gene. As vertebrates and primitive
metazoans (*Hydra vulgaris*) both express CB receptors the gene must have evolved prior to the species ancestral divergence, 600 millions years past (Lee, 1999; McPartland and Pruitt, 2002, p. 89).

Likewise, we may rightly infer from the deeper divergence demonstrated in VR phylogenetics that the common CB/VR ligand, anandamide, served the evolutionarily previous VR.

McPartland and Pruitt, 2002, p. 93:

> "Comparing the CB gene tree . . . with the VR gene tree . . . illustrates deeper divergences in the latter. For example, human and rat orthologs of CB_1 share 97% identity, whereas human and rat orthologs of VR1 share only 85% identity. The VR gene tree has diverged into six major branches, while the CB gene tree has only two: CB_1 and CB_2. The lowest branch of the CB tree has 47% similarity, whereas the lowest branch of the VR tree has 30% similarity, again indicative of deeper divergence. The deeper sequence divergences reflect deeper physiological divergences. CB_1 and CB_2 still recognize each other's ligands (although their relative affinities have diverged), whereas the VR homologs have widely diverged in their gating mechanisms. Since the degree of divergence is correlated with evolutionary time, this analysis suggests the primordial VR receptor predated the primordial CB receptor."

With a few more pieces of information, we will soon begin to see our way around the problem. The connection between the secondary CB and evolutionarily primary VR systems is reflected in systemic cross-talk, neuronal co-localization and the commonality of ligands and various receptor affinities demonstrated, to the point that the two systems may arguably be categorized as belonging to one taxonomic classification (ibid. pp. 80-81; Szolcsányi 2000). The CB/VR systemic coupling is very complex, and counter-mediational in some cases, with the same ligand creating opposing effects at different receptors in the same neurons (ibid.).

The primordial CB gene likely diverged from a related GPCR, like: EDG-1, 600 million years past. Those evolved from older GPCRs gated by biogenic amines, which date back some 1200 million years ago when plants and animals first diverged (Peroutka and Howell 1994). Then, we understand that all GPCRs are younger than the *ionotropic glutamate receptor* (iGluR) (Chiu et al. 1999), iGluRs being ligand gated ion channels related to VR1. VR1 belonging to the family of

TRP gated ion channels, the ancestors of which are found in *D. melanogaster* and *C. elegans*, with receptors activated by arachidonic acid, anandamide's precursor (Harteneck, Plant and Schultz 2000; McPartland and Pruitt, 2002, p. 95). So, CB evolved from VR, and VR is related to iGluR. This author has deduced glutamate to be the very oldest of all neurotransmitters! See: (Norman, 2015*d*).

Now the analysis is clear:

1. Genes which encode receptors and so receptors themselves evolve using the known mechanisms of: Gene duplication events, splice variants, and single nucleotide polymorphisms (SNPs). These mutations are kept, *if said adaptation is advantageous*.

2. When plants and animals diverged after springing from a common ancestry, many similar active chemical products and genetic constituents emerged, as is in evidence even today as demonstrated above.

3. Animals consume plants, and hence, they consume the many biologically related constituents within plants.

4. The genes of our most distant ancestors after the initial split between plants and animals 1200 million years past adapted via the aforementioned mechanisms to both,

a. imbibed exogenous biologically related chemical constituents, and,

b. endogenous biochemistry as well,

and those mutations *which were advantageous*, were kept. Lifting of evolutionary selective constraints (as in the case yielding the CB_2 gene), permitted even greater functional advantage and divergence in those cases.

Ergo: The General hypotheses:

1. After 1200 million years the CB receptors *and* their pre-formative evolutionary predecessors (and those of other system components), have developed along with cannabis and its ancestors in turn, and so, the reason we find such complex and profound pharmacological utility in the phytochemistry of cannabis is no surprise: we have ONLY kept those mutations which have *brought advantage* from the addition of that mutation.

2. Cannabis is a treasure trove of complex pharmacology which works synergistically against pathology as a necessary consequence of the fact that over the course of 1200 million years, the CB receptors *and* their pre-formative evolutionary forbearers (and those of other system components), have adapted exactly as evolution would have them adapt: *to form advantage* of those exact chemicals, in ***those exact complex distributions***. Again: Mutations are kept, *if said adaptation is advantageous*.

No wonder this plant seems as if by "magic" to possess so many advantages! The "magic" is no surprise at all, it is a synergistic interactive dynamic born of 1200 million years of evolution. Due to *our* evolution, this plant *must* have these many benefits, and function to our greatest possible advantage.

Please do note, the process is ongoing even now! Splice variants in CNR1 have been found (Shire et al. 1995); (Tsai, Wang, and Hong 2000) located a microsatellite polymorphism in CNR1; Gadzicki, Muller-Vahl, and Stuhrmann (1999) found a SNP, a point mutation in a CB_1 gene. And even more important: there are millions of SNPs in the human genome, including over a dozen in CNR1and CNR2 (McPartland and Pruitt, 2002, p. 94). Anandamide's reduced affinity for VR1 in comparison to CB_1 may be seen in this context as evidence of the further effects of evolutionary processes. The process which has gained us this health, is ongoing.

We will now look to history and see if we can support this hypothesis, and also, attempt to understand why these very avenues which offer up a clear pathway to the treatment and cure of disease based upon profound evolutionary connectivity, are scorned and the the potential benefits left aside. Perhaps then we may advance past these barriers, to the benefit of all.

Note: There likely are now and will be in the future other interpretations of the complex emerging genetic data which may place or propose a different progenitor to the CB receptors and/or their ligands. Be that as it may, the essential process of receptor adaptation as here defined, should accommodate any such small analytic alteration of lineage in stride. Whatever the lineage: We and our ancestors have developed along with cannabis and its ancestors in turn, and so, the reason we find such complex and profound pharmacological utility in the phytochemistry of cannabis is no surprise: we have ONLY retained those mutations which have *brought advantage* from the addition of that mutation.

Due to *our* evolution, this plant *must* have these many benefits, and function to our greatest possible advantage.

References for this section found in **References, List Three**.

4. The History and the Future

We are now in a position to present evidence and historical information in support of our hypotheses as currently derived, then sharpen those hypotheses into final form. Primarily, if our supposition of evolutionary adaptivity is correct, we should see evidence of the complex products of advantageous adaptivity. Next, a more detailed examination and analysis of the now explicable evolutionarily founded synergistic effects will be articulated. We will then look to history and along with what we have derived from empirical studies advance preliminary recommendations concerning the safety and utility of the raw drug, next, we will draw our hypotheses into specific form, and with the addition of further historical information, clear recommendations for future research will be defined. To those ends we will outline:

a. deep and complex interwoven systemic involvement of cannabis and cannabinoids within the context of broad therapeutic augmentation of many diseases as a necessary consequence of perhaps over a billion years of advantageous adaptation.

b. evidence of the synergistic evolutionarily derived proliferative dynamics between phytochemical constituencies within human pathology yielding a potential pathway to the treatment and possible cure of many diseases: *utilization of the full or partial spectrum of the full proliferation of phytochemical constituencies*—to utilize rather than fight evolution.

c. the long historical record of the utility of cannabis demonstrative of its remarkable efficacy, excellent risk/benefit profile and hence supporting the copious and safe *utility of the raw drug and its basic preparations*.

d. The General, Strong and Weak hypotheses.

e. *Further history, analysis and subsequent assessment of causes of current problems and impediments, then, the proper course to advance toward cure for both the individual and industry.*

Evidence of evolutionary complex-adaptivity as "advantage" manifest across pathologies

Remembering quite strictly that the rather substantial aforementioned empirical data presented here is deeply condensed, highly abbreviated and limited as to disease types and the specific mechanisms through which those pathologies are affected, we may condense the data even further using only a few of the many diseases mentioned without risk of losing our way. Let us ask the question implied by point ***"a"*** above:

"As we examine the evidence, is it more reasonable to deduce that: We do indeed see evidence of hypercomplex deeply interdigitated systemic phytochemical mediational processes within human biology across diverse pathologies indicative of millions, or perhaps over a billion years of advantageous evolution?—or—Do we not?"

Let us omit from our altready abbreviated list all reference to: Allergy, Asthma, Autism, Brain

Trauma, Cystic Fibrosis, Dystonia, Fibromyalgia, GERD, Herpes, MRSA, Cholangiocarcinoma, Cervical cancer, Lymphoma, Melanoma, Oral Cancer, Squamous Cell Carcinoma, Thyroid Cancer, Colitis, Depression, Diabetes, Epilepsy/Seizures, Parkinson's and most all information concerning Heart Protection which has been previously presented in this text. To further condense what remains *after* said omissions we have [all references in sub-section below found in Clinical Applicability

References, List Two]:

ALS (Lou Gehrig's Syndrome):
In (Bilsland and Greensmith, 2008) we read: "Cannabinoids exert anti-glutamatergic and anti-inflammatory actions through activation of the CB(1) and CB(2) receptors, respectively. Activation of CB(1) receptors may therefore inhibit glutamate release from presynaptic nerve terminals and reduce the postsynaptic calcium influx in response to glutamate receptor stimulation. Meanwhile, CB(2) receptors may influence inflammation, whereby receptor activation reduces microglial activation, resulting in a decrease in microglial secretion of neurotoxic mediators. Finally, cannabinoid agents may also exert anti-oxidant actions by a receptor-independent mechanism. Therefore the ability of cannabinoids to target multiple neurotoxic pathways in different cell populations may increase their therapeutic potential in the treatment of ALS."

Alzheimer's Disease:
CBD blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression; CBD demonstrates a combination of neuroprotective, anti-oxidative and anti-apoptotic effects against beta-amyloid peptide toxicity, and that inhibition of caspase 3 appearance from its inactive precursor, pro-caspase 3, by cannabidiol is involved in the signalling pathway for this neuroprotection. Also, due to its interaction at PPARγ, CBD was observed to stimulate hippocampal neurogenesis. CBD is able to modulate microglial cell function. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway.

THC the active component of marijuana, Delta9-tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of Alzheimer's disease. Δ9-tetrahydrocannabinol not only inhibits acetylcholinesterase activity it limits amyloidogenesis which may improve cholinergic transmission and delay disease progression. (Esposito et al. 2007; Iuvone et al. 2004; Esposito et al. 2007; Martin-Moreno et al. 2011; Esposito et al. 2006; Esposito et al. 2006; Campbell and Gowran, 2007.)

Arthritis:
Diseases involving inflammation, activation of the immune system and associated oxidative stress may be ameliorated to suppress T-cell-mediated immune responses by primarily inducing

apoptosis and suppressing inflammatory cytokines and chemokines. Cannabinoid receptor–ligand interactions may constitute a novel window of opportunity to treat inflammatory and autoimmune disorders. Cannabinoid receptor system present in the synovium may be an important therapeutic target. The cannabinoid CB(2) receptor plays a critical role in cannabinoid-mediated antinociception, particularly in models of chronic inflammatory pain. (Nagarkatti et al. 2009; Richardson et al. 2008; Rieder et al. 2010; Cox et al. 2007; Booz, 2011).

Atherosclerosis:
From (Pacher and Ungvári, 2008):
"These new findings, coupled with recent evidence demonstrating that CB2 receptor activation also attenuates TNF-α-induced endothelial cell activation, transendothelial migration of monocytes and monocyte/neutrophil-endothelial adhesion . . . , and decreases TNF-α-induced proliferation and migration of human coronary vascular smooth muscle cells by . . . modulating distinct signaling pathways, provide important new mechanistic insights on the possible pleiotropic effects of CB2 activation in atherosclerosis and other inflammatory disorders." From (Pacher and Steffens, 2009): ". . . activation of CB2 receptors in immune cells exerts various immunomodulatory effects, and the CB2 receptors in endothelial and inflammatory cells appear to limit the endothelial inflammatory response, chemotaxis, and inflammatory cell adhesion and activation in atherosclerosis and reperfusion injury."

Breast cancer:
CBD represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumor aggressiveness. THC fails to act as an estrogen or androgen and appears to reduce 17,-estradiol-induced proliferation of breast cancer cell lines by a mechanism which is independent of AR and probably does not involve ER either. These results support the notion that THC controls cell proliferation through activation of cannabinoid receptors, independently of AR and ER, and thus might also be used in patients with hormonesensitive tumors. The mechanism of Delta(9)-tetrahydrocannabinol (THC) antiproliferative action in these cells, . . . involves the modulation of JunD, a member of the AP-1 transcription factor family. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. Δ9-Tetrahydrocannabinol Inhibits cell cycle progression in human breast cancer cells through Cdc2 Regulation. (McAllister et al. 2007; Von Bueren et al. 2008; Caffarel et al. 2008; Caffarel et al.2010; Caffarel et al. 2006).

Colorectal cancer:
The cannabinoid δ9-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. Both CB1 and CB2 cannabinoid receptor activation induces apoptosis in colon cancer cells, and this is mediated by the *de novo* synthesis of ceramide. Signaling through CB1/CB2 receptor increases ceramide production via a mechanism that involves TNF-α. Cannabinoids inhibit cyclooxygenase enzyme activity. Cannabinoid receptor agonists induce phosphatases and phosphatase-dependent apoptosis in cancer cell lines; however, the role of the CB receptor in mediating this response is ligand-dependent. (Greenhough et al. 2007; Cianchi et al. 2008; Ruhaak et al. 2011).

Glioma (brain cancer):
THC-induced apoptosis in glioma C6.9 cells may rely on a CBI receptor-independent stimulation of sphingomyelin breakdown. Cannabinoids cause decreased VEGF levels and VEGFR-2 activation in the tumors. Cannabinoids work to signal apoptosis by a pathway involving cannabinoid receptors, sustained ceramide accumulation and Raf1/extracellular signal-regulated kinase activation. Different sensitivity to the anti-proliferative effect of CBD in human glioma cells and non-transformed cells that appears closely related to a selective ability of CBD in inducing ROS production and caspase activation in tumor cells. Cannabinoids inhibit glioma cell invasion by down-regulating matrix metalloproteinase-2 expression. Delta 9-tetrahydrocannabinol inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells: Delta(9)-THC is shown to significantly affect viability of GBM cells via a mechanism that appears to elicit G(1) arrest due to downregulation of E2F1 and Cyclin A. Local administration of Delta(9)-tetrahydrocannabinol (THC), the major active ingredient of cannabis, down-regulates TIMP-1 expression. CBD exerts its antitumoral effects through modulation of the LOX pathway and of the endocannabinoid system, suggesting a possible interaction of these routes in the control of tumor growth. THC stimulates an endoplasmic reticulum (ER) stress-related signaling pathway, which activates autophagy via inhibition of the Akt/mTORC1 axis. (Sánchez et al. 1998; Blázquez et al. 2004; Galve-Roperh et al. 2000; Massi etal.2006; Blázquez et al. 2008; Galanti et al. 2008; Blázquez et al. 2008; Massi et al. 2008; Salazar et al. 2009).

Leukemia:
Cannabidiol, acting through CB2 and regulation of Nox4 and p22(phox) expression, may be a novel and highly selective treatment for leukemia. Delta-9-tetrahydrocannabinol and delta8-tetrahydrocannabinol inhibited RNA and protein synthesis in a fashion analagous to the inhibition of DNA synthesis in L1210 murine leukemia. Two non-psychotropic cannabinoids, cannabidiol (CBD) and cannabidiol-dimethylheptyl (CBD-DMH), induced apoptosis in a human acute myeloid leukemia (AML) HL-60 cell line. Caspase-3 activation was observed after the cannabinoid treatment, and may represent a mechanism for the apoptosis. Synergistic interactions between THC and the cytotoxic agents in leukemic cells are present. Raf-1/MEK/ERK/RSK-mediated Bad translocation played a critical role in THC-induced apoptosis in Jurkat cells. (McKallip et al. 2006; Tucker et al. 1977; Gallily et al. 2003; Liu et al. 2008; McKallip et al. 2006; Jia et al.2006).

Lung Cancer:
Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. Increased expression of TIMP-1 mediates an anti-invasive effect of cannabinoids. Cannabinoids induce ICAM-1, thereby conferring TIMP-1 induction and subsequent decreased cancer cell invasiveness. Decrease of plasminogen activator inhibitor-1 may contribute to the anti-invasive action of cannabidiol on human lung cancer cells. (Ramer and Hinz,

2008; Ramer et al. 2010; Ramer et al. 2010; Ramer et al. 2012).

Neuroblastoma:
Cannabinoid and nantradol compounds decrease cyclic AMP accumulation in neuronally derived cells, and that this results from an inhibition of basal and hormone-stimulated adenylate cyclase activity. The inhibition of adenylate cyclase was specific for psychoactive cannabinoids, since cannabinol and cannabidiol produced minimal or no response. A concentration-related stimulation of anandamide (arachidonylethanolamide) synthesis by delta 9-tetrahydrocannabinol (THC) was observed in N-18TG2 neuroblastoma cells. The endocannabinoid anandamide (AEA) is shown to induce apoptotic bodies formation and DNA fragmentation, hallmarks of programmed cell death, in human neuroblastoma CHP100 and lymphoma U937 cells. (Howlett, 1984; Howlett, and Fleming 1984; Burstein and Hunter, 1995; Maccarrone et al. 2000).

Pancreatic Cancer:
Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress–related genes, via the involvement of p8 via its downstream endoplasmic reticulum stress–related targets activating transcription factor 4 (ATF-4) and TRB3 in Δ9-tetrahydrocannabinol–induced apoptosis. THC stimulates an endoplasmic reticulum (ER) stress-related signaling pathway, which activates autophagy via inhibition of the Akt/mTORC1 axis. Autophagy is upstream of apoptosis in cannabinoid-induced cancer cell death and activation of this pathway is necessary for the anti-tumoral action of cannabinoids in vivo. As to combined effects: ROS-dependent activation of an autophagic program in the synergistic growth inhibition induced by GEM/cannabinoid combination in human pancreatic cancer cells is also indicated. (Carracedo et al. 2006; Salazar et al. 2009; Donadelli et al. 2011).

Prostate Cancer:
The cannabinoid receptor CB1 expressed in the prostate negatively regulates adenylyl cyclase activity through a pertussis toxin-sensitive protein. Cannabinoid receptor type 1 (CB1) activation inhibits small GTPase RhoA activity and regulates motility of prostate carcinoma cells. Endogenous cannabinoids and CB1 receptor agonists are potential negative effectors of PRL- and NGF induced biological responses. (Ruiz-Llorente et al. 2003; Nithipatikom et al. 2012; Melck et al. 2000).

HIV/AIDS:
Identification of possible mechanisms responsible for this modulation of disease progression is complicated due to the multiplicity of cannabinoid-mediated effects, tissue specific responses to the viral infection, multiple cellular mechanisms involved in inflammatory responses, coordinated neuroendocrine and localized responses to infection, and kinetics of viral replication. Emerging results from our studies reveal that the overall mechanisms mediating the protective effects of cannabinoids involve novel epigenomic regulatory mechanisms in need of systematic investigation. Macrophages and macrophage-like cells are important targets of HIV-1 infection at

peripheral sites and in the central nervous system. After infection, these cells secrete a plethora of toxic factors, including the viral regulatory trans-activating protein (Tat). This protein is highly immunogenic and also serves as a potent chemoattractant for monocytes. . . . Collectively, the pharmacological and biochemical knockdown data indicate that cannabinoid-mediated modulation of macrophage migration to the HIV-1 Tat protein is linked to the CB2 cannabinoid receptor. Delta-9-tetrahydrocannabinol (THC) and CP55940 exerted a concentration-related reduction in the migration of BV-2 cells towards Tat. Endocannabinoids (eCBs) include a group of lipid mediators that act as endogenous agonists at cannabinoid (CB(1), CB(2)) and vanilloid (TRPV1) receptors. In the last two decades a number of eCBs-metabolizing enzymes have been discovered that, together with eCBs and congeners, target receptors and proteins responsible for their transport and intracellular trafficking form the so-called "endocannabinoid system" (ECS). Within the central nervous system ECS elements participate in neuroprotection against neuroinflammatory/neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis. More recently, a role for eCBs has been documented also in human immunodeficiency virus-1 (HIV-1) envelope glycoprotein gp120-mediated insults, and in HIV-associated dementia (HAD). (Molina et al. 2011; Raborn and Cabral, 2010; Fraga, 2011; Bari et al. 2010).

We may now answer the question posed in point ***a***.:

"As we examine the evidence, is it more reasonable to deduce that: We *do* see evidence of hypercomplex deeply interdigitated systemic phytochemical mediational processes within human biology across diverse pathologies indicative of millions, or perhaps over a billion years of advantageous evolution?—or—Do we not?"

The answer is plain:
Yes. We *do* see evidence of hypercomplex deeply interdigitated systemic phytochemical mediational processes within human biology across diverse pathologies indicative of millions, or perhaps over a billion years of advantageous evolution. Point ***a.*** may be taken as evident.

Next we will review the evidence for the seemingly magical interactive synergies, complex conjunctive and proposed phytochemical entourage effects which our theory has made sensible to us.

Complex conjunctive and proposed phytochemical entourage effects: Evolution's answer.

We do hope the reader has taken note of those instances we have pointed out where combinative effects are evident with other substances such as opioids with which we have also evolved such as: In *Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey* (Weber et al. 2009), we read: "The present survey demonstrates its ameliorating potential for the treatment of chronic pain in central

neuropathy and fibromyalgia. A supplemental delta 9-THC treatment as part of a broader pain management plan therefore may represent a promising coanalgesic therapeutic option. . . . Opioid doses were reduced and patients perceived THC therapy as effective with tolerable side effects." In the paper *Synergy between Δ^9-tetrahydrocannabinol and morphine in the arthritic rat* (Cox et al. 2007), taking careful note of the relation between opioids (morphine) and THC in terms of tolerance and analgesic efficacy we read: "The isobolographic analysis indicated a synergistic interaction between Delta(9)-THC and morphine in both the non-arthritic and the arthritic rats. Since Freund's adjuvant-induced alteration in endogenous opioid tone has been previously shown, our data indicate that such changes did not preclude the use of Delta(9)-THC and morphine in combination. As with acute preclinical pain models in which the Delta(9)-THC/morphine combination results in less tolerance development, the implication of the study for chronic pain conditions is discussed." It appears from this informed vantage point, that cannabinoids could reduce tolerance to and hence dosages of opioids, alleviating the many deaths each year caused by the glut of profitable synthetic opioid prescriptions, ensuing tolerance and overdose, a hypothesis supported in present studies (Boehnke et al., 2016).

Please note, that cannabis had been used in Britain to treat drug addiction for many years [web ref. 2].

And we quote Russo and Marcu, (2017) for emphasis of this vital point:

"*Perhaps most relevant to current clinic and public health issues is the ability of THC to displace opiates from the μ-opioid receptor, as well as allosterically modulate the μ- and δ-opioid receptor to inhibit their activity between 1 and 10 μM (Lichtman, Sheikh, Loh, & Martin, 2001; Pertwee et al., 2010). This perhaps underlies the potential of cannabis as part of a viable solution to the opiate crisis in terms of treating addiction, withdrawal, and harnessing the benefits of cannabinoid-opiate coadministration in the clinic (Americans for Safe Access, 2016). When THC and morphine are coadministered, 1/4th the dose of morphine is required to reach significant reductions in pain (Naef et al., 2003).*"

Note also, that synthetics underperformed compared to phytochemical constituencies of Cannabis. In *Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells*, the text states (please note the synthetic drug's lesser performance): "Evidence of selective efficacy with WIN 55,212-2 was also observed but the selectivity was less profound, and the synthetic agonist produced a greater disruption of normal cell morphology compared to Delta(9)-THC." See evidence of increased efficacy of proliferations/extracts, phytochemical combinations and other synergies in: (Russo 2011; Carlini *et al*., 1974; Fairbairn and Pickens, 1981; Wilkinson *et al*., 2003; Ryan *et al*., 2006).

Note the complex multisystemic functionality of pathological amelioration: *Cannabinoid neuroimmune modulation of SIV disease* (Molina et al. 2011 [ref. list 2]): "Identification of possible mechanisms responsible for this modulation of disease progression is complicated due to the multiplicity of cannabinoid-mediated effects, tissue specific responses to the viral infection, multiple cellular mechanisms involved in inflammatory responses, coordinated neuroendocrine

and localized responses to infection, and kinetics of viral replication. Emerging results from our studies reveal that the overall mechanisms mediating the protective effects of cannabinoids involve novel epigenomic regulatory mechanisms in need of systematic investigation."

It appears that there is more happening here than single compounds mediating single systems. The full phytochemical proliferation seems to be involved as a complex and complimentary function of evolution and advantage, as will be supported below. Let us look more deeply into the details of those functional processes.

In the excellent studies (McPartland and Russo, 2001; Russo, 2011; Russo and Marcu, 2017) and references therein from which much of the following is derived, a plethora of interactive bio-mediational dynamics are revealed which enhance the pharmacological efficacy of other constituent phytochemical compounds or otherwise modulate the activity of those compounds so as to perhaps alleviate side-effects, such as that of THC related anxiety which is alleviated by CBD. In *Cannabidiol Enhances the Inhibitory Effects of Δ9 -Tetrahydrocannabinol on Human Glioblastoma Cell Proliferation and Survival*, closely *noting the interactive effects* (Marcul et al. 2010 [ref. list 2]), we read: "Our results suggest that the addition of cannabidiol to Δ9 -THC may improve the overall effectiveness of Δ9 -THC in the treatment of glioblastoma in cancer patients." Others have beneficial effects of different sorts. Terpenoids and flavonoids increase cerebral blood flow, enhance cortical functioning, kill respiratory pathogens and act as anti-inflammatory agents, and yet other beneficial effects are created through secondary constituent interactions. The raw drug, complete with all the interactive phytochemistry produces fewer side effects such as, dysphoria, depersonalization, anxiety, panic reactions, and paranoia than synthetic THC alone (McPartland and Russo, 2001; Grinspoon and Bakalar 1997). Throat irritation may be ameliorated by anti-inflamatory constituents, smoke borne mutagens by anti-mutagens and bacterial contamination by anti-bacterial elements (McPartland and Russo, 2001; Russo, 2011).

Synthesized within secretory cells the most prolific of which are the glandular trichomes, phytocannabinoids [see table one below for examples and synergies] and terpenoids [see table two below for examples and synergies] are both derivative of geranyl pyrophosphate, which is formed via the the deoxyxylulose pathway in cannabis (Fellermeier et al., 2001; Russo, 2011 p.1345). It appears that studies such as (Williamson, 2001) indicating the potentiation, antagonism and summations indicative of synergies across active and 'inactive' phytochemical components may be present, as demonstrated in CBD/THC interactions yielding reduced side effects demonstrative of antagonism. 4 basic synergistic interactivities as exemplified by Cannabis are postulated by (Wagner and Ulrich-Merzenich, 2009): (i) multi-target effects; (ii) pharmacokinetic effects such as improved solubility or bioavailability; (iii) agent interactions affecting bacterial resistance; and (iv) modulation of adverse events. (McPartland and Russo, 2001; Russo, 2011).

THC is a partial CB_1 and CB_2 agonist analogous to AEA allowing the endocannabinoid system to be targeted yielding therapeutic effects such as: analgesic, muscle relaxant and antispasmodic, bronchodilator, neuroprotective antioxidant, antipruritic agent in cholestatic jaundice, possessing 20 times the antiinflammatory power of aspirin and double that of hydrocortisone, without the problems associated with COX-1 and COX-2 inhibitors (Russo, 2011 p. 1348). THC stimulation

of CB_1 receptors induces in animals including: suppression of locomotor activity, hypothermia, catalepsy, and antinociceptive effects, CB_2 stimulation with pain relief and antiinflammatory activities, but not appetite stimulation (Russo and Marcu, 2017).

THC CB_1 receptor stimulation inhibits forskolin-stimulated adenylate cyclase, and induces inhibition N-, Q-, L-type calcium channels. Ion channels can be modulated in CB_1 stimulation through G proteins which activate inwardly rectifying potassium channels, and, MAP kinases (Russo and Marcu, 2017). MAP kinase pathways then, alter the activity of ERK1/2, c-Jun N-terminal kinase (JNK), p38 MAP kinase, and/or ERK5 proteins, controlling cell growth and metabolism. In (Russo and Marcu, 2017) we learn that: "CB_1 protein islocated in the nucleus of solitary tract (i.e., antiemetic effects), hypothalamus, motor systems, motor cortex, basal ganglia, cerebellum, spinal cord (motor neurons in spinal cord), eye, sympathetic ganglia (also enteric nervous system), immune system (bone marrow, thymus, spleen, tonsils), breast cancer cell lines, and other peripheral sites such as the heart, lungs, adrenals, kidneys, liver, colon, prostrate pancreas, testes, ovaries, and placenta."

THC CB_2 receptor stimulation leads to inhibition of forskolin-stimulated AC activation (ibid.) and likewise stimulates MAP kinases, however, lacks ion chanell effects as with CB1. Cell types include: bone marrow, thymus, spleen, tonsils, T and B lymphocytes, monocytes, NK cells, PMN, and mast cells, uterus, lung, bone (osteoclasts, osteoblasts, osteocytes), microglia, and brainstem neurons (ibid.). Please note, we read: "*11-hydroxy metabolites of THC that are generated by the liver from oral administration of THC interact more efficiently at CB_1 receptors.*" Emphasis added, *reader do take note*. Receptor independent mechanisms as mentioned earlier are also in play, particularly at higher concentrations.

Receptor and channel interactions are dose specific (Russo and Marcu, 2017):

At <1 μM: activates GPR18, GPR55, peroxisome proliferator activated receptor gamma (PPARγ) nuclear receptors and TRPA1 and TRPV2 cation channels, while enhancing non-CB receptors on sensory neurons mediating the release of calcitonin gene-related peptide (migraine effector) while potentiating glycine-ligated ion channels (pain relief), while also, antagonizing 5-HT_{3A} ligand-gated ion and the TRPM8 cation channel (ibid.).

Between 1 and 10 μM: Activation of PPARγ nuclear receptor, TRPV3 and TRPV4 cation channels, activational potentiation of β-adrenoceptors. Furthermore, THC inhibits: T-type calcium (Cav3) voltage-gated ion channels, potassium Kv1.2 voltage-gated ion channels and "conductance in Na+ voltage-gated ion channels (–), and conductance in gap junctions between cells at concentrations between 1 and 10 μM" (ibid.). Interactions with phosphlipases, lysophosphatidylcholine acyl transferase, lipoxygenase, Na^+-K^+-ATPase, Mg^{2+}-ATPase, CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C9, and monoamine oxidase activity are also in evidence, while, synaptic conversion of tyrosine to noradrenaline and dopamine is augmented, and also, norepinephrine-induced melatonin biosynthesis is inhibited (ibid.). THC has shown benefits for graft-vs-host-disease (GVHD) (ibid.).

Tetrahydrocannabinolic Acid (THCA-A) (immunomodulatory/antiinflammatory/neuroprotective/antineoplastic) condensed from Russo and Marcu (2017): (THCA-A) is a primary cannabis metabolite void of psychotropic effects which is synthesized in glandular trichomes and is the natural precursor to THC. THC is synthesized through (THCA-A) that is decarboxylated by UV exposure, prolonged storage, or heat. Representing up to 90% of the total THC in the cannabis plant, ~70% converts to THC when smoked. (THCA-A) can be found in the serum, urine, and oral fluid of cannabis users up to 8 hours past usage. A weak agonist of CB_1 and CB_2 receptors, THCA-A has a higher affinity for CB_1. THCA-A inhibits tumor necrosis factor-alpha (TNF-α) release, interacts with TRPM8 channels, stimulates and in turn desensitizes various TRP cation channels, inhibits enzymes which break down endocannabinoids and COX-1 and -2, stimulating the endocannabinoid system through increase of endogenous cannabinoids (Russo and Marcu, 2017 p. 15). Neurite morphology and cell life was increased in a Parkinson's model (Moldzio et al., 2012), and, reduced cell viability of various cancer cell lines in vitro (Moreno-Sanz, 2016). Access of THCA-A to the CNS is limited by the BBB.

Cannabidiol (CBD): Sedative, THC associated anxiety reduction, modulates THC as: a. an antagonist/reverse-agonist, b. signal transduction modulation via perturbing the fluidity of neuronal membranes, or, by affecting G-proteins that carry intracellular signals, c. reduction of cytochrome P450 3A11 metabolism blocking creation of *11-hydroxy THC which is 4 times as psychoactive as THC* and also *4 times as immunosuppressive*. CBD is a potent antipsychotic, which paradoxically increases dopamine activity and norepinephrine activity, while acting as a 5-HT uptake blocker, and, CBD does NOT decrease ACh activity in the hippocampus (associated with short term memory defects), unlike THC. CBD may help alleviate THC induced psychosis (Iseger and Bossong, 2015). CBD has antioxidant effects and, protects against glutamate toxicity, helps with Huntington's, and acts as an anticonvulsant. It appears to reduce airway inflammation caused by THC, inhibits erythema over THC, and halts cyclooxygenase activity (associated with cancer, pain and inflammation) (Williams, et al. 1999). CBD kills bacteria and fungi, so the Cannabis plant, may itself be more healthy to utilize as medication being to some increased degree free of said contaminants (McPartland and Russo, 2001).

CBD antagonizes CB1 receptors if THC is present although it has no affinity for those receptors, it down-mediates the THC induced symptoms of anxiety, tachycardia, hunger and sedation and, has been utilized within the one to one THC:CBD formulation of Sativex®, a well studied commercially available drug; CBD is an analgesic, a neuroprotective antioxidant more potent than ascorbate or tocopherol and a TRPV1 agonist without the noxious effects associated with capsaicin, which inhibits the uptake of AEA, and to some degree its hydrolysis, an antagonist on GPR55, and also on GPR18, helpful in disorders involving cell migration, notably endometriosis; it is an anticonvulsant, acts against nausea, is cytotoxic in breast cancer and other such cell lines, while being being cyto-preservative for normal cells, is an antagonist of necrosis factor-alpha in experiments involving arthritis, and stops prion accumulation and neuronal toxicity (Russo, 2011). Extracts show greater potency than the pure compound. CBD affects *methicillin-resistant Staphylococcus aureus* (MRSA) with a minimum inhibitory concentration (MIC) of 0.5–2 mg·mL-1 (Russo, 2011; Appendino et al., 2008).

Cannabidiolic acid, condensed from Russo and Marcu (2017):
Cannabidiolic acid is the natural precursor to CBD and along with CBD represents the most prolific two phytochemical components of european hemp, and can target GPR55, TRPA1,TRPV1, and TRPM8 at concentrations between 1 and 10 μM. and at higher concentrations can inhibit ECS degradation enzymes. Like CBD it can enhance 5-HT_{1A} receptor activation with greater receptor affinity than CBD, but, is not a CB1 agonist or antagonist.

Cannabinol (CBN): CBN is a non-enzymatic oxidative by-product of THC (Russo, 2011) the product of THC degradation, and enhances the effects of THC in man, increases the production of follicle-stimulating hormone and testicular testosterone (McPartland and Russo, 2001), has anti-convulsant effects, and, possesses anti-inflammatory properties as well. Its effects on dopamine and norepinephrine are not clear, and reports conflict. A CB_1 agonist and CB_2 agonist of 3 times greater affinity, implying immune system cell modulatory functioning. CBN stimulates the binding of GTP-γ-S half as well as THC, and, modulates thymocytes by attenuating the activity of the c-AMP response element-binding protein (CREB), nuclear factor κB (NF-κB), and interleukin-2 (IL-2) (McPartland and Russo, 2001, p. 107). CBN is a TRPV2 (thermo-sensor) agonist and could be utilized in burn treatment, appears to promote bone formation via the recruitment of quiescent mesenchymal stem cells in marrow, and inhibits breast cancer resistance protein, a cause of drug resistance to chemotherapeutic agents. CBN inhibits enzymes cyclooxygenase, lipoxygenase, and cytochrome P450 (CYP) enzymes (e.g., CYP1A1, CYP1A2, CYP2B6, CYP2C9, CYP3A4, CYP3A5, CYP2A6, CYP2D6, CYP1B1, and CYP3A7) (Russo and Marcu 2017). Also it stimulates the activity of phospholipases, and, recruitment of quiescentmesenchymal stem cells in marrow (10 μM), encouraging bone formation, and affecting breast cancer resistance proteins at increased concentrations (ibid.).

Cannabichromene (CBC): CBC reduces inflammation with analgesic effects and inhibits prostaglandin synthesis, while exhibiting potent antibacterial activity and some antifungal activity, superior to THC. Lacking effects upon cytochrome P450 enzymes it is not an anticonvulsant, yet, potentiates changes in heart rate created by THC. CBC demonstrates anti-inflammatory and analgesic activity, the ability to reduce THC intoxication in experiments, anti-fungal and antibiotic effects, and cytotoxicity in cancer cell lines (Ligresti et al., 2006). A TRPM8 antagonist, it may help with prostate cancer (De Petrocellis and Di Marzo, 2010), and have powerful effects against MRSA (MIC 1 $mg \cdot mL^{-1}$) (Russo, 2011 p. 1349). A strong AEA uptake inhibitor, and a moderate 5-HT_{1A} antagonist, it may function as an antidepressant (McPartland and Russo, 2001; Russo, 2011) [web ref. 1.]. CBC creates its pain reducing and anti-inflamatory effects as it stimulates and desensitizes TRP ankyrin-type 1 (TRPA1) cation channels, and, interacts with TRPV4 and TRPV3 cation channels, and desensitizes TRPV2 and TRPV4. It exerts a positive effect upon the viability of mammalian adult neural stem cell progenitor cells. TRP cation channels TRPA1, TRPV1–4, and TRPV8 are interactive with CBC (Russo and Marcu, 2017).

Cannabigerol (CBG): the biosynthetic precursor of CBC, CBD, and THC is a weak agonist at CB_1 and CB_2 receptors (Russo, 2011), which in rodent models inhibits 5-HT and norepinephrine uptake with less effectiveness than THC and CBD, and in older work is shown to inhibit GABA uptake

with greater potency then THC and CBD (McPartland and Russo, 2001). Analgesic effects, inhibition of erythema, and lipoxygenase blocking exceed THC. Antibacterial and like effects are greater than CBD, CBC and THC against gram-positive bacteria, mycobacteria, and fungi (McPartland and Russo, 2001). Next down in efficacy from CBD, CBG shows effects against breast cancer (Ligresti et al., 2006; Russo, 2011), and acts as a potent TRPM8 antagonist with possible application in prostate cancer (De Petrocellis and Di Marzo, 2010); a strong uptake inhibitor of AEA (De Petrocellis et al., 2011); and a potent agent against MRSA (Appendino et al., 2008; Russo, 2011 p. 13448). CBG is a powerful α-2 adrenoreceptor agonist with analgesic effects, and a 5-HT_{1A} antagonist of moderate proportion, suggesting possible antidepressant effects (Russo, 2011, p. 1349). Pain, inflammation, heat sensitization and possible effects upon prostate cancer are mediated by CBG through mechanisms including: antagonizing TRPV8 receptors and stimulating TRPV1, TRPV2, TRPA1, TRPV3, TRPV4, and α2-adrenoceptor activity (Russo and Marcu 2017).

Delta-8-THC (Δ8-THC): An isomer of delta-9-THC and effective antiemetic that is easy to synthesize which is free of psychoactive effects when administered to human subjects between the ages of 2-13 years (McPartland and Russo, 2001).

Tetrahydrocannabivarin (THCV) is a propyl analogue of Δ9-THC, 25% as psychoactive as Δ9-THC with abilities to moderate THC effects with faster onset and shorter duration, perhaps useful in treatment of migraine, demonstrating evidence of synergy with THC (McPartland and Russo, 2001; Russo, 2011). A CB_1 antagonist at low doses, and a CB_1 agonist at high doses, it may produce weight loss as demonstrated in experimental rodent models, increase energy expenditure and perhaps prevent seizures in the rodent cerebellum and pyriform cortex, and may also reduce pain (Russo, 2011; McPartland and Russo, 2001). It is a fractional component of southern African cannabis chemotypes (Russo and Marcu 2017).

Terpenoids:

The cannabis terpenoids limonene, myrcene, a-pinene, linalool, b-caryophyllene, caryophyllene oxide, nerolidol and phytol share the precursor geranyl pyrophosphate with phytocannabinoids and have been designated *Generally Recognized as Safe* by the US Food and Drug Administration and other regulatory agencies. Phytocannabinoid-terpenoid interactions could produce synergy with respect to the treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including *methicillin-resistant Staphylococcus aureus*) (Russo, 2011 p.1344).

Cannabis derives its potent scent from the 200 terpenoids found in the plant (Russo, 2011 p. 1349) [see chart two below for examples]. Terpenoids are formed of repeating units of isoprene (C_5H_8), such as monoterpenoids (with C_{10} skeletons), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), and triterpenoids (C_{30}) (McPartland and Russo, 2001). Terpenoids can range from “simple linear chains to complex polycyclic molecules, and they may include alcohol, ether, aldehyde, ketone, or ester functional groups.” (McPartland and Russo, 2001 p. 109). Terpenoids are essential oil (EO) or volatile oil components. They ordinarily vaporize at the same temperatures as THC ~157°C,

and being lipophilic, they permeate lipid membranes, and, may do also cross the Blood-Brain Barrier once inhaled. They may modulate THC effects and activity by *a.* binding to cannabinoid receptors; *b.* modulate the affinity of THC for its own receptor via THC sequestering, perturbation of annular lipids around the receptor, or by increasing neuronal membrane fluidity (ibid. p. 110). Terpenoids may remodel G-proteins, and alter the pharmacokinetics of THC by modification of BBB permeability. Some act as Prozac affecting uptake of 5-HT, others as tricyclic antidepressants affecting norepinephrine activity, dopamine activity as MAO inhibitors, and increase GABA as do the benzodiazepines. Effects upon 5-HT_{1A} and 5-HT_{2a} receptors support synergies within cannabis creating mood effects. β-caryophyllene, α-humulene, α-terpineol, and limonene, terpenoids present in cannabis, have been demonstrated to affect *Cryptococcus neoformans* strains isolated from HIV patients with *cryptococcal meningitis*. Monoterpenes in cannabis resin (ibid p. 112-114): "(1) inhibit cholesterol synthesis, (2) promote hepatic enzyme activity to detoxify carcinogens, (3) stimulate apoptosis in cells with damaged DNA, and (4) inhibit protein isoprenylation implicated in malignant deterioration (Jones 1999)." β-myrcene is the most prolific terpenoid in cannabis, an analgesic functioning as CBD, CBG, and CBC: through blocking the inflammatory effects of prostaglandin E_2 (Lorenzetti et al. 1991). Other cannabinoids in cannabis smoke perform similar functions, like carvacrol which is more effective than THC in this capacity. The effects may be cumulative. We read (McPartland and Russo, 2001 p. 115): "unfractionated cannabis essential oil exhibits greater antiinflammatory activity than its individual constituents, suggesting synergy (Evans et al. 1987)."

The cannabis terpenoids include but are not limited to:

Cannabis Monoterpenoids
1 β-Myrcene
2 D-Limonene
3 β-Ocimene
4 γ-Terpinene
5 α-Terpinene
6 α-Terpineol
7 α-Pinene
8 β-Pinene
9 Linalool
10 Camphene
11 Terpinolene
12 α-Phellandrene
13 γ-Cadinene
14 Δ3-Carene
15 ρ-Cymene
16 Fenchol
17 1,8-Cineole (Eucalyptol)
18 Pulegone

Cannabis Sesquiterpenoids

1 β-Caryophyllene
2 Caryophyllene Oxide
3 Humulene (α-Caryophyllene)
4 β-Elemene
5 Guaiol
6 Eudesmol Isomers
7 Nerolidol
8 Gurjunene
9 γ-Cadinene
10 β-Farnesene

We will review some few of those here.

Myrcene, a primary cannabis monoterpenoid, acts to synnergize the antibiotic effects of other constituents against *Staphylococcus aureus, Bacillus subtilis,* and *Pseudomonas aeruginosa,* and, inhibits cytochrome P450 2B1, an enzyme involved in the activation of promutagens, such as Aflatoxin B1, which is produced by moldy cannabis. Once aflatoxin B1 is acted upon by P450 2B1, it becomes hepatocarcinogenic. Hence, myrcene, just like limonene, α-pinene, α-terpinene, and citronellal, blocks this pathogenic process. The plant contains the antidotes to its own naturally occurring environmentally inculcated pathogens. Myrcene decreases inflammation via prostaglandin E-2 (PGE-2) and blocks hepatic carcinogenesis by aflatoxin (Russo, 2011 p. 1350). It is used in sleep preparations in Germany, and may be the predominant THC combinative synergistic sedative agent in Cannabis. β-Myrcene is the most prevalent terpene in chemovars in the United States, and is likely responsible for sedative effects in commercial preparations (Russo and Marcu 2017). It halts carcinogenic effects of aflatoxin in the liver, and may work as an analgesic through narcotic effect interactions mediated by α-2 adrenoreceptors. Osteoarthritis may be affected via inhibited NO production by IL-1β and, also lowered IL-1β-induced iNOS mRNA and protein by significant amounts well over 70% at even higher concentrations. Increased glutathione in tissues was associated with treatment of peptic ulcers with oral preparations. Synergies with THC and CBD are implied (Russo and Marcu 2017).

β-Caryophyllene (BCP) is the most common sesquiterpenoid in cannabis demonstrative of anti-inflammatory effects, and it is shown to decrease the vascular permeability of histamines with gastric cytoprotective effects, and, antimalarial effects (McPartland and Russo, 2001 p. 115). It gains its anti-inflamatory effects via PGE-1, with comparable potency to the toxic compound phenylbutazone (Russo, 2011 p. 1352). Caryophyllene is a full selective agonist at CB_2, which serves its antiinflamatory capacities, as said effects are reduced in CB_2 knockout animals (Russo and Marcu 2017). The same mechanism is responsible for effects upon nociception and pain, colitis and nephrotoxicity. β-Caryophyllene synergizes with THC to create antipruritic effects and gastric cytoprotection, and, with CBD to create antiinflammatory benefits (ibid.). Experiments demonstrate: “cardioprotective, hepatoprotective, gastroprotective, neuroprotective, nephroprotective, antioxidant, antiinflammatory, antimicrobial, and immunemodulator activities" (Russo and Marcu 2017). “BCP activates peroxisome proliferated activator receptors (PPARs) isoforms, inhibits pathways triggered by the activation of toll-like receptor complexes (i.e.,

CD14/TLR4/MD2), reduces immunoinflammatory processes, and exhibits synergy with μ-opioid receptor pathways" (Sharma et al., 2016; Russo and Marcu 2017). BCP is a homomeric nicotinic acetylcholine receptors (7-nAChRs) antagonist, and shows no effects mediated by serotonergic and GABAergic receptors (ibid.).

Limonene is a monocyclic monoterpenoid, the second most common terpenoid in some strains (chemovars) of cannabis which has demonstrated inhibition of thymic involution in stress-induced immunosuppression in mice (Ortiz de Urbina et al. 1989). Limonene may eliminate the need for synthetic antidepressant medications (Komori et al. 1995). Limonene inhibits *Aspergillus fungi* and their aflatoxins, and limonene as other terpenoids suppresses many fungi and bacteria (McPartland, 1997). d-Limonene blocks carcinogenesis by multiple mechanisms. It detoxifies carcinogens by inducing Phase II carcinogen-metabolizing enzymes (Crowell, 1999). It selectively inhibits the isoprenylation of Ras proteins, thus blocking the action of mutant *ras* oncogenes (Hardcastle et al. 1999). It induces redifferentiation of cancer cells (by enhancing expression of transforming growth factor β1 and growth factor II receptors), and it induces apoptosis of cancer cells (Crowell, 1999; McPartland and Russo, 2001, p. 116). Cannabinoids and Limonene both interfere with quorum-sensing in biofilm formation, indicating likely synergy (Russo and Marcu 2017). Chemotherapeutic properties, inducing apoptosis of breast cancer cells have been demonstrated; gastro-esophageal reflux is effected; inflammation, oxidative damage in human lens epithelial cells via regulation of caspase-3 and -9, Bax, and Bcl-2, as well as inhibition of p38 MAPK phosphorylation, suggesting utility in cataract treatment; an agonist at A_{2A} adenosine receptors to synergize activity with both THC and CBD; mitochondrial biogenesis, activated the AMPK energy regulator, increased brown adipocyte markers PGC-1α UCP1, and induced "browning" of 3T3-L1 adipocytes by activating β-3-AR and ERK signaling pathway to possibly ameliorate obesity, and, synergize with anorexic effects of CBD and THCV, and, modulatory effects of THC on weight balance (Russo and Marcu 2017).

Linalool is a noncyclic monoterpenoid, with sedative anxiolytic effects like the weaker citronellol and α-terpineol which are also found in cannabis. Combinations generate synergistic sedative effects, may mitigate THC associated anxiety and produce antidepressant effects (McPartland and Russo, 2001 p. 117). Terpenoids act synergistically with non-psychoactive CBD, which may decrease corticotropin-releasing factor (CRF) by inhibiting IFN-γ (Malfait et al. 2000). Linalool demonstrates antiglutamatergic activity (Russo, 2011 p. 1352). Immune potentiating effects of Linalool, analgesic and anticonvulsant effects in general, and, some anticonvulsant effects from the very small quantities in cannabis are implied (Russo and Marcu 2017). Anesthetic effects akin to procaine and menthol are evidenced. *P. acnes* are substantially improved in Linalool therapy. The pharmacokinetics of cannabis administration may be altered by Linalool via effects upon CYP enzymes, experiments with rodents suggest. Antileishmanial activity (acting against Leishmania parasites), possible effects reducing opioid dosages, and possible anticancer applications as bound into nano-component dosage structures are being fruitfully explored (Russo and Marcu 2017).

From (Nunes et al., 2010, p. 303; Russo, 2011 p. 1352) we may deduce a general effective mechanism: "Overall, it seems reasonable to argue that the modulation of glutamate and GABA neurotransmitter systems are likely to be the critical mechanism responsible for the sedative,

anxiolytic and anticonvulsant properties of linalool and EOs containing linalool in significant proportions."

Pulegone, a monocyclic monoterpenoid is found in cannabis and may alleviate the THC side effect of loss of short-term memory consolidation, perhaps having applications in Alzheimer's. AChE inhibition is the functional basis of the reduction in pathology, a property shared by other terpenines such as, limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, l-and d-carvone, 1,8-cineole, p-cymene, fenchone, and pulegone-1,2-epoxide (McPartland and Russo, 2001).

1,8-Cineole, a bicyclic monoterpenoid, is found in cannabis, the inhalation which increases cerebral blood flow and improves cortical activity. Antinociceptive analgesic and anti-inflammatory actions are in evidence and, antibacterial activity against *Bacillus subtilis*, as well as, antifungal properties against *Trichophyton mentagrophytes, Cryptococcus neoformans,* and *Candida albicans,* and 1,8-Cineole was effective in killing *Candida albicans* and *Escherichia coli*, stopped the reproduction of *Staphylococcus aureus*, and is antiviral against *Herpes simplex 2*. (McPartland and Russo, 2001, pp. 117-118).

α-Pinene, a bicyclic monoterpenoid has anti-inflammatory properties and acts as a bronchodilator. α-Pinene inhibits acetylcholinesterase implying Alzheimer's may be treated thus. α-pinene, α-terpineol, and terpinen-4-ol demonstrate antibiotic effects against *Staphylococcus aureus, S. epidermidis* and *Propionibacterium* acnes. α-Pinene and its isomer β-pinene are both effective against Hep-G2 (human hepatocellular carcinoma) and Sk-Mel-28 (human melanoma) tumor cells *in vitro* (Setzer et al. 1999; McPartland and Russo, 2001, pp. 118). This terpenoid is the most widely found in nature, occurring in conifers and many other plants (Russo, 2011 p. 1350), and functions as a broadspectrum antibiotic with action against MRSA. α-Pinene constitutes a memory aid, functioning as an acetylcholinesterase inhibitor (ibid.). α-pinene inhibited BEL-7402 human hepatoma cell growth (Chen et al., 2015).

α-Terpineol, terpinen-4-ol, and 4-terpineol are related monoterpenoids with possible sedative and radical scavenging and antioxidant effects (McPartland and Russo, 2001 p. 118). Terpinen-4-ol, α-terpineol, and α-pinene act as antibiotics suitable to affect *Staphylococcus aureus, S. epidermidis* and *Propionibacterium acnes*. Antimalarial effects are also possible (Campbell et al. 1997; McPartland and Russo, 2001).

Cymene, (p-cymene), is a monoterpenoid with biological actions against *Bacterioides fragilis, Candida albicans,* and *Clostridium perfringens* (Carson and Riley 1995; McPartland and Russo, 2001).

Borneol is a bicyclic monoterpenoid in cannabis which functions as an external treatment for purulent otitis media without toxicity.

Δ3-Carene is a bicyclic monoterpenoid and marker of "sativa" strains (chemovars) with anti-inflammatory properties (McPartland and Russo, 2001; Russo and Marcu, 2017).

Flavonoids present in cannabis, condensed from (McPartland and Russo, 2001):

Cannabis contains 20 aromatic, polycyclic phenols, or *flavonoids,* constituting ~ 1% of its weight some of which retain pharmacological activity after being vaporized into smoke where they may modulate the pharmacokinetics of THC in a way similar to CBD through the inhibition of P450 3A11 and P450 3A4 enzymes. Suppression of P450 is chemoprotective, via inhibition of activation of benzo[α]pyrene and aflatoxin B1, which are procarcinogens found in cannabis smoke.

Apigenin (Anxiolytic/Antiinflammatory/Estrogenic): perhaps alongside THC, inhibits tumor necrosis factor-alpha (TNF-α) which induces and maintains inflammation, thereby possibly alleviating symptoms of rheumatoid arthritis and multiple sclerosis. Apigenin and other flavonoids affect estrogen receptors, and may inhibit estradiolinduced proliferation of breast cancer cells. Apigenin is a flavone that binds to central benzodiazepine receptors to foster anxiolytic effects without side effects associated with synthetics.

Quercetin (Antioxidant/Antimutagenic/Antiviral/Antineoplastic): a flavonol and a potent antioxidant which works synergistically with other such compounds. McPartland and Russo (2001) speculates these compounds may "recycle" CBD inducing its chemical reactions as an antioxidant. Flavonoids block free radical formation: by scavenging superoxide anions; by quenching intermediate peroxyl and alkoxyl radicals, and by chelating iron ions (McPartland and Russo, 2001, pp. 121). Free radicals activate a transcription factor protein NF-κB leading to a chain of pathological events. Quercetin stops NF-κB formation through blocking the PKC-induced phosphorylation of an inhibitory subunit of NF-κB called IκB (Musonda and Chipman 1998), stoping carcinogenesis and inflamation, and may suppress HIV-1, and may synergize with CBN, which also downregulates NF-κB and counteracts the effects of THC, which could increase NF-κB activity (Daaka et al. 1997).

Cannflavin A (COX inhibitor/LO inhibitor): a prenylated flavone and a potent inhibitor of prostaglandin E2 in human rheumatoid synovial cells, and, inhibits cyclooxygenase (COX) enzymes and lipoxygenase (LO). The question of its volatility remains as preparations with alcohol may influence results obtained, so its activity within the context of smoking is unknown.

Russo (2011) draws the many threads together for us, and speculates along the following lines as to the *possible therapeitic targets* to best explore in order to make use of these interactive entourage effects across the proliferation of active and 'inactive' constituents:

Acne:

Lipid production in human sebocytes of sebaceous glands is under functional mediation of the endocannabinoid system, as apoptosis is controlled by AEA in a dose dependent way. CBD may attenuate the increased sebum production which is causal in acne. Limonene and pinene may offer supportive synnergistic augmentation of effects (Russo, 2011 pp. 1352-1353).

MRSA:

CBD and CBG inhibit MRSA (MIC 0.5–2 mg·mL-1) (Appendino et al., 2008). Pinene may augment effects (Russo, 2011 p. 1352).

Depression, insomnia, anxiety, dementia and addiction:

Addiction: Changes associated with opioid addiction in α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate glutamate and CB_1 receptor expression in the nucleus accumbens may be reversed with CBD. Left insula activation is associated with addictive mediation, and CBD down mediates left insula activation, implying an addictive treatment option. This author [R.N.] wonders if OCD could be treated with CBD also (perhaps with supplemental caryophyllene, see below), as the same insula activation may support symptoms in this case as well (Nakao et al., 2014; Stein et al., 2006). CBD appears to modify the ability of drugs to reenforce addictive behavior (and hypothetically, to restructure reward and reinforcement of obsessive behaviors as well). Myrcene, pinene and particularly *caryophyllene* could offer supplemental benefit to CBD treatment in addiction (Russo, 2011 p. 1354).

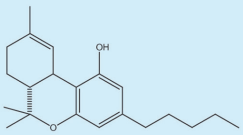
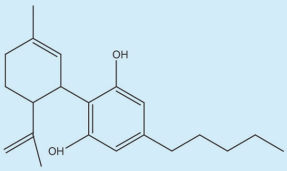
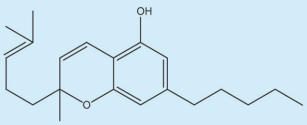
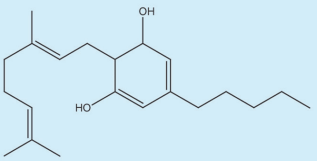
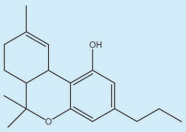
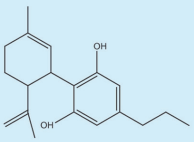
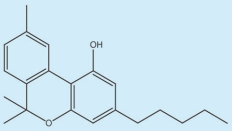
The endocannabinoid system mediates depression, anxiety from post traumatic stress disorder or physical pain, and also, the endocannabinoid system is involved with the mediation of psychosis (Russo, 2011 p. 1353). CBD- or CBG-predominant preparations including appropriate terpenoids and other secondary constituents may offer a safe alternative in the treatment of depressive symptomatology, by way of promotion of neurogenesis and increased plasticity. More sure is the complex role of CBD on $5\text{-}HT_{1A}$ activity, which theoretically underlies the demonstrated anti-anxiety effects and statistically valid improvements noted in experiments with social anxiety disorder (Russo, 2011 p. 1353). Anxiolytic limonene and linalool could be the proper synergistic additions in this sort of therapy (ibid.). Sleep promoting effects of cannabis (Russo et al., 2007) could potentially be increased by adding caryophyllene, linalool and myrcene (Russo, 2011 p. 1353).

THC is a acetylcholinesterase inhibitor that inhibits amyloid β-peptide aggregation in Alzheimer's (ibid.; Eubanks et al., 2006). CBD may also reduce β-amyloid in Alzheimer's with its attendant dementia (Iuvone et al., 2004; Esposito et al., 2006a,b), and also, offers potent antipsychotic effects (Iseger et al. 2015; Zuardi et al., 1991; 2006; Zuardi and Guimaraes, 1997; Russo, 2011). Limonene, pinene and linalool could improve needed effects. Interestingly, CBD in proportional doses to THC eliminates cognitive and memory deficits in cannabis smokers (Iseger et al. 2015; Russo, 2011).

Please see tables one and two below for examples of terpenoids, phytocannabinoids and their synergies (Russo, 2011).

Table 1

Phytocannabinoid activity table

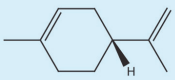
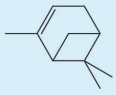
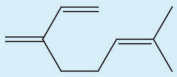
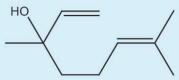
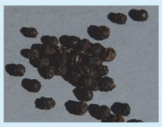
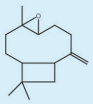
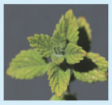
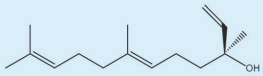
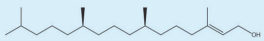
Phytocannabinoid structure	Selected pharmacology (reference)	Synergistic terpenoids
 delta-9-tetrahydrocannabinol (THC)	Analgesic via CB_1 and CB_2 (Rahn and Hohmann, 2009)	Various
	AI/antioxidant (Hampson *et al.*, 1998)	Limonene *et al.*
	Bronchodilatory (Williams *et al.*, 1976)	Pinene
	↓ Sx. Alzheimer disease (Volicer *et al.*, 1997; Eubanks *et al.*, 2006)	Limonene, pinene, linalool
	Benefit on duodenal ulcers (Douthwaite, 1947)	Caryophyllene, limonene
	Muscle relaxant (Kavia *et al.*, 2010)	Linalool?
	Antipruritic, cholestatic jaundice (Neff *et al.*, 2002)	Caryophyllene?
 cannabidiol	AI/antioxidant (Hampson *et al.*, 1998)	Limonene *et al.*
	Anti-anxiety via $5\text{-}HT_{1A}$ (Russo *et al.*, 2005)	Linalool, limonene
	Anticonvulsant (Jones *et al.*, 2010)	Linalool
	Cytotoxic versus breast cancer (Ligresti *et al.*, 2006)	Limonene
	↑ adenosine A_{2A} signalling (Carrier *et al.*, 2006)	Linalool
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
	Decreases sebum/sebocytes (Biro *et al.*, 2009)	Pinene, limonene, linalool
	Treatment of addiction (see text)	Caryophyllene
 cannabichromene	Anti-inflammatory/analgesic (Davis and Hatoum, 1983)	Various
	Antifungal (ElSohly *et al.*, 1982)	Caryophyllene oxide
	AEA uptake inhibitor (De Petrocellis *et al.*, 2011)	–
	Antidepressant in rodent model (Deyo and Musty, 2003)	Limonene
 cannabigerol	TRPM8 antagonist prostate cancer (De Petrocellis *et al.*, 2011)	Cannabis terpenoids
	GABA uptake inhibitor (Banerjee *et al.*, 1975)	Phytol, linalool
	Anti-fungal (ElSohly *et al.*, 1982)	Caryophyllene oxide
	Antidepressant rodent model (Musty and Deyo, 2006); and via $5\text{-}HT_{1A}$ antagonism (Cascio *et al.*, 2010)	Limonene
	Analgesic, α-2 adrenergic blockade (Cascio *et al.*, 2010)	Various
	↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007)	adjunctive role?
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
 tetrahydrocannabivarin	AI/anti-hyperalgesic (Bolognini *et al.*, 2010)	Caryophyllene *et al.* . . .
	Treatment of metabolic syndrome (Cawthorne *et al.*, 2007)	–
	Anticonvulsant (Hill *et al.*, 2010)	Linalool
 cannabidivarin	Inhibits diacylglycerol lipase (De Petrocellis *et al.*, 2011)	–
	Anticonvulsant in hippocampus (Hill *et al.*, 2010)	Linalool
 cannabinol (CBN)	Sedative (Musty *et al.*, 1976)	Nerolidol, myrcene
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
	TRPV2 agonist for burns (Qin *et al.*, 2008)	Linalool
	↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007)	adjunctive role?
	↓ breast cancer resistance protein (Holland *et al.*, 2008)	Limonene

5-HT, 5-hydroxytryptamine (serotonin); AEA, arachidonoylethanolamide (anandamide); AI, anti-inflammatory; CB1/CB2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; TRPV, transient receptor potential vanilloid receptor; MRSA, methicillin-resistant *Staphylococcus aureus*; Sx, symptoms.

Table one above used with the kind permission of Dr. Ethan Russo, from (Russo, 2011). See original article for references in chart above.

Table 2

Cannabis Terpenoid Activity Table

Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori *et al.*, 1995)	CBD
			Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT_{1A} (Komiya *et al.*, 2006)	CBD
			Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)	CBD, CBG
			Active against acne bacteria (Kim *et al.*, 2008)	CBD
			Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)	CBG
			Gastro-oesophageal reflux (Harris, 2010)	THC
α-Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil *et al.*, 1989)	CBD
			Bronchodilatory in humans (Falk *et al.*, 1990)	THC
			Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)	THC?, CBD
β-Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti *et al.*, 1991)	CBD
			Analgesic, antagonized by naloxone (Rao *et al.*, 1990)	CBD, THC
			Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)	THC
			Blocks hepatic carcinogenesis by aflatoxin (de Oliveira *et al.*, 1997)	CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001)	CBD, CBG?
			Sedative on inhalation in mice (Buchbauer *et al.*, 1993)	THC
			Local anesthetic (Re *et al.*, 2000)	THC
			Analgesic via adenosine A_{2A} (Peana *et al.*, 2006)	CBD
			Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)	CBD, THCV, CBDV
			Potent anti-leishmanial (do Socorro *et al.*, 2003)	?
β-Caryophyllene		 Pepper	AI via PGE-1 comparable phenylbutazone (Basile *et al.*, 1988)	CBD
			Gastric cytoprotective (Tambe *et al.*, 1996)	THC
			Anti-malarial (Campbell *et al.*, 1997)	?
			Selective CB_2 agonist (100 nM) (Gertsch *et al.*, 2008)	THC
			Treatment of pruritus? (Karsak *et al.*, 2007)	THC
			Treatment of addiction? (Xi *et al.*, 2010)	CBD
Caryophyllene Oxide		 Lemon balm	Decreases platelet aggregation (Lin *et al.*, 2003)	THC
			Antifungal in onychomycosis comparable to ciclopiroxolamine and sulconazole (Yang *et al.*, 1999)	CBC,CBG
			Insecticidal/anti-feedant (Bettarini *et al.*, 1993)	THCA, CBGA
Nerolidol		 Orange	Sedative (Binet *et al.*, 1972)	THC, CBN
			Skin penetrant (Cornwell and Barry, 1994)	–
			Potent antimalarial (Lopes *et al.*, 1999, Rodrigues Goulart *et al.*, 2004)	?
			Anti-leishmanial activity (Arruda *et al.*, 2005)	?
Phytol		 Green tea	Breakdown product of chlorophyll	–
			Prevents Vitamin A teratogenesis (Arnhold *et al.*, 2002)	–
			↑GABA via SSADH inhibition (Bang *et al.*, 2002)	CBG

Representative plants containing each terpenoid are displayed as examples to promote recognition, but many species contain them in varying concentrations. 5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AI, anti-inflammatory; CB_1/CB_2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; PGE-1/PGE-2, prostaglandin E-1/prostaglandin E-2; SSADH, succinic semialdehyde dehydrogenase.

Table two above used with the kind permission of Dr. Ethan Russo, from (Russo, 2011). See original article for references in chart above.

We may now address point ***b.*** raised above and ascertain if we may draw a sound evidence-based conclusion:

b. evidence of the synergistic evolutionarily derived proliferative dynamics between phytochemical constituencies within human pathology yielding a potential pathway to the treatment and possible cure of many diseases: *utilization of the full or partial spectrum of the full proliferation of phytochemical constituencies*—to utilize rather than fight evolution.

Please read above and observe the highly complex, emergent evolutionary adaptive intricacy of phytochemical constituents mediating bio-systemic outcomes and therapeutic dynamics, a synergy between the 400 active and 'inactive' chemicals in this plant. We may take point ***b.*** as evident.

A further potentially important augmentation of this basic stance will be articulated below as the Strong and Weak hypotheses, and their implications derived in subsequent analysis.

With over 400 chemicals within its constituency and evolutionary advantage shaping the intricacies of bio-systemic interactivity, systemic intra-relations, cross-mediational complexities and responses, we might begin to understand the nuanced, diverse and copious utility of this plant to some small degree. Next, we will address the history of this utility, and attempt to ascertain if the raw drug does indeed demonstrate past evidence of what appears to be both clear utility without addiction, and an excellent safety profile. Are these hundreds of studies actually valid science? If so, we should see a long history demonstrating just that if we are to recommend the raw drug with confidence as safe and useful. Is there evidence of safe use for thousands of years, or is this a dangerous, useless and addictive drug as the United States government says? Is such a history available in support of the hundreds of studies we have presented, or is this drug actually dangerous and ineffective?

Historical record of safe and effective use of cannabis

In (Russo, 2002) an excellent accounting of the basic history of the medicinal use of cannabis for pain is presented. The following is mainly condensed from that work and the references therein, save for the first paragraph. Other sources are noted separately.

The ability of Cannabis to alter conscious states has been known for some 12,000 years (Able, 1980; McPartland and Pruitt, 2002), and Cannabis has been cultivated for at least 6000 years (Atakan, 2012; Li, 1973). Evidence exists of traditional knowledge in China dating back 5000 years to the emperor of old, "Divine Plowman," Shen-Nung. The historical written record indicates extracts of *Cannabis Sativa* have been known to produce medicinal effects apart from their psychoactive properties as early as the third millennium BC, from which time Chinese texts describe therapeutic amelioration of pain and cramps (Mechoulam, 1986; Pacher et al. 2006). Chinese emperor Shen-nung (ca. 2000 B.C.) had recorded in the text *Pen-ts'ao Ching*, that cannabis positively affects rheumatism as if the condition were reversed, hence indicating possible anti-inflammatory actions (Hui-Lin, 1975; Burstein & Zurier, 2009). Recent archeological

evidence of the usage of Cannabis can be found in the 2700-year-old grave of a Caucasoid shaman: ". . . tetrahydrocannabinol, the psychoactive component of cannabis, its oxidative degradation product, cannabinol, other metabolites, and its synthetic enzyme, tetrahydrocannabinolic acid synthase, as well as a novel genetic variant with two single nucleotide polymorphisms. The cannabis was presumably employed by this culture as a medicinal or psychoactive agent, or an aid to divination." (Russo et al. 2008). [See "**References, List One"** for references in preceding paragraph, "**References, List Four"** for the remainder].

Julien (1849) described surgical procedures of physician Hoa-tho in the early 2nd century using hemp preparations as general anesthetics (Russo, 2002 p. 357):

"He gave to the sick person a preparation of hemp (Ma-yo), and, in a few moments, he became so insensible that it were as if he was plunged into rapture of loss of life. Then, following this instance, he practiced some overtures, incisions, amputations, and removed the cause of the malady; then he repaired the tissues with suture points, and applied liniments," (p. 197, translation EBR).

Dating between 1400 and 2000 BCE the Indian The Atharva Veda includes mention of bhang, the modern word for cannabis, as a sacred grass. Medical references date to Susruta in the 6th to 7th centuries BCE (Chopra & Chopra, 1957). Ayurvedic and Arabic traditional preparations using cannabis for migraine, neuralgic, and visceral pains is found in Dwarakanath (1965) (Russo, 2002, p. 358). Nunn (1996) demonstrated that Cannabis was used medicinally in ancient Egypt, in support of "the view of Dawson that the hiero-glyphic shemshemet means cannabis" (Russo, 2002 p. 358). Hemp remnants were found in the tomb of Akhenaten (Amenophis IV) from ~1350 BCE, cannabis pollen in the tomb of Rameses II from ~1224 BCE. Cannabis was used since the time of the pharos orally, rectally, vaginally, topically, in the eyes, and by fumigation (Russo, 2002 p. 358).

Taken from an ancient Papyrus, Ramesseum III, 1700 BCE: "A treatment for the eyes: celery; hemp; is ground and left in the dew overnight. Both eyes of the patient are to be washed with it early in the morning" (Mannische 1989 p. 82). One thinks at once of modern treatment for glaucoma. From (Ebers Papyrus 821) we see the 19th century usage as an aid in childbirth with a vaginal introduction of cannabis prepared in this case, with honey (Ghalioungui, 1987).

Assyrian medical documents mainly from second millennium BCE, according to Thompson (1924; 1949) indicate the presence of analgesic and other psychological effects. Thompson (1924) concludes:

"The evidence thus indicates a plant prescribed in AM [Assyrian manuscripts] in very small doses, used in spinning and rope-making, and at the same time a drug used to dispel depression of spirits. Obviously, it is none other than hemp, Cannabis sativa, L." (p. 101). Sumerian texts tell of internal use for depression and staying the menses and presumably arthritis as referred to by "poison" of all limbs (p.222).

Ancient Israel/Palestine/Judea: a tomb in BeitShemesh contained the skeleton of a 14-year-old girl. Gray carbonized material was analyzed, and chromato-graphic and nuclear magnetic resonance spectroscopy evidence of delta-6-tetrahydrocannabinol was recovered. (Zias, et al., 1993): "We assume that the ashes found in the tomb were cannabis, burned in a vessel and administered to the young girl as an inhalant to facilitate the birth process" (p. 363).

Greek and Roman Empires: 1st century CE, Dioscorides' Materia Medica (Dioscorides, 1968): "Cannabis is a plant of much use in this life for ye twistings of very strong ropes, ... but being juiced when it is green is good for the pains of the ears" (p. 390). Pliny (1951): "The root boiled in water eases cramped joints, gout too and similar violent pains. It is applied raw to burns, ..." (Book XX, XCVII, p. 153).

The Islamic World:
9th century, Sabur ibn Sahl in Persia in his dispensatorium, Al-Aqrabadhin Al-Saghlr in (Kahl, 1994), interpretation of the text by Dr. Indalecio Lozano: "ibn Sahl prescribed a compound medicine containing cannabis juice that was used to treat a variety of aching pains and migraine that was instilled into the nostril of the afflicted patient." (Russo, 2002 p. 358). 12th century, Al-Biruni (Biruni & Said, 1973): "Galen says: 'The leaves of this plant [cannabis] cure flatus — Some people squeeze the fresh (seeds) for use in ear-aches. I believe that it is used in chronic pains'" (p. 346). 13th century Umar ibn Yusuf ibn Rasul suggested cannabis for ear and head pains (Lewis, Menage, Pellat & Schacht, 1971). 17th century in Indonesia, Rumphius studied cannabis treatment of pleuritic chest pains and hernias (Rumpf & Beekman, 1981). (Russo, 2002 p. 359).

Western Medicine:

England 1640, from the Theatrum Botanicum: The Theater of Plants (Parkinson & Cotes, 1640) John Parkinson writes: "Hempe is cold and dry. the Dutch as one saith doe make an Emulsion out of the seede, for it openeth the obstructions of the gall, and causeth digestion of choller therein: the Emulsion or decoction of the seede, stayeth laskes and fluxes that are continuall, easeth the paines of the collicke: and allayeth the troublesome humours in the bowels: . . . The decoction, of the roote is sayd to allay inflammations in the head or any other part, the herbe it selfe, or the distilled water thereof performeth the like effect; the same decoction of the rootes, easeth the paines of the goute, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes: it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter," (p. 598)

1758, Marcandier Trait.4 du chanvre [Treatise on Hemp] translated into English (1764): "The grain and the leaves being squeezed, while they are green, and applied, by way of cataplasm, to painful tumours, are reckoned to have a great power of relaxing and stupefying. The root of it boiled in water, and applied in the form of a cataplasm, softens and restores the joints of fingers or toes that are dried and shrunk. It is very good against the gout, and other humours that fall upon the nervous, muscular, and tendinous parts. It abates inflammations, dissolves tumours, and hard swellings upon the joints. Beat and pounded in a mortar, with butter, when it is still fresh, it is applied to burns, which it relieves greatly when it is often renewed," (pp. 24, 26). Linnaeus notes pain

reducing properties Materia Medica (Linne, 1772): "narcotica, phantastica, dementans, anodyna, repellens," (p. 213). Chomel (1782) points out hemp seed oil for pain and healing of burns.

O'Shaughnessy (1839) introduced his ideas on “Indian Hemp” used in extract form to treat patients suffering from rabies, cholera, tetanus, infantile convulsions, and painful rheumatological conditions. Clendinning (1843) published results of 18 patients with headaches, abdominal pain and tumor, lacerations, joint pains and gout. Hemp extracts proved effective: “I have no hesitation in affirming that in my hand its exhibition has usually, and with remarkably few substantial exceptions, been followed by manifest effects as a soporific or hypnotic in conciliating sleep; as an anodyne in lulling irritation; as an antispasmodic in checking cough and cramp; and as a nervine stimulant in removing languor and anxiety, and raising the pulse and spirits; and that these effect have been observed in both acute and chronic affections, in young and old, male and female” (p. 209). Donovan (1845) describes the use of cannabis resin with success in treating neuropathic and musculoskeletal pain, and hemp leaf oil on hemorrhoids and neuralgic pains with few side effects (Russo, 2002 p. 359).

Christison (1851) advocates cannabis as a successful treatment of tetanus, augmenting labor, and neuralgic and musculoskeletal pain. Grigor (1852) found success in 7 cases of 16 tested using cannabis to augment labor and remarked: “the contractions acquire great increase of strength . . it is capable of bringing the labour to a happy conclusion considerably within a half of the time that would other have been required" (p. 125). Sir John Russell Reynolds, physician to Queen Victoria successfully treated her dysmenorrhea with a cannabis extract throughout her adult life. Do closely note his comments! Reynolds (1868): “This medicine appears capable of reducing over-activity of the nervous centres without interfering with any one of the functions of organic, or vegetal life. The bane of many opiates and sedatives is this, that the relief of the moment, the hour, or the day, is purchased at the expense of tomorrow's misery. In no one case to which I have administered Indian hemp, have I witnessed any such results” (p. 160). (Russo, 2002 pp. 359-360). Silver (1870) treated cases of menorrhagia and dysmenorrhea, and his associate treated over 100 cases with success within three doses of cannabis. Practical Therapeutics (Waring, 1874) stated of cannabis: "Of a good extract, gr. 1/4 to gr. 1/2, rarely gr. j, in the form of pill, is very effective in some forms of neuralgia" (p. 159). Michel (1880) endorsed cannabis for neuralgic afflictions after extensive review. Two letters to the British Medical Journal endorse Cannabis Indica extract for menorrhagia treating pain and bleeding within several doses (Batho, 1883; Brown, 1883; Russo, 2002 p. 360).

Rennie (1886) reports cure using cannabis tinctures of acute and chronic dysentery and its attendant pain. Dr. Hobart Hare (1887) published an article within which we find the text: “CANNABIS INDICA has been before the profession for many years as a remedy to be used in combating almost all forms of pain, yet, owing to the variations found to exist as to its activity, it has not received the confidence which I think it now deserves. I have found the efficient dose of a pure extract of hemp to be as powerful in relieving pain as the corresponding dose of the same preparation of opium. . . . During the time that this remarkable drug is relieving pain a very curious psychical condition sometimes manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the

range of hearing" (pp. 225-226). This author [R.N.] would like the reader to see this statement in light of the role of cannabis as a "dissociative anesthetic."

Farlow (1889) wrote of rectal preparations of cannabis: "Cannabis has few equals in its power over nervous headaches such as women with pelvic troubles are subject to" (p. 508). Aulde (1890) stated: "As a remedy for the relief of supraorbital neuralgia no article perhaps afford better prospects than cannabis . ." (p. 118). Suckling (1891) in his article "On the Therapeutic Value of Indian Hemp states: "I have met with patients who have been incapacitated for work from the frequency of the attacks [of migraine], and who have been enabled by the use of Indian hemp to resume their employment" (p. 12). Mattison (1891) states: Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence. My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic" (pp. 270-271).

Mackenzie (1894) describes utility treating "neuralgias, headache, including chronic daily headache, tabetic (syphilitic) pain, functional gastrointestinal pain (corresponding to modern idiopathic bowel syndrome, or "spastic colon"), and pruritic disorders" (Russo, 2002 p. 360). An American 1898 drug handbook (Lilly, 1898) states: "Not poisonous according to best authorities, though formerly so regarded. Antispasmodic, analgesic, anesthetic, narcotic, aphrodisiac. Specially recommended in spasmodic and painful affections ..." (p. 32). The famous British pharmacologist Dixon (1899) stated: "In cases where an immediate effect is desired the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, and exhaustion a few inhalations produce an almost immediate effect, the sense of depression, headache, feeling of fatigue disappear and the subject is enabled to continue his work, feeling refreshed and soothed. I am further convinced that its results are marvellous in giving staying power and altering the feelings of muscular fatigue which follow hard physical labour" (p. 1356). Migraine, dental neuralgia, gastralgia, enteralgia, cerebral tumor, and herpes zoster may be treated with cannabis indica according to Shoemaker (1899).

As to acute and prophylactic treatment of migraine the acknowledged father of modern medicine Sir William Osier (Osier & McCrae, 1915) stated: "Cannabis indica is probably the most satisfactory remedy. Seguin recommends a prolonged course of the drug" (p. 1089). The Dispensatory of the United States of America (Remington, et al. 1918) (p. 280) contains the text: "Cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness. . . . For its analgesic action it is used especially in pains of neuralgic origin, such as migraine, but is occasionally of service in other types" (Russo, 2002 p. 361). Hare (1922) states: "For the relief of pain, particularly that depending on nerve disturbance, hemp is very valuable" (p. 181). Horchester (1930) notes concerning use in labor: "As far as is known, a baby born of a mother intoxicated with cannabis will not be abnormal in any way" (p. 1165). "Morris Fishbein (Fishbein, 1942), editor of the Journal of the American Medical Association notes even though it had become by that time a political impossibility that, oral preparations of cannabis are the best choice in the treatment of menstrual (catamenial) migraine. In Britain the drug was permitted to be used in practice somewhat longer, its virtues and uses touted as being "above opiates and barbiturates in the treatment of the pain of hospitalized patients with duodenal ulcers" (Douthwaite, 1947; Russo,

2002 p. 361).

We are now in a position to draw sound conclusions based firmly on sufficient evidence, and so answer the following questions posed, and recommend for or against the prescription and use of the raw drug: cannabis. To the following questions:

Is there evidence of safe use for thousands of years, or is this a dangerous, useless and addictive drug as the United States government says? Is such a history available in support of the hundreds of studies we have presented, or is this drug actually dangerous and ineffective?

We may answer rightly without fear of error: *Yes*, cannabis is safe and effective, and then in turn, *No* cannabis is not physically addictive or dangerous. That accusation is groundless and false. There is both copious modern empirical evidence and copious historical evidence of safe, effective medical use of cannabis stretching back many thousands of years; *cannabis* having served many ancient cultures including the ancient Egyptians. Read closely and know: this is not a physically addictive drug and in simple fact, is and has been used to curb tolerance and addiction to addictive opiates and reduce their dosages. As to point ***c.*** above:

c. the long historical record of the utility of cannabis demonstrative of its remarkable efficacy, excellent risk/benefit profile and hence supporting the copious and safe *utility of the raw drug and its basic preparations*.

The historical record along with modern empirical evidence is now accounted for in support of the efficacy of the raw drug. We may take point ***c.*** as evident.

We may make our first recommendation:

The raw drug cannabis is safe and effective, and so, cannabis should be available for prescription and medicinal use in those areas where it is legal to do so.

We will soon be in a position to review additional history supporting these ideas of adaptation and advantage and also understand why a drug with such a long-proven record of safe and effective usage has been turned into a pharmacological pariah, and then advance a particular course of action which may lead to a swift and hopeful outcome for the treatment of many diseases. To accomplish that, we must first distill our general hypotheses into specific forms.

The General, Strong and Weak hypotheses.

From the General hypotheses, the Strong and Weak hypotheses may then be drawn.

The General hypotheses:

1. After 1200 million years the CB receptors *and* their pre-formative evolutionary predecessors (and those of other system components), have developed along with cannabis and its ancestors in

turn, and so, the reason we find such complex and profound pharmacological utility in the phytochemistry of cannabis is no surprise: we have ONLY kept those mutations which have *brought advantage* from the addition of that mutation.

2. Cannabis is a treasure trove of complex pharmacology which works synergistically against pathology as a necessary consequence of the fact that over the course of 1200 million years, the CB receptors *and* their pre-formative evolutionary forbearers (and those of other system components), have adapted exactly as evolution would have them adapt: *to form advantage* of those exact chemicals, in ***those exact complex distributions***. Again: Mutations are kept, *if said adaptation is advantageous*.

The Strong hypothesis:

Systemic adaptation in humans stemming from human ancestors/progenitors involving cannabis and its ancestors/progenitors is sufficiently deep due to 600 million to 1.2 billion years of evolution including times of famine, that the removal of dietary cannabis and longstanding medicinal preparations has actively led *to the new emergence of disease*. Hence, cannabis and its seeds, medicinal preparations, the raw drug and extracts may prevent, treat or cure disease to restore a missing dietary and medicinal constituent.

The Weak hypothesis:

Systemic adaptation in humans stemming from human ancestors/progenitors involving cannabis and its ancestors/progenitors is sufficiently deep due to 600 million to 1.2 billion years of evolution including times of famine, that dietary cannabis, medicinal preparations, the raw drug and extracts may prevent, treat or cure many diseases.

With a few brief pieces of history and analysis, we will be able to present our final recommendations.

The suppression of cannabis in modern medicine: "Anecdotal Evidence," law, research funding and the credibility barrier.

Those who have bothered to take note all have noticed the incomprehensible dearth of research into what by all informed accounts is a treasure trove of potential medical benefit: *the interactive medicinal constituency within cannabis*. One finds a great many studies aimed at ***single synthetic chemical molecules*** (with those relatively few studies concerning phytocannabinoids focusing again, mainly on *single* component actions). This bazaar strategy which ignores a full 1.2 billion years of evolution in an unlikely attempt to find a *single synthetic molecule* which will do the job evolution has wisely ascribed to a host of evolutionarily justified phytochemicals, has quite predictably been a failed effort, as one would expect. The drug companies are as the reader will soon understand, in a rare position of power which enables them to misdirect research into the endocannabinoid system along unlikely pathways in an effort to create profits, even as the more likely pathway evolution has cleared toward cure is left aside, to the painful or even deadly

detriment of millions, creating a true unacknowledged human tragedy under the name of "the patentable molecule" [Appendix 1.]. We will now detail the history which has wrongly changed the course of medical research and its chosen pharmacological targets, make plain the difficulty and in so doing find with equal clarity what we believe to be the correct solution.

The United States is arguably the largest influence on worldwide medical scientific research and, its database PubMed is the very benchmark of reputable trustworthy information to which all turn as the gold standard of "real" science. Although today, the drug companies themselves have full legal rights to arbitrate the distribution of funding for applicable PubMed studies, meaning studies are routinely by law denied publication *unless funded by approved agencies* or, are part of a particular approved journal in a disciplinary niche which is in the main dismissed, thus rigging the system as will be articulated below…it was not always so. The history of cannabis in America is surprising, and its seeming erasure from the minds of the public even more so.

The first marijuana law in America was to make growing indian hemp mandatory in 1619 in Jamestown colony Va. More such laws followed in Massachusetts in 1631, Connecticut in 1632, and the Chesapeake colonies in the mid 1700s. Cannabis hemp was legal tender in the Americas from 1631 to the 1800s, and one could pay one's taxes in cannabis hemp for over 200 years. George Washington grew cannabis as did Thomas Jefferson, and, between 1763 and 1767 one could be jailed for NOT growing hemp in Virginia. The US census of 1850 counted 8327 hemp plantations of at least 2000 acres each. Cannabis extract medicines were the second or third most prescribed medications between 1842 and the 1890s, and were sold and produced through the 1930s by Eli Lilly, Squibb, Smith Brothers, Parke-Davis, Tildens, and others, during which time, not one single death was reported due to these medicines, nor were there reports of abuse or mental disorders, save for reports of new user disorientation. (Herer, 1990; Herndon, 1963; Able, 1980; Allen, 1900; Mikuriya, 1973; Cohen and Stillman 1976; Roffman, 1982; Clark, 1929).

It is very important to understand that cannabis was the main source of strong, soft cloth; hemp fabric has been woven since ~8000 BC, and being one of the strongest natural fibers on the planet it is also used for ropes and sails, fiber and paper as George Washington himself was aware, for he used hemp paper to break away from American dependency upon the paper products of England; it is used in paints, the seeds are pressed to gain oil for lubrication, diesel combustion and fueling lamps, methanol fuel can cheaply be produced from cannabis hemp as Henry Ford demonstrated, and so can gasoline by using cracking technology of the usual sort; food oils and protein may be gained from the seeds for humans and animals alike (cannabis seed once sustained American bird populations), and this protein source which was once the mainstay of porridges and gruel sustained populations through famine in Australia (along with the leaves eaten for roughage) and served those same dietary purposes in other countries throughout history (Frazier, 1972; Herer, 1990 pp. 26,42), being uniquely well suited to consume, as it contains 65 percent globulin *edestin* (from the Latin for edible) and high levels of albumin (Herer, 1990; Cohen and Stillman, 1976). It was the uses of cannabis hemp for *paper, fiber and fuel* which first led to its censorship and illegality, as the petrochemical industries, paper and synthetic fiber giants came into their own and wished to crush the competition. If used today, the hemp pulp process created in 1916 [see: Dewey and Merrill 1916 Bullrtin #404 USDA] could replace 40 to 70 percent of all pulp paper using

cannabis, an *annual crop* which surpasses trees in productivity by a ratio of one acre of cannabis hemp equalling 4.1 acres of trees in paper pulp production over a twenty year rotation, with up to 7 times less pollution (Herer, 1990). At first, the drug companies just as many other industries and even the AMA itself, were *all set against* the legal stricture of cannabis. Power itself—paper and the petrochemical giants had other ideas. Cannabis could end the need to cut down forests or use the processes these paper making industries depended upon, cannabis hemp challenged the use of new synthetic fibers and fuels made from petrochemicals and so, cannabis represented a potential billion dollar threat in the monetary valuation of the time (Pop. Mech, Feb, 1938; Herer, 1990 p. 21) A uniquely American mixture of greed, falsehood, politics, racism and corrupt legal process led to the divisive result we see before us today. [the following in the main condensed from (Herer, 1990; Bonnie and Whitebread, 1974; Mikuriya, 1973)].

William Randolph Hearst was the publisher of newspapers and the father of the despicable propaganda known as *yellow journalism*. In his papers he relentlessly attacked African Americans, and Mexicans. Hearst owned the paper companies which supplied his newspapers, such as Hearst Paper Manufacturing Division, Kimberly Clark USA, St. Regis, and, virtually all other timber, paper, and large newspaper holdings. DuPont had just patented a new sulphuric acid process for wood pulp paper in 1937 which would *account for 80% of its railroad shipping for the next 50 years* (Herer, 1990, p. 22). Hearst himself was responsible by weight of sheer repetition for the new word, *Marijuana*, which was ascribed to the cannabis plant with two results: 1. The sinister sounding name allowed him to demonize the drug and those populations using it, and 2. The scientific, medical and industrial communities were unaware that the benevolent plant *cannabis* and not some other named *marijuana,* was in fact being attacked and primed for suppression.

In the mid 30s cannabis hemp fiber stripping machines became very efficient in the conservation and separation of the fiber from the high-cellulose hurd used to make paper. Dupont's new synthetic fibers could not compete with cannabis, nor could petrochemical fuels, a fact which was demonstrated by Henry Ford's very *inexpensive* production from cannabis hemp of methanol at his plantation "Iron Mountain," which kept Standard Oil (Rockefeller) and Shell Oil (Rothschild) subsidizing oil prices for years to snuff the threat (Herer 1990 p. 43). DuPont's enormous wealth was backed by even more wealth, that of Andrew Mellon, of The Mellon Bank of Pittsburg. Also, in the prejudicial view of these powerful men, 'objectionable' populations in need of suppression such as African Americans and Mexicans smoked this substance, which was somehow also tied into the insidious music these men hated, Jazz, and later, Rock and Roll. Power understood, it was time to secretly use the legal system and the press to make cannabis illegal, and demonize its users (Herer, 1990).

Mellon was Hoover's secretary of the treasury, and in 1931 he appointed his nephew-in-law Harry J. Anslinger to be head of the Federal Bureau of Narcotics and Dangerous Drugs, a post he retained for 31 years. In apparent anticipation of the success of the suppression which would yield the market to *sulphuric-acid-processed tree-based paper, synthetic fibers and petrochemicals,* the DuPont stockholder annual report advised investment even though the depression was evident, and foreshadowed the collusion between government and industry which has become so very common today as to be the norm: it was anticipated that there would be "radical changes" from "the revenue

raising power of the government…converted into an instrument for forcing acceptance of sudden new ideas of industrial and social reorganization." (ibid. pp. 22-23). Taxes and laws were to be created, society shaped with propaganda, and money made.

Tax codes introduced for machine guns were the springboard (Bonnie and Whitebread, 1974), the legislation which had been designed in secret meetings over the last two years was ready, and quickly advanced through the Ways and Means committee rather than normal channels, so as to avoid scrutiny. The public and medical profession, industry and conservation groups were unaware that the scant talk of a bill prohibiting some demon plant named marijuana, was in fact referring to cannabis. Two days before the 1937 hearing to pass the marijuana bill, the AMA understood that the plant which Congress was to outlaw, was none other than cannabis, the benign substance used at that time in the United States safely for over one hundred years. Dr. James Woodward of the AMA noted that the reason he knew nothing of it, was that the meetings had been held *in secret* by the treasury department for the last two years! He argued to the Committee, that science was just beginning to understand the many chemicals in this medication, and this would deny the world any such medical advancements. His testimony was dismissed curtly (Bonnie and Whitebread. 1974; and congressional testimony in Herer, 1990). When the bill came up two days later for review in Congress, a lie was told. The floor raised the question as to the position of the AMA and if they had indeed been consulted. Representative Vinson answering for the Ways and Means Committee replied with a bold faced lie as follows: "Yes we have, a Dr. Wharton [note wrong name] (and the AMA) are in complete agreement." Upon that lie, the law was codified in September of 1937. (Herer, 1990, p. 25; Mikuriya, 1973; Bonnie and Whitebread 1974). The testimony consisted mainly of Anslinger reading from Hearst's fictitious yellow journalism newspaper articles aloud. Anslinger stated at one point to Congress in 1937 that: "Marijuana is the most violence causing drug in the history of mankind." Anslinger also stated to Congress as fact that approximately 50% of all violent crime in the US was caused by Spaniards, Mexican Americans, Greeks, and Negroes, and that all these crimes could be traced directly to marijuana. Each and every such assertion has been proven false (Bonnie and Whitebread, 1974; Sloman, 1979). It is interesting to note in this context that soon, Hearst would claim in the midst of the red scare, converse to his previous propaganda, that cannabis would lead not to rampant *violence*, but instead to "Zombie Pacifism."

Doctors continued to prescribe cannabis, and Anslinger prosecuted them to the tune of 3000 doctors in 1939, turning the AMA to the side of the government in exchange for dropping said prosecutions. Now, the AMA would accept the line of the federal government, evidence not withstanding (Herer, 1990 p. 27).

The next truly relevant and we believe tragic event, took place in the 1970s. In 1964 the famed Dr. Raphael Mechoulam synthesized THC. Just as the amazing potential of cannabis was so clear in the 1930s to the AMA, now again the fact began to surface, the research/cannabis ban had been softening, and the intellectual tenor become more positive. In November of 1975 all of America's leading cannabis researchers met at the Alisomar Conference Center in Pacific Grove, California. All participants appeared to agree, the need for research into this most promising drug was profound, as was the hope which could be available. Mechoulam himself believed cannabis would

soon be one of the world's major medicines. However, in 1976 a tragic turn of events took place. From (Herer, 1990 p. 32):

"This time the research ban was accomplished when American pharmaceutical companies successfully petitioned the federal government to be allowed to finance and judge 100% of the research.

The previous 10 years of research had indicated a tremendous potential for the therapeutic uses of marijuana, and this potential was quietly turned over to private hands—not for the benefit of the public, but to suppress the information.

This plan, the drug manufacturers petitioned, would allow our private drug companies time to come up with patentable synthetics of the cannabis molecules, at no cost to the federal government, and a promise of 'no highs.'"

See also: (Dach et al. 2015) p. 165.

Now the dearth of research into the fruitful pathway of evolution's proper design and the poor result of modern science to make use of this plant is explained. Indeed, this author [R.N.] has felt the sting of this cheat. My team had uncovered a new approach to pharmacology that used quantum information alone to create nontoxic drug *effects*, with no need for any costly, toxic pharmaceutical drugs whatsoever. The published paper written by myself along with three qualified coauthors: a retired senior mathematics and physics lecturer and *two* MDs, was refused by PubMed because: *It was not funded by an approved source* (Norman et al. 2016).

The effect is clear: the science is either not created at all as it is unfunded, or it is not read, taken seriously, seen or believed if it is published. When a fact is placed before a scientist, they rightly reply: "That is not believable. There is only anecdotal evidence." Of course that is true—The research has been suppressed! Evidence of "cure," without a carefully controlled well funded study is worthless science, "anecdotal evidence." This means we must understand the situation and reverse the typical insight to find the actual fact, and so deduce—*anecdotal evidence becomes primary*, for that evidence is all which remains for us to see of the intentionally hidden pathway to treatment and cure.

We are now in a position to analyze such evidence and then, make our conclusive recommendations.

There are many hundreds of anecdotal examples of treatment and cure. Rather than list them all, each unsubstantiated by study, it will be most helpful to select the best example available which demonstrates *repeatability* and the *full potential best case result* and use what then is presumably due to both repeatability and demonstrated best case outcome the most reliable and important evidence to conduct our analysis.

The case of Rick Simpson is that which fits the bill. We see many repeatable cures: Cancers.

Diabetes. Heart problems. Depression. Pain. Ulcers. Anxiety. Allergy. More. All with an: *Excellent safety profile*. Some 60 pieces of patient testimony along with doctors' confirmations of cures of those various patients' illnesses were readied, yet not permitted into court as evidence in support of the medical efficacy of cannabis preparations in Simpson's trial for violation of laws concerning controlled substances. Approximately four dozen accounts from those effectively treated and/or cured were dismissed in earlier proceedings, then, 10 pieces of patient testimony of successful treatment with six doctors' confirmations of cure were refused admission into the final proceedings: *a total of some 60+ pieces of suppressed evidence*. In light of the many studies presented here demonstrating just those sorts of effects claimed, the ancient history of safe use of cannabis, and, the current climate of suppression, these claims although untested by strict scientific measures, are certainly possible. These cases and this likely incidence of suppression are taking place in Canada, where we see the same combination of money and law, influencing a familiar and in this author's opinion, perhaps even a *criminal* outcome [web ref. 6 Rick Simpson, Run From the Cure].

The method of treatment is a highly concentrated extract made from cannabis-indica [web ref. 6,7,8]. Video footage of the extremely simple production process and further detail are available in [web ref. 6] which must also be viewed and understood closely to gain the necessary basics of this information. The following is quoted from [web ref. 7]. READER DO NOTE, we *do not recommend* the following procedure which is presented here for informational purposes *only*. The following are the *exact method of production and the authentic dosage instructions* used to create the claimed curative effects. Take heed: *it is essential to utilize a fan and directly ventilate rapidly accumulating flammable fumes. The following procedure must only be conducted out of doors in a safe location free of debris to avoid fire*. Only use cannabis which has been tested and approved for pesticide residues, mold and contamination. The following instructions are from Rick Simpson's own site, presented mainly complete with little editing or modification. [web ref. 7,8].

> **"PRODUCING THE OIL**
>
> Place the starting material in a bucket of good depth to prevent the oil solvent mix from splashing out during the washing process. Then, dampen the bud with the solvent being used and then crush the bud material using a length of wood such as a piece of 2×2. After the bud has been crushed, add more solvent until the bud material is completely immersed in the solvent. Work the bud material for three to four minutes with the length of wood you used to crush it.
>
> Then slowly pour the solvent oil mix off into another clean container, leaving the starting material in the original container, so it can be washed for the second time. To perform the second wash, add fresh solvent to the starting bud material again, until it is once more immersed in the solvent, and then work it for another three to four minutes, with the piece of wood you have been using.
>
> Then, pour the solvent oil mix from the second wash, into the same container that is holding the solvent oil mix from the first wash you did. Trying to perform a third wash on the

remaining plant material, produces very little oil and it would be of much less medicinal value as a medicine. But if you chose to do so the resulting oil from the third wash, could be used to help treat minor problems such as skin conditions.

The first wash dissolves 75 to 80% of the available medicinal resins off the starting material; the second wash then removes most of whatever resin that is of benefit, which remains. Oils produced from the first wash are the most potent medicinally but if high-grade starting material is used, oil from the second wash also has strong medical benefits as well.

If, for some reason, you have to work with material that is not as medicinally active as it should be, it is best to use the oil from the first wash only for internal use and then start to grow, or look for starting material that is of better quality. Remember, quality is more important than quantity and the more medical values the finished oil contains, the better it will work as a medicine.

Use something such as clean water containers, with a small opening at the top and insert funnels into the openings, then put large coffee filters in the funnels. Pour the solvent oil mix from the first and second washes, into the coffee filters and allow the solvent oil mix to drain into the containers, which are holding the funnels and filters to remove any unwanted plant material etc.

The more funnels and containers you use, the faster the oil solvent mix will be filtered. Once the oil solvent mix has been filtered, it is now ready to have the solvent boiled off. I should also mention that if you are using high quality bud, after the oil solvent mix has been filtered it often looks about the same as gasoline or at times it can be somewhat darker.

Remember that the solvent you are using was clear, so the yellow or darker color the solvent has taken on, is actually due to the healing resins which are now dissolved within it. If you do not already own one, you can purchase an inexpensive large rice cooker with an open top that has both high and low heat settings, to boil the solvent off the oil effectively. But make sure that the rice cooker is set up in a well-ventilated area and then place a fan nearby, to blow away the fumes as the solvent boils off.

This will prevent the fumes from condensing and posing a danger. Rice cookers are designed not to burn the rice as it cooks. So the temperature sensors which are built into these devices, will automatically switch the cooker back on the low heat setting, if the temperature within the cooker begins to get too high.

When producing oil, if the temperature gets a little over 300°F (148°C), it will begin to vaporize the cannabinoids off the oil and, of course, you do not want this to occur. If a rice cooker is working properly, it will automatically come off the high heat setting at roughly 210 to 230°F or (100 to 110°C), which is above the temperature where most people say decarboxylation is said to occur.

This temperature is still well below the point that THC and other cannabinoids will vaporize off the oil, which remains in the rice cooker. This is why I strongly recommend the use of a rice cooker, to those who have never produced oil before, since it eliminates any danger of harming the oil in question. Plus the resulting oil is decarboxylated, which is also important, so the oil can achieve its full medicinal benefits.

I suggest that people should not try to use crock-pots and similar appliances to produce oil. When I first tried to produce the oil, I used a crock-pot and since I did not know how much heat these devices can generate, the oil overheated and was ruined.

So I think it's only sensible that a beginner should start out by using a rice cooker and follow my instructions carefully. For by simply doing so, it can save someone new to producing this oil a lot of grief. A distilling device can also be used to produce this medication and reclaim the solvent that is being used. This method really does make more sense than using a rice cooker.

But stills which are designed to boil off solvents safely are expensive and most people, do not know how to operate one of these devices properly. If one is available, I prefer to use a still myself, but, in some countries, owning a still is against the law. If one is serious and wants to produce large amounts of oil, look into distilling and educate yourself in the proper use of this equipment.

Always make sure there are no sparks, open flames, or red-hot elements in the area while you are filling the rice cooker or boiling the solvent off, because the fumes produced from solvents are very flammable and quite toxic. I have used this same process hundreds of times and have never had a mishap, but for your own safety, please follow the instructions and make sure the area is well ventilated. I also caution you to avoid breathing in the fumes that solvents produce, since they can have unpleasant effects on anyone nearby.

It is also important to note that some of the airflow from the fan, should be directed towards the bottom of the rice cooker, since fumes from the solvent can often accumulate there. If you look at the bottom of a rice cooker you will find one or two small vents and if the fumes from the solvent enters these vents it could cause a fire.

So I have found that by aiming the airflow from the fan at approximately the center of the rice cooker, the airflow will still carry the fumes from the top of the rice cooker away and will also prevent these fumes from accumulating under the rice cooker at the same time. Make sure that the fan is running and produces enough airflow to blow away the fumes and if you are using a multi speed fan you will probably find that the lower speed settings will accomplish this task.

Then fill the rice cooker until it is about three quarters full of oil solvent mix, this allows room for the oil solvent mix to boil off without splashing over. Place the rice cooker on its

high heat setting and then begin boiling the solvent off. Never attempt to do this without the use of a fan, since the solvent fumes could accumulate and if they come into contact with the heating element within the rice cooker, it could cause these fumes to ignite.

As the level in the rice cooker drops, continue to carefully add the solvent oil mix you have remaining, until you have nothing left. When the level in the rice cooker comes down for the last time and has been reduced to about two inches of solvent oil mix remaining. Add about 10 to 12 drops of water to the solvent oil mix, which remains in the rice cooker. This small amount of water allows the remaining solvent, to boil off the oil which remains in the rice cooker more readily and it also helps to cleanse the oil of solvent residue, as the last of the solvent is being boiled off.

When there is very little remaining in the cooker, I usually put on a pair of gloves and then pick up the cooker and begin swirling its contents. This is done with the airflow from the fan still taking the fumes away and it can speed up the finishing process slightly. As the heat within the rice cooker increases, the cooker will automatically switch from the high heat setting and then go to its low heat setting, which prevents the oil within the cooker from overheating.

As the last of the solvent is being boiled off, you will hear a crackling sound from the oil that is left in the cooker and you will see quite a bit of bubbling taking place in the oil that remains. Also, you will notice what looks like a small amount of smoke coming off the oil in the rice cooker, but don't be concerned, since this is mostly just steam produced from the few drops of water that you added.

After the rice cooker has automatically switched to its low heat setting, I usually let it cool until it can be switched to the high heat setting again. After the cooker has automatically switched itself to the low heat setting for the second time, I then take the inner pot out of the cooker and pour its contents into a stainless steel measuring cup.

I have found that some strains of cannabis can produce an oil, which is actually finished and ready to use after the rice cooker has switched itself to the low heat setting for the second time, but in most cases it is still best the finish the oil properly. There will be a small amount of oil remaining in the pot that you will find almost impossible to get out, unless you use something like dry bread to absorb the oil, while it is still warm. Then, small amounts of this bread can be eaten as a medicine, but remember it can sometimes take an hour or more before you feel its effects.

. . . . [omitted material]. . . .

Take the oil that you poured into the stainless steel measuring cup and put it on a gentle heating device such as a coffee warmer to evaporate off whatever water remains in the oil. Quite often, it only takes a short time to evaporate the remaining water off, but also some strains produce more natural terpenes and flavonoids than others. These terpenes and

flavonoids can cause the oil you now have on the coffee warmer to bubble for quite some time and it may take a while for such oils to cease this activity.

When the oil on the coffee warmer has little or no bubbling activity visible, take the oil off the coffee warmer and allow it to cool a bit, after which it can be drawn up into the plastic syringes for use.

Another way to finish the oil without the use of a coffee warmer, is to put the oil in an oven set at 120°C or about (250°F) for about thirty minutes to an hour. Both of these methods work very well to bring the oil to a finished state.

Then, using plastic applicators or syringes with no needles that should be available from your local drug store, use the plunger of the syringe, to slowly draw the warm oil up into the syringes and then allow it to cool. As the oil comes down to room temperature, the resin or oil which contain the healing cannabinoids, will become a thick grease-like substance and it is then ready to use as a medicine. Sometimes the resin is so thick that it can be hard to force it out of the syringes when cooled. If such a thing happens, simply put the syringe in a cup of hot water, then in a short time you should be able to squeeze your dosage out more easily.

There are times when a patient could force too much oil from the syringe, but if this happens, just pull back on the plunger of the syringe and the excess oil can usually be drawn back into the syringe, without too much difficulty. On average, a dry pound of material will require about 2 gallons (8-9 liters) of solvent to do the two washes which are required. If you plan to produce the oil from more or less starting material, simply do the math to determine roughly how much solvent will be needed.

From start to finish, it usually takes three to four hours to accomplish the whole process, and then the medicine is sitting there ready to be used. It should also be mentioned that this oil has an extremely long shelf life. But for long-term storage, I would put it in a dark bottle with a tight lid or a stainless steel container. If kept in a cool dark place when stored, it can maintain its medicinal potency for a great number of years. At first, it may seem daunting for some to try to produce their own medicine but in reality, this process is extremely simple." [web ref. 7]

Let the reader be aware of the fact that these extracts may be created using the above method with grain alcohol (ethanol) in the highest proof available (~190) so as to negate the possibility of toxins from the solvent remaining in the final product due to improper methods of manufacture. See also [web ref 6] for background information concerning this very simple method of manufacture utilized in these many reportedly successful treatments.

Here are Rick Simpson's exact dosage instructions as per this best case of anecdotal evidence, presented mainly unaltered, as detailed in [web ref. 8]:

DOSAGE INSTRUCTIONS

It usually takes the average person about 90 days to ingest the full 60 gram or 60 ml oil treatment. I suggest that people start with three doses per day, about the size of a half a grain of short grained dry rice. The patient should take this dosage every 8 hours, early in the morning, then again in the afternoon and then they should take their final dose of the day, about an hour before bedtime. It should also be noted that as a patient begins to ingest this oil, the patient does not normally feel the oil's effects until about an hour after they have taken their dosage, so please be aware of this fact. A beginner's dose such as I am describing would equal about ¼ of a drop.

After four days at this dosage which should be taken three times a day, most people are then able to increase their doses by doubling the amount of their dosage every four days. By following this simple procedure, many patients have reported that they felt that they had not experienced the high, which this oil can cause. But in truth no two of us are the same and we all have different tolerances, so some will be able to up their dosages more quickly than others. In reality, even if one does become what is commonly referred to as being high this will not harm them in any way, if the oil they are ingesting was produced from the sedative strains of Indica, which I recommend and the resulting oil was produced in the proper way.

It takes the average person anywhere from 3 to 5 weeks to get to the point where they can ingest 1 gram or 1 ml per day. Once they reach this dosage they can continue at this rate until their medical issues are brought under control. This means that after the patient has become accustomed to the oils use, each dose they are ingesting will equal 8 to 9 drops every 8 hours and in many cases, I have seen patients that have had no trouble ingesting even far more. It takes a dosage roughly the size of two grains of short grained dry rice to equal one drop, so once the patient has become accustomed to the oils use they are actually ingesting doses which equal 16 to 18 grains of rice per dose.

In some cases I have even seen patients who had no fear of this medication, ingest the full 60 gram treatment in one month and after doing so, many of them were declared to be cancer free.

By using the method which I am describing, it allows your body time to build up a tolerance for this medication slowly and once the patient becomes accustomed to the oils effects, most patients actually report that they enjoy taking it.

We all have different tolerances for any medication and your size or body weight has little to do with your tolerance for hemp oil and even children can take the same dosage as adults, with no detrimental effects.

WARNING ABOUT THE USE OF THIS MEDICATION WHEN USING OTHER DRUGS

We are not medical doctors, so for any questions regarding the use of RSO alongside various pharmaceuticals please consult a medical doctor who supports the use of medical cannabis and who has experience with it.

Be aware when commencing treatment with hemp oil that it will lower your blood pressure, so if you are currently taking blood pressure medication, it is very likely that you will no longer require its use. Often patients will try to continue using their blood pressure medication, but if it is taken along with the oil their combined effect, can bring the patient's blood pressure down to uncomfortable levels. It's a good idea for those beginning treatment with the oil, to check their blood pressure often and then reduce their intake of other blood pressure medications as their blood pressure levels reduce. In the event that a patient is already suffering with low blood pressure, I have had reports from people who have this condition and they stated that simply drinking some water when they began to feel uncomfortable did help to some degree. Those who have low blood pressure, may in some cases find it necessary to ingest even smaller doses of this medication and to increase their dosages accordingly. But since this medication really does not present a danger, I think that their bodies will adjust to the oil's effects in a short time, after which they should experience little or no difficulty with its use.

Diabetics should also be aware that they will usually find that their need for insulin will be reduced and it may even decrease to the point, where they will no longer require its use at all and the same goes for most other pharmaceuticals as well. Diabetics are diagnosed with type1 or type 2 diabetes and no matter what type you suffer from, it is still beneficial to use this oil because not only will it decrease your need for insulin, it will also protect your body from all the other harm this disease can cause.

Also, please be aware that when the patient takes RSO (Rick Simpsons Oil) many people find if they are using any pharmaceuticals such as **steroids / painkillers / morphine** it makes horrible side effects when mixed, so many people reduce their medications by half on day one – then reduce and stop the medications over 7 to 14 days – mixing the medications with the oil can produce undesirable side effects – the symptoms / side effects of the medications can be exacerbated.

The main conditions / medications we warn about are the heart, blood pressure and diabetes and to closely monitor the levels over 3 months or so.

INGESTING YOUR DOSAGES

Many people today are suggesting that patients should be placing the dosage they are ingesting under their tongue, or they should be sticking their dosage to their gums, which is now known as tacking. Although methods such as this can get the medicinal cannabinoids into the patient's body, I really do not agree with these methods because oils can often have a bad taste that can linger in the mouth for quite some time. I feel that by

simply placing the dosage in the patient's mouth, would have benefits for those who have gum infections and problems of this nature, but in most cases I believe that their dosage should just be swallowed. The proper oil is a thick grease like substance, so when I ingest my dosage I simply put it on my finger and then place it on my teeth, after which I drink cold water and then use my tongue to remove it from my teeth and then I swallow. By using this method, I can usually take my dosages without hardly tasting the oil at all and I think that most patients would prefer to do the same, but there are also other simple methods which can be used to avoid the bad taste.

The patient's dosage can be placed on a small piece of bread and the bread can then be folded over to cover the dosage and then it can be placed in the patient's mouth and swallowed much like a pill with water. Another good method to avoid the taste, is to place the dosage between two thin slices of fruit such as bananas and then place it in the patient's mouth so it can be swallowed as well. If the oil is produced properly, often it really does not have an unpleasant taste that will linger, but the simple methods I have described should help patients ingest their dosages more easily. The name of the game, is to simply get the oil into the patient's body in the easiest and most pleasant way possible, so I think following the methods I have described should be given serious consideration.

SUPPOSITORIES

For quite some time now, many people have been showing an interest in using this medication in suppository form, because they think that by doing so they can avoid becoming high and for some, this might be somewhat true. I have used this oil in suppository form myself, but when I took quite a large dose in this manner I cannot say that I did not feel its effects. I actually think that in some cases using suppositories is a very good idea, since I believe the oil should be placed as close as possible, to the medical problem which is being treated.

Therefore, *for someone who is suffering with something such as prostate or bowel cancer, I believe that it could be more beneficial for their medical problems, to use the oil in this manner.*

But still, I have seen many patients with these same medical disorders, heal themselves by simply ingesting their dosages by mouth, so I will leave the method you wish to use up to you.

When the oil is used as a suppository, the medicinal cannabinoids this oil contains go directly into the blood stream by passing the liver.

But for those who are suffering with such things as stomach or liver cancer etc. I believe that it would be more beneficial to ingest the oil by mouth. If you intend to use suppositories to treat your medical problems, then the suppositories should contain the same amount of oil, you would normally ingest by mouth and the dosage should be increased in the same

manner.

Suppositories are fairly simple to prepare, but one should be careful about how much oil they contain, so in the beginning it may take some effort on your part to get the dosage right. Usually drugstores will supply suppository molds and all you have to do, is use a substance such as shay butter and then apply heat until it becomes a liquid, at which point you can add the oil and then fill the molds. It's a good idea to put the molds after being filled in a refrigerator, to allow the substance they now contain to harden up and after doing so, the suppositories are then ready for use. In addition, drugstores can usually supply empty gel caps and the patient's dosage can be put into the gel caps and then used as a suppository or can be taken by mouth, the gel cap will then disintegrate leaving the oil where you need it to be placed.

As I stated I do think that suppositories do have their uses, but I find this method to be quite time consuming and one must be careful about the amount of oil being added, so I still prefer to take my doses by mouth.

It should also be mentioned that this oil has many anti-aging qualities and it can also rejuvenate vital organs. So don't be surprised if the patient who is using it, begins to look a bit younger and any other problems they were having with their kidneys or other vital organs could simply disappear as well.

When people are ingesting the oil, I like to see them stay within their comfort zone, but the truth is, the faster you take the oil the better your chance of surviving, if you are suffering from a serious condition such as cancer.

MAINTENANCE DOSES

At the end of their treatment most people continue taking the oil, but at a much reduced rate. *About 1 to 2 grams a month would be a good maintenance dose*, just a drop or two at night before bedtime is all that is generally required to maintain good health. Often I am asked if this oil must be taken with food, but from my experience it seems to make little difference, so I will leave that for the patient themselves to decide. I feel that there is little need in most cases for anyone to overdose on the oil, unless they actually have a life threatening condition such as stage 4 cancer, which is putting their life in danger and they wish to bring this disease under control more quickly. Even in cases like this, it is usually not necessary to take overdoses but if one chooses to, then I really have no problem with them taking the oil in excess. Since in reality, unlike many pharmaceutical medications which our medical systems supply, an overdose of hemp oil really does not do any harm and cannot bring about your death.

The main side effect of this medication is sleep and rest, which plays a very important role in the healing process. Usually, within an hour or so after taking a dose, the oil is telling you to lay down and relax. Don't try to fight the oil's sleepy effects, just lay down and get

comfortable, then allow the oil to give you the rest and relaxation you require to heal properly. The effects of the oil may cause your mind to wander a bit and often patients will be somewhat unsteady on their feet when they begin to use this medication. But as the patient builds up their tolerance, these effects will diminish quickly. Usually within 3 to 4 weeks, the daytime tiredness associated with this treatment after the patient takes their dosage just fades away, but the patient continues to sleep very well at night.

I also suggest that *patients should not try to drive their cars,* until they become more accustomed to the oil's effects, after which they are then able to drive safely once more. Once you become used to the oil's effects it does not impair your ability to drive in any way, because unlike alcohol and many pharmaceuticals, this oil does not impair your motor skills.

DISCONTINUING THE USE OF DANGEROUS ADDICTIVE PAIN MEDICATIONS

The only time I would recommend that people start out with larger doses, would be if their life was really in danger or to get them off addictive and dangerous pain medications, supplied by the medical system.

When patients begin the oil treatment and they have been using these addictive medications to alleviate the pain, they usually cut their pain medications in half and they will also probably find that they no longer require the use of most other pharmaceutical drugs as well. Many dangerous pain medications like hydro-morphine are very addictive in nature and patients, will have a hard time ceasing their use due to the withdrawal symptoms they will suffer, because they have become badly addicted to these substances. The oil will allow patients who are ingesting it, to suffer much less withdrawal symptoms from the medications they were using and it can usually replace the use of these dangerous medications in 2 to 3 weeks and often even less time is required. The object is to ingest enough oil to reduce the pain and to help the patient, get off these dangerous medications as quickly as possible.

For the most part, pharmaceuticals are little more than toxins anyway and once the patient begins ingesting the oil, often the presence of these toxic drugs can begin to give them stomach problems. This is caused because the oil recognizes these chemicals and poisons for what they really are and the oil wants to expel them from the patient’s body. Once the patient stops ingesting these so- called drugs, their stomach problems will then just disappear and in most cases they will find that the only medication they really require is the oil. For those who are suffering from terminal cancer, the oil will either cure their cancer or in cases where it is too late to affect a cure, the oil will allow them to experience little or no pain and at least then they can die with dignity. Even if a patient has been given only a short time to live by the doctors, do not think of their situation as being hopeless, for very often the oil is still able to bring them back to a state of good health.

If the cancer cannot be reversed with the use of this oil, it is not unusual for the patient to live on for many month's longer than expected and during that extra time the oil gives them, they often can experience a very good quality of life.

DOSAGE INSTRUCTIONS FOR THOSE WHO HAVE BEEN DAMAGED BY CHEMOTHERAPY AND OR RADIATION ETC.

Hemp oil has a very high success rate in the treatment of all forms of cancer and now there is no shortage of testimonials available on the internet, from individuals who have used this oil successfully to do just that. But unfortunately, many people who came to me seeking help, had already been badly damaged from the chemotherapy and radiation treatments the medical system supplied. The damage such treatments can cause have a lasting effect and people who have suffered the effects of such treatments are the hardest to cure. But even those who have suffered all this horrible damage to their bodies, still have a good chance to make a full recovery, if they follow my instructions. When those who have been damaged from these so-called treatments ask for my advice, I tell them to ingest 180 grams or 180 ml's of high quality oil, as quickly as they can and this will give them the best chance to survive.

The extra 120 grams or 120 ml's that I advise them to ingest, is needed to undo all the damage that these horrible treatments have left behind in the patient's body. Once the patient has become accustomed to the oil's use, they should not encounter any problems ingesting 180 grams or 180 ml's in 5 to 6 months and often they can even accomplish this much more quickly. . . . . .

TREATING SKIN CANCER

If you can acquire a small quantity of properly produced oil, it will definitely work to treat skin cancer effectively and usually it only takes a few grams of this oil to accomplish the task. Grow or purchase some good high quality bud from sleepy sedative strains of Indica, which have a THC content of 20% or more. Then take about 30 grams of this bud and produce the oil from it, following my instructions which I have made available on my website phoenixtears.ca.

It should also be mentioned that in the treatment of skin cancer, oils produced from Sativa strains can be used effectively as well, since when applied topically the patient does not experience its energizing effects.

This amount of starting material should produce 4 to 5 grams of high grade oil. Apply the oil to the skin cancer and cover it with a bandage, apply fresh oil and a new bandage every 3 or 4 days and the cancer should soon disappear. I always tell people to continue treatment until the cancer is gone, then they should continue to treat the area for about two more weeks just as if the cancer was still there, for this will eliminate any cancer cells which could still remain. Doing this will ensure that all the cancer cells are dead and I have never seen a skin cancer return if my instructions are followed. If you've had skin cancer for

quite some time and the cancer is well established, it may take some time to cure.

But usually even in quite severe cases the cancer will disappear in less than three weeks. In an extreme case it may take longer but if so, then just keep up the treatment until it is gone. Many people can cure their skin cancer in no time, but it all depends on your own rate of healing and how deeply embedded the cancer has become. One should also remember that I am not just talking about cancer here, apply this oil to a third degree burn and watch what happens, the burn heals painlessly in a very short time and leaves no scars. When one considers all the suffering that patients in burn units are put through, why is this simple herbal medication not available to burn victims? This is only the tip of the iceberg folks, for the simple truth is, if you have properly produced oils from the cannabis plant at your disposal, you will probably find that it is the most effective medication to treat any medical condition you can name. I do not call properly produced oils from different varieties of this plant, a cure all for no good reason and once the truth about its true healing powers become better known, I'm sure that everything I am now telling you will become common knowledge." [web ref. 8]

Please note, the instructions provided for cancer [web ref. 6] clearly indicate *oral consumption* as the correct route of administration in that case. Review of video testimonial and other evidence revealed a pattern: heavy sedation for a month before tolerance developed. We are now in a position to present our analysis, recommendations and conclusions concerning the endocannabinoid system in human pathology.

Recommendations and conclusions concerning the endocannabinoid system in human pathology.

An initial observation:
The strange "moral" preoccupation with removing the "high" from cannabis in order to create acceptable medical treatments is a relic of the *false moral justifications used to suppress research* and impose a social agenda upon the people for overarching monetary, usury purposes (see above). If a patient with a painful, injurious or terminal disease is perhaps sleepy, smiling, happy, or too dreamy to operate a motor-vehicle for three months as they heal is utterly unimportant. The objection to a "high" in such a case, is farcical, silly, and cruel. This is simply an attempt to *generate profit* by creating patentable, ineffective, synthetic molecules while leaving aside the lives and health of our fellow humans with no concern. The objection to a "high" experienced by someone suffering of disease, is truly asinine. *Asinine*. I hope that is clear as a bell. My first recommendation: begin research into drug effects in all cases for *any and all disease types*, with *no concern whatsoever* for a "high." Let the warm glow this drug provides, help the sick as it is intended to do. To do otherwise is cruel, unethical, *foolish*, and wrong.

Analysis and recommendations:

I:

Oral consumption of extracts and cancer (with monitoring of ER+ or triple-positive breast cancer): a proposed modus operandi explaining dramatic anecdotal results and further implications:

1. The clear effects of THC in causing apoptosis in cancer cells while preserving healthy cells is remarkable (see section describing clinical efficacy and many mechanisms of effects). We may recall that 11-hydroxy THC is produced via first pass metabolism of delta-9-THC in the small intestine and liver when orally consumed, and, that 11-hydroxy THC is *four times* as immunosuppressive, and also, *four times* as psychoactive. The heavy initial sedation of patients indicates this preponderance of 11-hydroxy THC.

2. ***Key inference***: The production of 11-hydroxy THC in first pass metabolism is likely why oral administration is most effective.

Ergo:
3. a. Preparations pre-laden in additional 11-hydroxy THC and possessing delta-9-THC to encourage further 11-hydroxy THC production upon consumption may well be more effective than current methods.

b. Tumoral injections supplemented with, or constituent of 11-hydroxy THC may be more effective than using delta-9-THC alone in glioma surgery.

Recommendation:
The success of Rick Simpson's method using cannabis indica extracts in cases of severe cancer may be due to the route of *oral administration*, which yields high levels of 11-hydroxy THC, implying that the *supplemental addition of 11-hydroxy THC to basic extracts used may speed recovery, possibly extend benefits to more cases, and, could produce more efficacious surgical interventions in cases such as glioma*.

4. It is possible that CBD in a one to one (or other) ratio may aid the ability of delta9- and added 11-hydroxy THC to permeate cancerous tissues (a supposition derived from CBD's effects in fluidizing cell membranes (Pertwee, 2014)), and also, affect cure by other THC independent mechanisms (see clinical efficacy section above). [Note: CBD interferes with the synthesis in first pass metabolism of 11-hydroxy-delta9-THC from delta-9-THC via inhibition of cytochrome enzymes (Pertwee, 2014)].

Please do note: Clinical studies appear to *contradict* the following clinical observation: Breast cancers of the ER+ or triple-positive type, require a 1:1 or less ratio of delta-9-THC to CBD, even so far as 1:3 may be beneficial. Such cancers could *possibly spread* with THC in high doses, an unexpected situation determined by clinical experience. Other breast cancer types respond well to a typical high 4:1 THC to CBD ratio. A 1:1 THC to CBD ratio appears safe for all breast cancer

types. [Web ref. 3,4].

As these observations are apparently contradicted by clinical studies, it is unclear if any problem exists or not, hence, we recommend monitoring of these specific cases with great care to account for any uncertainty.

Recommendation:
[CBD:delta9-THC:11-hydroxy-delta9-THC] extracts for oral consumption in cases of cancer, and pure mixtures suitable for surgical interventionary measures should be tested.

II:

Profile restored preparations:

The General Strong and Weak hypotheses all imply the possibility of increased healing effects created by way of Profile Restored Preparations. The patient 1.2 billion year evolutionary advantage gained through the resultant hypercomplex synergies which mediate overall bio-systemic expression have been partially lost to focus the medicinal profile by way of creating an extract rich in primary active constituents. Please recall that extracts made with heat often lose mono-terpenoids and of course, lack other primary constituents found in the original phyto-profile which could aid overall therapeutic efficacy, a property based in evolutionary processes and the complimentary complexity of their result.

Recommendation:
Studies should be conducted analyzing the comparative efficacy of ordinary extracts with those extracts which restore the original chemical profile of the plant from which that extract is derived to create a *restored preparation* which contains trace amounts of the lost original elements.

III:

Strong and Weak implications for receptor adaptive compounds and prophylactic implications:

In Pertwee's (2014) "The handbook of cannabis" he concludes that cannabis is part of an evolutionary matrix through which over 30 million years of evolution and coadaptation, the fit for mammalian herbivore physiology was created and, that thousands of years of accelerated adaptivity followed at the hands of human interaction and intention. We have advanced the more radical idea, that the ancestors of these later mammalian species also did adapt in like fashion alongside the ancestors of cannabis, to find a figure of 600 million years for the primordial CB gene, and then 1.2 billion years at the split between plants and animals to include complete cannabinoid receptor and other pre-formative adaptive evolutionary component process.

Other animals and man both sustained themselves by eating cannabis seeds which form in the female plants' buds, which are of course rich in flowering terpenoids and other cannabinoids in various proportions—most of all THCA-A. We propose this as the interaction through which

receptor and systemic adaptivity proceeded in herbivores.

The Weak hypothesis then implies we may treat disease and be kept healthy to add to our diets both cannabis seed, and the juice of the buds of the fresh mature female plant which contain the active cannabinoid THCA-A in preponderance, and other cannabinoids and phytochemicals in the correct proportions.

The Strong hypothesis implies we may treat disease and be kept healthy to add to our diets both cannabis seed, and the juice of the buds of the fresh mature female plant which contains the active cannabinoid THCA-A in preponderance, and other cannabinoids and phytochemicals in the correct proportions, and, this hypothesis *also implies that diseases themselves*, such as Alzheimer's disease and cardiovascular disease, inflammatory disorders, Parkinson's and cancers, may actually *emerge not to have these basic dietary constituents* to which we have adapted included in our diet. The cancer clusters and disease increases we see, may be attributable in some part to the intentional 'legal' removal of cannabis from the diet.

Recommendation:
I advise all who read this work to add these non-psychoactive constituents to their diet at once. Hulled hemp seeds are readily available in most countries.

IV:

Strong and General-(2) hypotheses, the population derivative proliferative spectrum and pathology

The Strong and General-(2) hypotheses imply that the proliferative spectrum of phytochemical constituents as distributed within those specific varieties of cannabis with which populations have evolved, should provide the greatest benefit by way of evolutionarily selected advantage. The implication is that one may analyze cannabis samples and so derive the proliferative constituent profile associated with those cannabis strains (chemovars) which were most used by each individual population. Those particular cannabis constituent profiles then, should demonstrate the greatest efficacy available for prophylactic use against the potential onset of pathology, and perhaps also, demonstrate superior efficacy within treatment regimens derived. The Strong and General-(2) hypotheses then go further, and suppose *the actual emergence of pathology* may in fact be due in part to the absence of these same phytochemical distributions. It appears possible that to add *these* distributions to augment specific pathology-targeted preparations and extracts might facilitate synergistic effects as profile restored preparations.

Populations *absent* cannabis treatable disease types *may* indicate associated strain (chemovar) proliferative spectrum specific efficacy against said disease.

Recommendations for Industry:

The pharmaceutical industry seems not to recognize the unique position it is in. In cannabis it is quite clear that we see the opening of the gateway to the future through the patient reserve and careful processes of our evolutionary past. In the case that *even some portion* of the many claimed patient reports of cure and their doctors' supporting testimony from those people receiving the treatment provided by Rick Simpson are accurate, by implication, we can infer through the worldwide yearly cancer death toll of ~8.2 million for 2012 [web ref. 5], that the suppression of this research although accomplished by *legal means*, may constitute a *criminal act* by any sound ethical standard. This purposeful avoidance of the pathway evolution has so well prepared for us in order to secure patentable molecules at the expense of human lives is short sighted, sure to fail to gain much ground as it is set against the very design of the bio-system, and most importantly, this is a very foolish approach *from the perspective of generating profit*. I insist and assert: The drug companies stand on the cusp of the most astronomical windfall they have ever conceived of reaping! Mankind may benefit, and massive profits will then come rolling in as never before for the pharmaceutical companies, all without any need to curtail the medical rights of humane access each person is due to this plant.

Obviously it is impossible to deny that it is inhumane and wrong, *a criminal act*, to refuse humans who are ill access to this medication through medical channels or otherwise, should it be legal to do so. People must always have full rights to the maintenance of their own health *themselves*, or we see crime. With this in mind and without any implied conflict: massive amounts of money in excess of any ever produced could be made by the pharmaceutical companies if they were to patent specific proliferations of cannabis derived phytochemicals which are demonstrated to cure and treat disease more effectively and with greater consistency and superior known shelf-life over the crude extracts available to the public through those aforementioned proper channels. The public would pay massively to have assured quality, reliable effects of higher potency and a tested product known not to be deteriorated as it is properly preserved and prepared. In this way, all could have what they need: the poor could have the raw extract through proper channels and so have this option concerning their health, and the rich could buy a more reliable and effective version assuring the pharmaceutical giants more money than they have ever known, and a real boost in their public image as well. Greed need not curtail human rights to a benevolent plant, to be twice satisfied and fat with new wealth. No crime is needed to reap even these untold benefits for both humanity and industry.

How is this to be accomplished? The answer is plain: through controlled breeding of cannabis to focus the plant's production of cannabinoids, terpenoids and other vital constituents. The esteemed Dr. Russo was kind enough to send a pre-print of a paper under consideration for review, which the reader should look for when it is available: *Pharmacological Foundations of Cannabis Chemovars: No "Strain," No Gain*, by Mark A. Lewis, Ethan B. Russo and Kevin Smith presently under review at the journal *Planta Medica* at the time of this writing. This is ideal science suitable as a sustainable approach to the controlled derivation of potent and well targeted therapies using the correct phytochemicals and full component proliferations evolution as provided. In this way the cannabis plant may produce the appropriate phytochemicals needed to create targeted

preparations, drugs and extracts using combinative synergies with control and accuracy.

I will likewise caution clearly and in the strongest possible terms *directly against the forced genomic manipulation/engineering of the cannabis plant using gene editing technology*, as once again, evolution has in her patient and right way slowly and carefully woven the fabric of health for us in great complexity and nuance, and only in greedy arrogance and abject foolishness could we imagine any but the worst possible result to naively cut and arrange the very threads of the evolutionary fabric which sustains us. Such foolishness could well represent *a crime with irretrievable and tragic results*. The deep and unpredictable consequences of such irresponsible, overarching usury behavior are clearly well beyond our ability to predict. Evolution's complex weaving may heal us should we be wise enough to approach her gifts with respect, rather than pry them apart in avarice and hubris.

Conclusion:

The human endocannabinoid system has evolved from a primordial CB gene which dates back some 600 million years, and in turn, that ancient gene evolved from genetic progenitors 1.2 billion years distant marking the separation of plants and animals themselves. The patient forge of evolution has created an interdigitated tapestry of bio-systemic phytochemical interactive complexity resultant of advantageous design. Her "magic" is in fact but slow and careful progress. For this reason mankind has utilized cannabis for millennia for nourishment, fiber, fabric and also to treat and heal a prolific variety of maladies. However, historically recent legal obstructions and falsehoods have curtailed progress toward the development of the many benefits promised in this phytochemical pharmacopeia. One may even hypothesize due to the deep evolutionary connections and subsequent systemic adaptation that the suppression of this once socially and medically fundamental plant which served and fed mankind for eons, might actually produce the emergence of disease. The fact that cannabis *treats* disease is no longer open for debate, nor has it been for thousands of years. To imagine otherwise, is to neglect all of history.

We have proven with hundreds of studies and documented historical detail that the raw drug cannabis is *safe, non-addictive and effective*, and so, cannabis should be available for prescription by medical professionals to aid in those conditions treatable with its effects.

We have articulated the legal maneuverings and history behind the current suppression of proper research, and suggested that therefore, anecdotal evidence must then assume priority. Analysis of such evidence indicates: a. the possibility of these claims being accurate is supported by the depth of the phylogenetics; b. the possibility of these claims being accurate is supported by a massive amount of empirical science articulating effects on the systems and pathologies in question; c. the possibility of these claims being accurate is supported by the historically recorded multitude of uses stemming from an ancient evolutionary profile of advantageous adaptation in human systemic balance and functioning, hence, the seemingly 'magical' ability of cannabis to affect multiple pathologies. This profound medical utility is in fact *a necessary result* of evolution and advantage.

Modern history offers us a dichotomy:

"Humanity may choose to make wise and potent use of the evolutionary gifts provided by cannabis, or, humanity may seek to make profit and set its sights against the better course in order to exploit human misery for monetary gain."

This dichotomy frames modern medicine's bitter choice. We suggest that this dichotomy is in the case of cannabis: *False*—and that massive profits can be made by the pharmaceutical companies by way of patenting proven rightly preserved targeted phytochemical proliferations of high quality and reliable standards (instead of molecules), while allowing the less effective raw drug and general simple extracts to remain available, thereby reaping enormous profit while allowing the basic rights of humankind to be fulfilled unimpeded by arbitrary and cruel law.

Cannabis as a medicine has been suppressed entirely due to financial and political motives. It is effective, cheap and safe. The time has come, and is in fact long overdue, for research to be established in human cancer trials utilizing hyper-potent general and targeted cannabis indica extracts. It appears possible that millions of lives could be improved, or even saved. The idea of "no highs" as a benchmark for treatment of deep illness is absurd, cruel and utterly contemptible. Patients should have a choice of treatment options which include this remedy. *11-hydroxy-delta9-THC* appears to be an *unacknowledged key* in creating beneficial effects in many stubborn cancers. Treatment options of greater efficacy are implied so, this new and clear pathway must be tested.

A program involving consenting patients exploring the above mentioned claims concerning cancers and the basic extract as outlined, then preparations involving supplemental *11-hydroxy-delta9-THC* (and other combinations) could begin to help those afflicted immediately.

Profile restored preparations, and the *Population derivative proliferative spectrum* may aid progress, and, the reintroduction of cannabis into the diet appears to this author as a prophylactic necessity.

Only openly permitted and well funded research conducted by honest uninfluenced researchers will reform the system and bring the medicinal fruits of this plant to careful harvest and so, provide health to those in need. Free and unfettered access to this information aimed at doctors and the public may begin the process of ending the research suppression, and also, apparent suppression of this treatment option. This document is intended to provide that suppressed information and begin the process of initiating worldwide independent research and dissemination of these treatment options. It is possible that *cancer and a host of other disorders may be treated and in some cases cured using phytochemicals derivative of cannabis*. The suppression of this fact, may well be harming millions, and creating great suffering. The medical research system is a shambles of deception, and in bringing this information to patients and medical professionals directly, it may be possible to plainly expose the falsehood of monetary influence, provide these options to doctors and the public directly for immediate voluntary use and subsequent proper empirical evaluation, and in this way circumvent the effect of these deplorable maneuverings and the system which

supports them and so, end the deception, suppression and suffering. That is the hope and opinion of this author.

References for this section found in **References, List Four**.

References, List One:

Abel, E. (1980). *Marijuana: The first 12,000 years*. Plenum Press: NY.

Aizpurua-Olaizola, Oier; Soydaner, Umut; Öztürk, Ekin; Schibano, Daniele; Simsir, Yilmaz; Navarro, Patricia; Etxebarria, Nestor; Usobiaga, Aresatz (2016). Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes. *Journal of Natural Products*. 79 (2): 324–331. PMID 26836472. doi:10.1021/acs.jnatprod.5b00949.

Andre, C. M., Hausman, J.-F., & Guerriero, G. (2016). *Cannabis sativa*: The Plant of the Thousand and One Molecules. *Frontiers in Plant Science*, *7*, 19. http://doi.org/10.3389/fpls.2016.00019 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740396/

Atakan, Z. (2012). Cannabis, a complex plant: different compounds and different effects on individuals. *Therapeutic Advances in Psychopharmacology*, *2*(6), 241–254. http://doi.org/10.1177/2045125312457586

Basu S, Ray A, Dittel BN (2011). Cannabinoid receptor 2 is critical for the homing and retention of marginal zone B lineage cells and for efficient T-independent immune responses. *Journal of Immunology*. **187** (11): 5720–32. PMC 3226756 . PMID 22048769. doi:10.4049/jimmunol.1102195.

Burstein, S. H., & Zurier, R. B. (2009). Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation. *The AAPS Journal*, *11*(1), 109. http://doi.org/10.1208/s12248-009-9084-5.

Callén L, Moreno E, Barroso-Chinea P, Moreno-Delgado D, Cortés A, Mallol J, Casadó V, Lanciego JL, Franco R, Lluis C, Canela EI, McCormick PJ (2012) Cannabinoid receptors CB1 and CB2 form functional heteromers in brain. *J Biol Chem. 287(25):20851-65.*

Carlini EA, Karniol IG, Renault PF, Schuster CR. (1974) Effects of marihuana in laboratory animals and in man. *Br J Pharmacol*. 50:299–309. [PMC free article] [PubMed]

Demuth DG, Molleman A (2006). "Cannabinoid signalling". *Life Sciences*. **78** (6): 549–63. PMID 16109430. doi:10.1016/j.lfs.2005.05.055.

De Petrocellis L1, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, Stott CG, Di Marzo V. (2011) Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol*. 163(7):1479-94. doi: 10.1111/j.1476-5381.2010.01166.x.

Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC (1988). Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 34: 605–613.

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G et al. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258: 1946–1949.

Fairbairn JW, Pickens JT. Activity of cannabis in relation to its delta'-trans-tetrahydro-cannabinol content. *Br J Pharmacol*. 1981;72:401–409. [PMC free article] [PubMed]

Gaoni Y, Mechoulam R (1964a). Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 86: 1646–1647.

Gaoni Y, Mechoulam R (1964b). The structure and function of cannabigerol, a new hashish constituent. Proc Chem Soc 1: 82.
Gaoni Y, Mechoulam R (1966). Cannabichromene, a new active principle in hashish. Chem Commun 1: 20–21.

Gill EW, Paton WD, Pertwee RG (1970). Preliminary experiments on the chemistry and pharmacology of cannabis. Nature 228: 134–136.

Hui-Lin L. (1975) *The origin and use of cannabis in Eastern Asia*. In: Rubin V., editor. *Cannabis and Culture*. The Hague: Mouton.

Izzo AA (2004). "Cannabinoids and intestinal motility: welcome to CB2 receptors". *British Journal of Pharmacology*. **142** (8): 1201–2. PMC 1575197 . PMID 15277313. doi:10.1038/sj.bjp.0705890.

Kenney, S., Kekuda, R., Prasad, P., Leibach, F., Devoe, L. and Ganapathy, V. (1999) Cannabinoid receptors and their role in the regulation of the serotonin transporter in human placenta. Am *J Obstet Gynecol* 181: 491–497.

Li H. (1973) An archaeological and historical account of cannabis in China. *Economic Botany* 28: 437–448

Lovinger DM (2008) Presynaptic modulation by endocannabinoids. *Handb Exp Pharmacol*. (184):435-77. DOI: 10.1007/978-3-540-74805-2_14
https://www.ncbi.nlm.nih.gov/pubmed/18064422

McPartland, J. and Pruitt, P. (2002) Sourcing the Code
Searching for the Evolutionary Origins of Cannabinoid Receptors, Vanilloid Receptors, and Anandamide. *Journal of Cannabis Therapeutics*, Vol. 2(1)
http://dx.doi.org/10.1300/J175v02n01_04
http://www.tandfonline.com/doi/abs/10.1300/J175v02n01_04

Mechoulam R, Shvo Y (1963). Hashish-I. The structure of cannabidiol. Tetrahedron 19: 2073–2078.

Mechoulam, R. (1986) *The pharmacohistory of cannabis sativa.* In: Mechoulam, R., editor. *Cannabis as Therapeutic Agent*. CRC Press; Boca Raton, FL. p. 1-19.

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR et al. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 50: 83–90.

PACHER, P., BÁTKAI, S., & KUNOS, G. (2006). The Endocannabinoid System as an Emerging Target

of Pharmacotherapy. *Pharmacological Reviews*, *58*(3), 389–462. http://doi.org/10.1124/pr.58.3.2.

Pacher, P., & Mechoulam, R. (2011). Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Progress in Lipid Research*, *50*(2), 193–211. 10.1016/j.plipres.2011.01.001

Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R (2006). "The emerging role of the endocannabinoid system in endocrine regulation and energy balance". *Endocrine Reviews*. **27** (1): 73–100. PMID 16306385. doi:10.1210/er.2005-0009.

Pertwee RG (2006) The pharmacology of cannabinoid receptors and their ligands: an overview. *Int J Obes (Lond).* Suppl 1:S13-8.
DOI: 10.1038/sj.ijo.0803272 https://www.ncbi.nlm.nih.gov/pubmed/16570099

Pertwee, R., Howlett, A., Abood, M., Alexander, S., Di Marzo, V. and Elphick, M. (2010) International Union of Basic and Clinical Pharmacology. LXXIX.
Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol Rev* 62: 588–631.

Radwan MM, Elsohly MA, Slade D, Ahmed SA, Khan IA, Ross SA. (2009). Biologically active cannabinoids from high-potency Cannabis sativa.
J Nat Prod. 2009 ;72(5):906-11. doi: 10.1021/np900067k.

Russo, E. B., Jiang, H.-E., Li, X., Sutton, A., Carboni, A., del Bianco, F., … Li, C.-S. (2008). Phytochemical and genetic analyses of ancient cannabis from Central Asia. *Journal of Experimental Botany*, *59*(15), 4171–4182. http://doi.org/10.1093/jxb/ern260
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2639026/

Russo EB (2011) Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. Aug;163(7):1344-64. doi: 10.1111/j.1476-5381.2011.01238.x.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/
https://www.ncbi.nlm.nih.gov/pubmed/21749363

Ryan D, Drysdale AJ, Pertwee RG, Platt B. (2006) Differential effects of cannabis extracts and pure plant cannabinoids on hippocampal neurones and glia. *Neurosci Lett*. 408:236–241. [PubMed]

Shoemaker JL, Ruckle MB, Mayeux PR, Prather PL (2005). Agonist-directed trafficking of response by endocannabinoids acting at CB2 receptors. *The Journal of Pharmacology and Experimental Therapeutics*. **315** (2): 828–38. PMID 16081674. doi:10.1124/jpet.105.089474.

Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K et al. (1995). 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun 215: 89–97.

Vollner L, Bieniek D, Korte F (1969). [Hashish. XX. Cannabidivarin, a new hashish constituent]. Tetrahedron Lett 3: 145–147.

Wilkinson JD, Whalley BJ, Baker D, Pryce G, Constanti A, Gibbons S, et al. (2003) Medicinal cannabis: is delta9-tetrahydrocannabinol necessary for all its effects? *J Pharm Pharmacol*. 55:1687–1694. [PubMed]

Wright KL, Duncan M, Sharkey KA (2008). Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. *British Journal of Pharmacology*. **153** (2): 263–70. PMC 2219529 . PMID 17906675. doi:10.1038/sj.bjp.0707486.

Web References:

1. https://npgsweb.ars-grin.gov/gringlobal/taxonomylist.aspx?category=species&type=genus&value=Cannabis&id=2034

2. https://en.wikipedia.org/wiki/Cannabis

3. https://en.wikipedia.org/wiki/Depolarization-induced_suppression_of_inhibition

4. http://www.news-medical.net/health/Phytocannabinoids.aspx

5. https://en.wikipedia.org/wiki/Cannabinoid_receptor_type_1

6. https://en.wikipedia.org/wiki/Cannabinoid_receptor_type_2

7. https://en.wikipedia.org/wiki/Cannabinoid

8. http://www.seattletimes.com/seattle-news/marijuana/dea-says-marijuana-has-no-medical-use-pot-remains-listed-as-dangerous/

References, List Two:

Aguado, T., Carracedo, A., Julien, B., Velasco, G., Milman, G., Mechoulam, R., Alvarez, L., Guzmán,L., Galve-Roperh, I. (2007). Cannabinoids Induce Glioma Stem-like Cell Differentiation and Inhibit Gliomagenesis. *The Journal of Biological Chemistry*. 282, 6854-6862. doi: 10.1074/jbc.M608900200 http://www.jbc.org/content/282/9/6854.long

Alexander, A., Smith, P.F., Rosengren, R.J. (2009). Cannabinoids in the treatment of cancer. *Cancer Lett.* 285(1):6-12. doi: 10.1016/j.canlet.2009.04.005.

Alpini, G., & DeMorrow, S. (2009). Changes in the Endocannabinoid System May Give Insight into new and Effective Treatments for Cancer. *Vitamins and Hormones*, *81*, 469–485. http://doi.org/10.1016/S0083-6729(09)81018-2

Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., et al. (2008) Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *J Nat Prod*. 71:1427–1430. DOI: 10.1021/np8002673
https://www.ncbi.nlm.nih.gov/pubmed/18681481 DOI: 10.1021/np8002673

Ashton, C.H., Moore, P.B. (2011). Endocannabinoid system dysfunction in mood and related disorders. *Acta Psychiatr Scand*. 124(4):250-61. doi: 10.1111/j.1600-0447.2011.01687.x. https://www.ncbi.nlm.nih.gov/pubmed/21916860

Ashton, C.H., Moore, P.B., Gallagher, P., Young, A.H. (2005). *Journal of Psychopharmacology* 19(3)

293–300 10.1177/0269881105051541

Ashton, J.C., Smith, P.F. (2007). Cannabinoids and cardiovascular disease: the outlook for clinical treatments. *Curr Vasc Pharmacol.* 5(3):175-85. https://www.ncbi.nlm.nih.gov/pubmed/17627561?ordinalpos=1&itool=PPMCLayout.PPMCAppController.PPMCArticlePage.PPMCPubmedRA&linkpos=5

Assaf, F., Fishbein, M., Gafni, M., Keren, O., Sarne Y. (2011). Pre- and post-conditioning treatment with an ultra-low dose of Δ9-tetrahydrocannabinol (THC) protects against pentylenetetrazole (PTZ)-induced cognitive damage. *Behav Brain Res*. 220(1):194-201. doi:10.1016/j.bbr.2011.02.005. https://www.ncbi.nlm.nih.gov/pubmed/21315768

Bahremand, A., Shafaroodi, H., Ghasemi, M., Nasrabady, S.E., Gholizadeh, S., Dehpour, A.R. (2008). The cannabinoid anticonvulsant effect on pentylenetetrazole-induced seizure is potentiated by ultra-low dose naltrexone in mice. *Epilepsy Res*. 81(1):44-51. doi:10.1016/j.eplepsyres.2008.04.010. https://www.ncbi.nlm.nih.gov/pubmed/18502613

Bambico, F.R., Katz, N., Debonnel, G., Gobbi, G. (2007). Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. *J Neurosci*. 27(43):11700-11. DOI: 10.1523/JNEUROSCI.1636-07.2007 https://www.ncbi.nlm.nih.gov/pubmed/17959812

Bari, M., Rapino, C., Mozetic, P., Maccarrone, M. (2010). The endocannabinoid system in gp120-mediated insults and HIV-associated dementia. *Exp Neurol*. 224(1):74-84. DOI:10.1016/j.expneurol.2010.03.025 http://sci-hub.io/10.1016/j.expneurol.2010.03.025

Bento, A.F., Marcon, R., Dutra, R.C., Claudino, R.F., Cola, M., Leite, D.F., Calixto, J.B., (2011). β-Caryophyllene inhibits dextran sulfate sodium-induced colitis in mice through CB2 receptor activation and PPARγ pathway. *Am J Pathol.*;178(3):1153-66. doi:10.1016/j.ajpath.2010.11.052. https://www.ncbi.nlm.nih.gov/pubmed/21356367

Bermúdez-Silva, F.J., Suárez, J., Baixeras, E., Cobo, N., Bautista, D., Cuesta-Muñoz, A.L., Fuentes, E., Juan-Pico, P., Castro, M.J., Milman, G., Mechoulam, R., Nadal, A., Rodríguez de Fonseca, F. (2008). Presence of functional cannabinoid receptors in human endocrine pancreas. *Diabetologia*. 51(3):476-87. https://www.ncbi.nlm.nih.gov/pubmed/18092149 DOI: 10.1007/s00125-007-0890-y

Biegon, A. (2004). Cannabinoids as neuroprotective agents in traumatic brain injury. *Curr Pharm Des*.10(18):2177-83. https://www.ncbi.nlm.nih.gov/pubmed/15281893

Bifulco, M., Laezza, C., Valenti, M., Ligresti, A., Portella, G., DI Marzo, V. (2004). A new strategy to block tumor growth by inhibiting endocannabinoid inactivation. *FASEB J*. 18(13):1606-8. DOI: 10.1096/fj.04-1754fje https://www.ncbi.nlm.nih.gov/pubmed/15289448

Bifulco, M., Malfitano, A.M., Pisanti, S., Laezza, C. (2008). Endocannabinoids in endocrine and related tumours. *Endocr Relat Cancer*. 15(2):391-408. doi: 10.1677/ERC-07-0258. https://www.ncbi.nlm.nih.gov/pubmed/18508995

Bilsland, L.G., Greensmith, L. (2008) The endocannabinoid system in amyotrophic lateral sclerosis. *Curr Pharm Des.* 2008;14(23):2306-16. https://www.ncbi.nlm.nih.gov/pubmed/18781981

Blaas, K. (2008). Treating depression with cannabinoids. *Cannabinoids* 3(2):8-10 http://www.cannabis-med.org/english/journal/en_2008_02_2.pdf

Blake, D.R., Robson, P., Ho, M., Jubb, R.W., McCabe, C.S. (2005). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*. 45 (1): 50-52. DOI:https://doi.org/10.1093/rheumatology/kei183

Blázquez, C., Carracedo, A., Barrado, L., Real, P.J., Fernández-Luna, J.L., Velasco, G., Malumbres, M., Guzmán, M. (2006). Cannabinoid receptors as novel targets for the treatment of melanoma. *FASEB J*. 20(14):2633-5. DOI: 10.1096/fj.06-6638fje https://www.ncbi.nlm.nih.gov/pubmed/17065222

Blázquez, C., Carracedo, A., Salazar, M., Lorente, M., Egia, A., González-Feria, L., Haro, A., Velasco, G., Guzmán, M. (2008). Down-regulation of tissue inhibitor of metalloproteinases-1 in gliomas: a new marker of cannabinoid antitumoral activity? *Neuropharmacology.* 54(1):235-43.

Blázquez, C., Casanova, M.L., Planas, A., Gómez Del Pulgar, T., Villanueva, C., Fernández-Aceñero, M.J., Aragonés, J., Huffman, J.W., Jorcano, J.L., Guzmán, M. (2003). Inhibition of tumor angiogenesis by cannabinoids. *FASEB J.* 17(3):529-31.

Blázquez, C., González-Feria, L., Álvarez, L., Haro, A., Casanova, M.L., Guzmán, M. (2004). Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas. *Cancer Research.* DOI: 10.1158/0008-5472.CAN-03-3927 http://cancerres.aacrjournals.org/content/64/16/5617

Blázquez, C., Salazar, M., Carracedo, A., Lorente, M., Egia, A., González-Feria, L., Haro, A., Velasco, G., Guzmán, M. (2008). Cannabinoids Inhibit Glioma Cell Invasion by Down-regulating Matrix Metalloproteinase-2 Expression. *Cancer Res*. 2008 Mar 15; 68(6):1945-52. DOI: 10.1158/0008-5472.CAN-07-5176

Blevins, R.D., Dumic, M.P. (1980). The effect of delta-9-tetrahydrocannabinol on herpes simplex virus replication. *J Gen Virol*. 49(2):427-31.DOI: 10.1099/0022-1317-49-2-427 https://www.ncbi.nlm.nih.gov/pubmed/6255077

Booz, G.W. (2011). Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radic Biol Med.*51(5):1054-61. doi:10.1016/j.freeradbiomed.2011.01.007. https://www.ncbi.nlm.nih.gov/pubmed/21238581

Borrelli, F., Aviello, G., Romano, B., Orlando, P., Capasso, R., Maiello, F., Guadagno, F., Petrosino, S., Capasso, F., Di Marzo, V., Izzo, A.A. (2009). Cannabidiol, a safe and non-psychotropic ingredient of the

marijuana plant Cannabis sativa, is protective in a murine model of colitis. *J Mol Med (Berl)*. 87(11):1111-21. doi: 10.1007/s00109-009-0512-x. https://www.ncbi.nlm.nih.gov/pubmed/19690824

Braun, A., Engel, T., Aguilar-Pimentel, J.A., Zimmer, A., Jakob, T., Behrendt, H., Mempel, M. (2011) Beneficial effects of cannabinoids (CB) in a murine model of allergen-induced airway inflammation: Role of CB1/CB2 receptors.
Immunobiology, Volume 216, Issue 4, Pages 466-476

Burstein, S.H., Hunter, S.A. (1995). Stimulation of anandamide biosynthesis in N-18TG2 neuroblastoma cells by delta 9-tetrahydrocannabinol (THC). *Biochem Pharmacol*. 49(6):855-8.
https://www.ncbi.nlm.nih.gov/pubmed/7702643

Burstein, S. H., & Zurier, R. B. (2009). Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation. *The AAPS Journal*, 11(1), 109. http://doi.org/10.1208/s12248-009-9084-5
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664885/?tool=pubmed

Cabral,G.A., Griffin-Thomas, L. (2008). Cannabinoids as Therapeutic Agents for Ablating Neuroinflammatory Disease. *Endocr Metab Immune Disord Drug Targets*. 8(3): 159–172.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2750822/?tool=pmcentrez

Cabral, G.A., McNerney, P.J., Mishkin, E.M. (1987). Interaction of delta-9-tetrahydrocannabinol with rat B103 neuroblastoma cells. *Arch Toxicol*. 60(6):438-49.
http://www.ncbi.nlm.nih.gov/pubmed/2821958

Caffarel, M. M., Andradas, C., Mira, E., Pérez-Gómez, E., Cerutti, C., Moreno-Bueno, G., … Sánchez, C. (2010). Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Molecular Cancer*, *9*, 196. http://doi.org/10.1186/1476-4598-9-196
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917429/?tool=pmcentrez

Caffarel, M.M., Moreno-Bueno, G., Cerutti, C., Palacios, J., Guzman, M., Mechta-Grigoriou, F., Sanchez, C. (2008). JunD is involved in the antiproliferative effect of Delta9-tetrahydrocannabinol on human breast cancer cells. *Oncogene.* 27(37):5033-44. doi:10.1038/onc.2008.145.
https://www.ncbi.nlm.nih.gov/pubmed/18454173

Caffarel, M.M., Sarrió, D., Palacios, J., Guzmán, M., and Sánchez, C. (2006). Δ9-Tetrahydrocannabinol Inhibits Cell Cycle Progression in Human Breast Cancer Cells through Cdc2 Regulation. DOI**:** 10.1158/0008-5472.CAN-05-4566 *Cancer Research* (Cancer Res 2006; 66(13): 6615-21)
http://cancerres.aacrjournals.org/content/66/13/6615

Callaway, J.1., Schwab, U., Harvima, I., Halonen, P., Mykkänen, O., Hyvönen, P., Järvinen, T. (2005). Efficacy of dietary hempseed oil in patients with atopic dermatitis. *J Dermatolog Treat.* 16(2):87-94.
DOI: 10.1080/09546630510035832

Campbell, V.A., Gowran, A. (2007). Alzheimer's disease; taking the edge off with cannabinoids? *Br J Pharmacol.* 152(5): 655–662. doi: 10.1038/sj.bjp.0707446
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190031/?tool=pubmed

Carlini, E.A., Cunha, J.M. (1981). Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol*. 21(8-9 Suppl):417S-427S.
https://www.ncbi.nlm.nih.gov/pubmed/7028792

Carracedo, A., Gironella, M., Lorente, M., Garcia, S., Guzmán, M., Velasco, G., Iovanna, J.L. (2006). Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress–Related Genes. DOI: 10.1158/0008-5472.*CAN-06-0169*
http://cancerres.aacrjournals.org/content/66/13/6748

Carter, G.T., Abood, M.E., Aggarwal, S.K., Weiss, M.D. (2010) Cannabis and amyotrophic lateral sclerosis: hypothetical and practical applications, and a call for clinical trials. *Am J Hosp Palliat Care*. 27(5):347-56. doi: 10.1177/1049909110369531.

Carter, G.T., Rosen, B.S. (2001) Marijuana in the management of amyotrophic lateral sclerosis. *Am J Hosp Palliat Care***.** 18(4):264-70 (ISSN: 1049-9091)
http://www.medscape.com/medline/abstract/11467101

Casanova, M. L., Blázquez, C., Martínez-Palacio, J., Villanueva, C., Fernández-Aceñero, M. J., Huffman, J. W., … Guzmán, M. (2003). Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. *Journal of Clinical Investigation*, *111*(1), 43–50.
http://doi.org/10.1172/JCI200316116
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC151833/

Chakravarti, B., Ravi, J., & Ganju, R. K. (2014). Cannabinoids as therapeutic agents in cancer: current status and future implications. *Oncotarget*, *5*(15), 5852–5872.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171598/

Cianchi, F., Papucci, L., Schiavone, N., Lulli, M., Magnelli, L., Vinci, M.C., Messerini, L., Manera, C., Ronconi, E., Romagnani, P., Donnini, M., Perigli, G., Trallori, G., Tanganelli, E., Capaccioli, S., Masini, E.(2008). Cannabinoid Receptor Activation Induces Apoptosis through Tumor Necrosis Factor α–Mediated Ceramide *De novo* Synthesis in Colon Cancer Cells. *Clinical Cancer Research*. DOI: 10.1158/1078-0432.CCR-08-0799
http://clincancerres.aacrjournals.org/content/14/23/7691.long

Cilio, M.R., Thiele, E.A., Devinsky, O. (2014). The case for assessing cannabidiol in epilepsy. *Epilepsia*. 55(6):787-90. doi: 10.1111/epi.12635.
https://www.ncbi.nlm.nih.gov/pubmed/24854434

Comelli, F., Bettoni, I., Colleoni, M., Giagnoni, G., Costa, B. (2009). Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress. *Phytother Res*. 23(12):1678-84. doi: 10.1002/ptr.2806.
https://www.ncbi.nlm.nih.gov/pubmed/19441010

Consroe, P., Benedito, M.A., Leite, J.R., Carlini, E.A., Mechoulam, R. (1982). The differential effects of CBD suggest that the cannabinoid acts to inhibit seizure spread in the CNS by an action on GABA, but not glycine, mechanisms. *Eur J Pharmacol*. 83(3-4):293-8.
https://www.ncbi.nlm.nih.gov/pubmed/6129147

Consroe, P., Sandyk, R., Snider, S.R. (1986). Open label evaluation of cannabidiol in dystonic movement

disorders. *Int J Neurosci*. 30(4):277-82.
https://www.ncbi.nlm.nih.gov/pubmed/3793381

Contassot, E., Tenan, M., Schnüriger, V., Pelte, M.F., Dietrich, P.Y. (2004). Arachidonyl ethanolamide induces apoptosis of uterine cervix cancer cells via aberrantly expressed vanilloid receptor-1. *Gynecol Oncol.* 93(1):182-8.
https://www.ncbi.nlm.nih.gov/pubmed/15047233
Cox, M.L., Haller, V.L., Welch, S.P. (2007). The antinociceptive effect of Delta9-tetrahydrocannabinol in the arthritic rat involves the CB(2) cannabinoid receptor. *European journal of pharmacology.* 570:1-3 pg 50-6. PubMed ID
17588560 http://dx.doi.org/10.1016/j.ejphar.2007.05.024
http://www.sciencedirect.com/science/article/pii/S0014299907006255

Cox, M.L., Victoria L. Haller, V.L., Welch, S.P. (2007). Synergy between Δ^9-tetrahydrocannabinol and morphine in the arthritic rat. *European Journal of Pharmacology.*
http://dx.doi.org/10.1016/j.ejphar.2007.04.010. Volume 567, Issues 1–2, Pages 125–130
http://www.sciencedirect.com/science/article/pii/S0014299907004700
Croxford, J.L. (2003). Therapeutic potential of cannabinoids in CNS disease. *CNS Drugs*. 17(3):179-202.
https://www.ncbi.nlm.nih.gov/pubmed/12617697

Cudaback, E., Marrs, W., Moeller, T., & Stella, N. (2010). The Expression Level of CB1 and CB2 Receptors Determines Their Efficacy at Inducing Apoptosis in Astrocytomas. *PLoS ONE*, *5*(1), e8702.
http://doi.org/10.1371/journal.pone.0008702
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806825/?tool=pubmed

Cudaback, E., Stella. N. (2007). Targeting astrocytomas and invading immune cells with cannabinoids: a promising therapeutic avenue. *Mol Neurobiol.* 36(1):36-44.
https://www.ncbi.nlm.nih.gov/pubmed/17952650?dopt=Abstract

Davis, J.P., Ramsey, H.H. (1949). Anti-epileptic Action of Marijuana-Active Substances. Reprinted from *Federation Proceedings, Federation of American Society for Experimental Biology*, vol. 8, lY49, p. 284
https://docs.google.com/viewer?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbnxnZW9yZ2lhaGI4ODV8Z3g6N2QxNDZmNDFkMGExNmRiMQ

De Filippis, D., Esposito, G., Cirillo, C., Cipriano, M., De Winter, B. Y., Scuderi, C., ... Iuvone, T. (2011). Cannabidiol Reduces Intestinal Inflammation through the Control of Neuroimmune Axis. *PLoS ONE*, 6(12), e28159. http://doi.org/10.1371/journal.pone.0028159
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232190/?tool=pubmed

De Lago, E., Fernández-Ruiz, J. (2007) Cannabinoids and neuroprotection in motor-related disorders. *CNS Neurol Disord Drug Targets.* 6(6):377-87.
https://www.ncbi.nlm.nih.gov/pubmed/18220777

Denson, T.F., Earleywine, M. (2006). Decreased depression in marijuana users. *Addict Behav.* 31(4):738-42. DOI: 10.1016/j.addbeh.2005.05.052
https://www.ncbi.nlm.nih.gov/pubmed/15964704

Deshpande, L. S., Blair, R. E., Nagarkatti, N., Sombati, S., Martin, B. R., & DeLorenzo, R. J. (2007). Development of pharmacoresistance to benzodiazepines but not cannabinoids in the hippocampal neuronal culture model of status epilepticus. *Experimental Neurology*, *204*(2), 705–713. http://doi.org/10.1016/j.expneurol.2007.01.001 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2094113/?tool=pmcentrez

Díaz-Laviada, I. (2011). The endocannabinoid system in prostate cancer. *Nat Rev Urol*. 8(10):553-61. doi: 10.1038/nrurol.2011.130. https://www.ncbi.nlm.nih.gov/pubmed/21912423

Di Carlo, G., Izzo, A.A. (2003) Cannabinoids for gastrointestinal diseases: potential therapeutic applications. *Expert Opin Investig Drugs*. 12(1):39-49. DOI: 10.1517/13543784.12.1.39 https://www.ncbi.nlm.nih.gov/pubmed/12517253

Donadelli, M., Dando, I., Zaniboni, T., Costanzo, C., Pozza, E.D., Scupoli,M.T., Scarpa, A., Zappavigna, S., Marra, M., Abbruzzese, A., Bifulco, M., Caraglia, M., Palmieri, M. (2011). Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism. *Cell Death and Disease*. 2, e152; doi:10.1038/cddis.2011.36; http://www.nature.com/cddis/journal/v2/n4/pdf/cddis201136a.pdf

Durst, R., Danenberg, H., Gallily, R., Mechoulam, R., Meir, K., Grad, E., Beeri, R., Pugatsch, T., Tarsish, E., Lotan, C. (2007). Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. *Am J Physiol Heart Circ Physiol.* 293(6):H3602-7. DOI: 10.1152/ajpheart.00098.2007 https://www.ncbi.nlm.nih.gov/pubmed/17890433

Durst, R., Lotan, C. (2011). The Potential for Clinical Use of Cannabinoids in Treatment of Cardiovascular Diseases. *Cardiovascular Therapeutics* 29 (2011) 17–22 C doi:10.1111/j.1755-5922.2010.00233.x http://onlinelibrary.wiley.com/store/10.1111/j.1755-5922.2010.00233.x/asset/j.1755-5922.2010.00233.x.pdf;jsessionid=8D3E1645E47E2E19C725381FB5714BDF.f04t02?v=1&t=izooa9xi&s=f0a8ba9ba9eee48dc5870bfc205837e5baf64209

El-Alfy, A. T., Ivey, K., Robinson, K., Ahmed, S., Radwan, M., Slade, D., … Ross, S. (2010). Antidepressant-like effect of Δ9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa* L. *Pharmacology, Biochemistry, and Behavior*, *95*(4), 434–442. http://doi.org/10.1016/j.pbb.2010.03.004 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2866040/?tool=pubmed

El-Remessy, A. B., Al-Shabrawey, M., Khalifa, Y., Tsai, N.-T., Caldwell, R. B., & Liou, G. I. (2006). Neuroprotective and Blood-Retinal Barrier-Preserving Effects of Cannabidiol in Experimental Diabetes. *The American Journal of Pathology*, *168*(1), 235–244. doi: 10.2353/ajpath.2006.050500 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1592672/?tool=pubmed

Esposito, G., De Filippis, D., Carnuccio, R., Izzo, A.A., Iuvone, T. (2006). The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. *J Mol Med (Berl).* 84(3):253-8. https://www.ncbi.nlm.nih.gov/pubmed/16389547

Esposito, G., De Filippis, D., Maiuri, M.C., De Stefano, D., Carnuccio, R., Iuvone, T. (2006). Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. *Neurosci Lett.* 399(1-2):91-5.
https://www.ncbi.nlm.nih.gov/pubmed/16490313

Esposito, G., C Scuderi, C., Savani, C., Steardo, L.Jr., D De Filippis, D., P Cottone, P., Iuvone, T., V Cuomo, V., Steardo, L. (2007). Cannabidiol *in vivo* blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression. *Br J Pharmacol.* 151(8): 1272–1279.
doi： 10.1038/sj.bjp.0707337
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2189818/?tool=pmcentrez

Esposito, G., Scuderi, C., Valenza, M., Togna, G.I., Latina, V., De Filippis, D., Cipriano, M., Carratù, M.R., Iuvone, T., Steardo1, L. (2011) Cannabidiol Reduces Aβ-Induced Neuroinflammation and Promotes Hippocampal Neurogenesis through PPARγ Involvement. *PLoS One.* 6(12): e28668.
doi: 10.1371/journal.pone.0028668
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230631/?tool=pubmed

Eubanks, L.M., Rogers, C.J., Beuscher, A.E., Koob, G.F., Olson, A.J., Dickerson, T.J., Janda, K.D. (2006). A molecular link between the active component of marijuana and Alzheimer's disease pathology. *Mol Pharm.* 3(6): 773–777. doi: 10.1021/mp060066m
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562334/

Fernández-Ruiz, J. (2009). The endocannabinoid system as a target for the treatment of motor dysfunction. *Br J Pharmacol*. 156(7):1029-40. doi: 10.1111/j.1476-5381.2008.00088.x.
https://www.ncbi.nlm.nih.gov/pubmed/19220290

Fernández-Ruiz, J., Pazos, M.R., García-Arencibia, M., Sagredo, O., Ramos, J.A. (2008). Role of CB2 receptors in neuroprotective effects of cannabinoids. *Mol Cell Endocrinol*. 286(1-2 Suppl 1):S91-6. doi: 10.1016/j.mce.2008.01.001.
https://www.ncbi.nlm.nih.gov/pubmed/18291574

Fiz, J., Durán, M., Capellà, D., Carbonell, J., & Farré, M. (2011). Cannabis Use in Patients with Fibromyalgia: Effect on Symptoms Relief and Health-Related Quality of Life. *PLoS ONE*, 6(4), e18440.
http://doi.org/10.1371/journal.pone.0018440
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3080871/?tool=pubmed

Flygare, J., Gustafsson, K., Kimby, E., Christensson, B., Sander, B. (2005). Cannabinoid receptor ligands mediate growth inhibition and cell death in mantle cell lymphoma. *FEBS Lett.* 579(30):6885-9. DOI: 10.1016/j.febslet.2005.11.020
https://www.ncbi.nlm.nih.gov/pubmed/16337199?dopt=Abstract

Foroughi, M., Hendson, G., Sargent, M.A., Steinbok, P. (2011). Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas--possible role of Cannabis inhalation. *Childs Nerv Syst*. 27(4):671-9. doi: 10.1007/s00381-011-1410-4. DOI: 10.1007/s00381-011-1410-4

Fowler, C.J., Gustafsson, S.B., Chung, S.C., Persson, E., Jacobsson, S.O., Bergh, A. (2010). Targeting the endocannabinoid system for the treatment of cancer--a practical view. *Curr Top Med Chem*. 10(8):814-27.
https://www.ncbi.nlm.nih.gov/pubmed/20370711?dopt=Abstract

Fraga, D., Raborn, E.S., Ferreira, G.A., Cabral, G.A. (2011). Cannabinoids inhibit migration of microglial-like cells to the HIV protein Tat. *J Neuroimmune Pharmacol.* 6(4):566-77. DOI: 10.1007/s11481-011-9291-6 https://www.ncbi.nlm.nih.gov/pubmed/21735070

Freimuth, N., Ramer. R., Hinz, B. (2010). Antitumorigenic effects of cannabinoids beyond apoptosis. *J Pharmacol Exp Ther*. 332(2):336-44. doi: 10.1124/jpet.109.157735.
https://www.ncbi.nlm.nih.gov/pubmed/19889794

Fride, E. (2002). Cannabinoids and Cystic Fibrosis: A Novel Approach to Etiology and Therapy. *Journal of Cannabis Therapeutics*, Vol. 2(1)
http://www.cannabis-med.org/data/pdf/2002-01-2.pdf

Fride, E. (2004). The endocannabinoid-CB receptor system: Importance for development and in pediatric disease. *Neuro Endocrinol Lett*. 25(1-2):24-30.

Gaffal, E., Cron, M., Glodde, N., Tüting, T. (2013). Anti-inflammatory activity of topical THC in DNFB-mediated mouse allergic contact dermatitis independent of CB1 and CB2 receptors. *Allergy*. 68(8):994-1000. doi: 10.1111/all.12183. Epub 2013 Jul 29.

Galanti, G., Fisher, T., Kventsel, I., Shoham, J., Gallily, R., Mechoulam, R., Lavie, G., Amariglio, N., Rechavi, G., Toren, A. (2008). Delta 9-tetrahydrocannabinol inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells. *Acta Oncol*. 47(6):1062-70. DOI: 10.1080/02841860701678787
http://www.ncbi.nlm.nih.gov/pubmed/17934890

Gallant, M., Odei-Addo, F., Frost, C.L., Levendal, R.A. (2009). Biological effects of THC and a lipophilic cannabis extract on normal and insulin resistant 3T3-L1 adipocytes. *Phytomedicine*. 16(10):942-9. doi: 10.1016/j.phymed.2009.02.013.
https://www.ncbi.nlm.nih.gov/pubmed/19345076
Gallily, R., Even-Chena, T., Katzavian, G., Lehmann, D., Dagan, A., Mechoulam, R. (2003). Gamma-irradiation enhances apoptosis induced by cannabidiol, a non-psychotropic cannabinoid, in cultured HL-60 myeloblastic leukemia cells. *Leuk Lymphoma*. 44(10):1767-73. DOI: 10.1080/1042819031000103917

Galve-Roperh, I., Sánchez, C., Cortés, M.L., Gómez del Pulgar,T., Izquierdo, M., Guzmán, M. (2000). Anti-tumoral action of cannabinoids: Involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nature Medicine* **6**, 313 – 319. doi:10.1038/73171

Gallily, R., Even-Chena, T., Katzavian, G., Lehmann, D., Dagan, A., Mechoulam, R. (2003). Gamma-irradiation enhances apoptosis induced by cannabidiol, a non-psychotropic cannabinoid, in cultured HL-60 myeloblastic leukemia cells. *Leuk Lymphoma*. 44(10):1767-73. DOI: 10.1080/1042819031000103917

Gauter, B., Rukwied, R., Konrad, C. (2004). Cannabinoid agonists in the treatment of blepharospasm--a case report study. *Neuro Endocrinol Lett*. 25(1-2):45-8.
https://www.ncbi.nlm.nih.gov/pubmed/15159681

Gertsch, J. (2008). Anti-inflammatory cannabinoids in diet: Towards a better understanding of CB2 receptor action? *Communicative &Integrative Biology*, 1(1), 26–28. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2633791/?tool=pmcentrez

Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J.-Z., Xie, X.-Q., ... Zimmer, A. (2008). Beta-caryophyllene is a dietary cannabinoid. *Proceedings of the National Academy of Sciences of the United States of America*, 105(26), 9099–9104 http://doi.org/10.1073/pnas.0803601105 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2449371/?tool=pmcentrez

Ghosh, P., Bhattacharya, S.K. (1978). Anticonvulsant action of cannabis in the rat: role of brain monoamines. *Psychopharmacology (Berl)*. 59(3):293-7. https://www.ncbi.nlm.nih.gov/pubmed/104333

Gong, H. Jr., Tashkin, D.P., Simmons, M.S., Calvarese, B., Shapiro, B.J., (1984). Acute and subacute bronchial effects of oral cannabinoids. *Clinical Pharmacology and Therapeutics* 35(1): 26-32 http://doi.org/10.4155/fmc.09.93 http://www.cannabis-med.org/studies/ww_en_db_study_show.php?s_id=44

Greenhough, A., Patsos, H.A., Williams, A.C. et al. (2007). The cannabinoid δ9-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. *Int J Cancer* 21:2172–80. https://www.ncbi.nlm.nih.gov/pubmed/17583570

Grinspoon, L. (2010) A Novel Approach to the Symptomatic Treatment of Autism http://www.beyondthc.com/wp-content/uploads/2013/08/GrinspoonAutism.pdf

Gruber, A.J., Pope, H.G. Jr., Brown, M.E. (1996). Do patients use marijuana as an antidepressant? *Depression*. 4(2):77-80. DOI: 10.1002/(SICI)1522-7162(1996)4:2<77::AID-DEPR7>3.0.CO;2-C

Guerrero, A. V., Quang, P., Dekker, N., Jordan, R. C. K., & Schmidt, B. L. (2008). Peripheral Cannabinoids Attenuate Carcinoma Induced Nociception in Mice. *Neuroscience Letters*, *433*(2), 77–81. http://doi.org/10.1016/j.neulet.2007.12.053 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771220/

Guindon, J. and Hohmann, A. G. (2011), The endocannabinoid system and cancer: therapeutic implication. British Journal of Pharmacology, 163: 1447–1463. doi:10.1111/j.1476-5381.2011.01327.x http://onlinelibrary.wiley.com/doi/10.1111/j.1476-5381.2011.01327.x/full

Gustafsson, S.B., Lindgren, T., Jonsson, M. et al. (2009). Cannabinoid receptor-independent cytotoxic effects of cannabinoids in human colorectal carcinoma cells: synergism with 5-fluorouracil. *Cancer Chemother Pharmacol*. 63: 691. doi:10.1007/s00280-008-0788-5 http://link.springer.com/article/10.1007%2Fs00280-008-0788-5

Gustafsson, K., Wang, X., Severa, D., Eriksson, M., Kimby, E., Merup, M., Christensson, B., Flygare, J., Sander, B. (2008). Expression of cannabinoid receptors type 1 and type 2 in non-Hodgkin lymphoma: growth inhibition by receptor activation. *Int J Cancer*. 123(5):1025-33. doi: 10.1002/ijc.23584. https://www.ncbi.nlm.nih.gov/pubmed/18546271

Guzmán, M. (2005). Effects on cell viability. *Handb Exp Pharmacol.* (168):627-42. https://www.ncbi.nlm.nih.gov/pubmed/16596790

Guzmán, M., Duarte, M.J., Blázquez, C., Ravina, J., Rosa, M.C., Galve-Roperh, I., Sánchez, C., Velasco, G., González-Feria, L. (2006). A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer.* 95(2): 197–203. doi: 10.1038/sj.bjc.6603236 https://www.ncbi.nlm.nih.gov/pubmed/16804518

Hamelink, C., Hampson, A., Wink, D.A., Eiden L.E. and Robert L. Eskay R.L. (2005) Cannabidiol, Antioxidants, and Diuretics in Reversing Binge Ethanol-Induced Neurotoxicity. *Journal of Pharmacology and Experimental Therapeutics* 314 (2) 780-788; DOI:https://doi.org/10.1124/jpet.105.085779

Hamtiaux, L., Hansoulle, L., Dauguet, N., Muccioli, G. G., Gallez, B., & Lambert, D. M. (2011). Increasing Antiproliferative Properties of Endocannabinoids in N1E-115 Neuroblastoma Cells through Inhibition of Their Metabolism. *PLoS ONE*, *6*(10), e26823. http://doi.org/10.1371/journal.pone.0026823 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3203169/?tool=pubmed

Hartley, J. P., Nogrady, S. G., & Seaton, A. (1978). Bronchodilator effect of delta1-tetrahydrocannabinol. *British Journal of Clinical Pharmacology*, 5(6), 523–525. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1429361/

Hepburn, C.Y., Walsh, S.K., Wainwright, C.L. (2011). Cannabidiol as an anti-arrhythmic, the role of the CB1 receptors *Heart.* 97:e8. http://dx.doi.org/10.1136/heartjnl-2011-301156.17 http://heart.bmj.com/content/97/24/e8.9

Hermanson, D.J., Marnett, L.J. (2011). Cannabinoids, endocannabinoids, and cancer. *Cancer Metastasis Rev*. 30(3-4):599-612. doi: 10.1007/s10555-011-9318-8. https://www.ncbi.nlm.nih.gov/pubmed/22038019

Hill, A.J., Weston, S.E., Jones, N.A., Smith, I., Bevan, S.A., Williamson, E.M., Stephens G.J., Williams, C.M., Whalley, B.J. (2010). Δ^9-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia*. 51(8):1522-32. doi:10.1111/j.1528-1167.2010.02523.x. https://www.ncbi.nlm.nih.gov/pubmed/20196794

Horváth, B., Mukhopadhyay, P., Haskó, G., Pacher, P. (2012). The endocannabinoid system and plant-derived cannabinoids in diabetes and diabetic complications. *Am J Pathol*. 180(2):432-42. doi: 10.1016/j.ajpath.2011.11.003. http://www.ncbi.nlm.nih.gov/pubmed/22155112

Howlett, A.C. (1984). Inhibition of neuroblastoma adenylate cyclase by cannabinoid and nantradol compounds. *Life Sci*. 35(17):1803-10. https://www.ncbi.nlm.nih.gov/pubmed/6090851

Howlett, A.C., Fleming, R.M. (1984). Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membranes. *Mol Pharmacol*. 26(3):532-8. https://www.ncbi.nlm.nih.gov/pubmed/6092901

Iuvone, T., Esposito, G., Esposito, R., Santamaria, R., Di Rosa, M., Izzo, A.A. (2004) Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem.* 89(1):134-41.
https://www.ncbi.nlm.nih.gov/pubmed/15030397

Izzo, A.A., Camilleri, M. (2008). Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. *Gut.* 57(8):1140-55. doi: 10.1136/gut.2008.148791.
https://www.ncbi.nlm.nih.gov/pubmed/18397936

Izzo, A.A., Camilleri, M.E. (2008). Merging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. *Gut.* 57:1140-1155.
http://dx.doi.org/10.1136/gut.2008.148791

Izzo, A.A., Camilleri, M. (2009). Cannabinoids in intestinal inflammation and cancer. *Pharmacol Res.* 60(2):117-25. doi: 10.1016/j.phrs.2009.03.008.
https://www.ncbi.nlm.nih.gov/pubmed/19442536

Jamontt, J., Molleman, A., Pertwee, R., & Parsons, M. (2010). The effects of Δ9-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and *in vitro* motility disturbances in rat colitis. *British Journal of Pharmacology*, *160*(3), 712–723. http://doi.org/10.1111/j.1476-5381.2010.00791.x
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931570/?tool=pubmed

Jia, W., Hegde, V.L., Singh, N.P., Sisco, D., Grant, S., Nagarkatti, M., Nagarkatti, P.S. (2006). Δ9-Tetrahydrocannabinol-Induced Apoptosis in Jurkat Leukemia T Cells Is Regulated by Translocation of Bad to Mitochondria. *molecular cancer research.*
DOI: 10.1158/1541-7786.MCR-05-0193
http://mcr.aacrjournals.org/content/4/8/549

Jiang, W., Zhang, Y., Xiao, L., Van Cleemput, J., Ji, S., Bai, G., Zhang, X. (2005). Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. *J Clin Invest.* 115(11):3104-3116. doi:10.1172/JCI25509.
http://www.jci.org/articles/view/25509

Johnson, J.R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E.D., Potts, R., Fallon, M.T. (2010). Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 39(2):167-79. doi:10.1016/j.jpainsymman.2009.06.008.

Jones, N. A., Hill, A. J., Smith, I., Bevan, S. A., Williams, C. M., Whalley, B. J., & Stephens, G. J. (2010). Cannabidiol Displays Antiepileptiform and Antiseizure Properties In Vitro and In Vivo. *The Journal of Pharmacology and Experimental Therapeutics*, *332*(2), 569–577.
http://doi.org/10.1124/jpet.109.159145
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2819831/?tool=pmcentrez

Jones, S., Howl, J. (2003). Cannabinoid receptor systems: therapeutic targets for tumour intervention. *Expert Opin Ther Targets*. 7(6):749-58. DOI: 10.1517/14728222.7.6.749
https://www.ncbi.nlm.nih.gov/pubmed/14640910

Karler, R., Turkanis, S.A. (1981). The cannabinoids as potential antiepileptics. *J Clin Pharmacol.* 21(8-9 Suppl):437S-448S.
https://www.ncbi.nlm.nih.gov/pubmed/6975285

Karsak, M., Gaffal, E., Date, R., Wang-Eckhardt, L., Rehnelt, J., Petrosino, S., Starowicz, K., Steuder, R., Schlicker, E., Cravatt, B., Mechoulam, R., Buettner, R., Werner, S., Di Marzo, V., Tüting, T., Zimmer, A. (2007). Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science*. 316(5830):1494-7. DOI:10.1126/science.1142265

Kimball, E.S., Schneider, C.R., Wallace, N.H., Hornby, P.J. (2006). Agonists of cannabinoid receptor 1 and 2 inhibit experimental colitis induced by oil of mustard and by dextran sulfate sodium. *American Journal of Physiology - Gastrointestinal and Liver Physiology*. Vol. 291 no. 2, G364-G371 DOI: 10.1152/ajpgi.00407.2005
http://ajpgi.physiology.org/content/291/2/G364

Kunos, G., & Pacher, P. (2004). Cannabinoids cool the intestine. *Nature Medicine*, 10(7), 678–679. http://doi.org/10.1038/nm0704-678]
http://www.gastrojournal.org/article/PIIS0016508505009297/abstract
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1859999/?tool=pmcentrez
https://www.ncbi.nlm.nih.gov/pubmed/19442536?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_R

Kuo, P., Holloway, R.H. (2010) Beyond acid suppression: new pharmacologic approaches for treatment of GERD. *Curr Gastroenterol Rep*. 12(3):175-80. doi: 10.1007/s11894-010-0102-7.
https://www.ncbi.nlm.nih.gov/pubmed/20425477

Kurz, R., Lindengasse, K,B. (2010). Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child. *Cannabinoids*;5(4):4-6
http://www.cannabis-med.org/data/pdf/en_2010_04_1.pdf

Lancz, G., Specter, S., Brown, H.K. (1991) Suppressive effect of delta-9-tetrahydrocannabinol on herpes simplex virus infectivity in vitro. *Proc Soc Exp Biol Med*. 196(4):401-4.
https://www.ncbi.nlm.nih.gov/pubmed/1848937?dopt=Abstract

La Porta, C., Bura, S.A., Negrete, R., Maldonado, R. (2014). Involvement of the endocannabinoid system in osteoarthritis pain. *Eur J Neurosci.* 39(3):485-500. doi:10.1111/ejn.12468.
https://www.ncbi.nlm.nih.gov/pubmed/24494687

Lee, M.J., Park, S.H., Han, J.H., Hong, Y.K., Hwang, S., Lee, S., Kim, D., Han, S.Y., Kim, E.S., Cho, K.S. (2011). The effects of hempseed meal intake and linoleic acid on Drosophila models of neurodegenerative diseases and hypercholesterolemia. *Mol Cells*. 31(4):337-42. doi: 10.1007/s10059-011-0042-6.
https://www.ncbi.nlm.nih.gov/pubmed/21331775

Leelawat, S., Leelawat, K., Narong, S., Matangkasombut, O. (2010). The dual effects of delta(9)-tetrahydrocannabinol on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration. *Cancer Invest.* 28(4):357-63. doi: 10.3109/07357900903405934.
https://www.ncbi.nlm.nih.gov/pubmed/19916793

Lew, G.M. (1996). Tau protein after delta-9-tetrahydrocannabinol in a human neuroblastoma cell line. *Gen Pharmacol.* 27(7):1141-3.
https://www.ncbi.nlm.nih.gov/pubmed/8981058

Liang, C., McClean, M. D., Marsit, C., Christensen, B., Peters, E., Nelson, H. H., & Kelsey, K. T. (2009). A Population-based Case-Control Study of Marijuana Use and Head and Neck Squamous Cell Carcinoma. *Cancer Prevention Research (Philadelphia, Pa.)*, *2*(8), 759–768. http://doi.org/10.1158/1940-6207.CAPR-09-0048
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2812803/?tool=pubmed

Ligresti, A., Moriello, A.S., Starowicz, K., Matias, I., Pisanti, S., De Petrocellis, L., Laezza, C., Portella, G., Bifulco, M., and Di Marzo, V. (2006). Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma. *The Journal of Pharmacology and Experimental Therapeutics* Vol. 318, No. 3 JPET 318:1375–1387
http://jpet.aspetjournals.org/content/jpet/318/3/1375.full.pdf !!***!! Read with care p. 1384-7

Liou, G. I. (2010). Diabetic retinopathy: Role of inflammation and potential therapies for anti-inflammation. *World Journal of Diabetes*, *1*(1), 12–18. http://doi.org/10.4239/wjd.v1.i1.12
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3083879/

Liou, G. I., A.Auchampach, J., Hillard, C. J., Zhu, G., Yousufzai, B., Mian, S., … Khalifa, Y. (2008). Mediation of Cannabidiol anti-inflammation in the Retina by Equilibrative Nucleoside Transporter and A2A Adenosine Receptor*. *Investigative Ophthalmology & Visual Science*, *49*(12), 5526–5531. http://doi.org/10.1167/iovs.08-2196
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2588644/?tool=pmcentrez

Liou, G.I., El–Remessy, A.B., Al–Shabrawey, M., Tsai, N.J., Roon, P., Caldwell, R.B. (2004). Cannabidiol Preserves Retinal Neurons and Reduces Vascular Permeability in Experimental Diabetes . *Invest. Ophthalmol. Vis. Sci.* 45(13):860. http://iovs.arvojournals.org/article.aspx?articleid=2406667

Liou, G., El-Remessy, A., Ibrahim, A., Caldwell, R., Khalifa, Y., Gunes, A., & Nussbaum, J. (2009). Cannabidiol As a Putative Novel Therapy for Diabetic Retinopathy: A Postulated Mechanism of Action as an Entry Point for Biomarker-Guided Clinical Development. *Current Pharmacogenomics and Personalized Medicine*, *7*(3), 215–222.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2955420/?tool=pubmed

Liou, G.I., El-Shishtawy, M.M., Ibrahim, A.S. (2011). Cannabidiol Dampens Streptozotocin-Induced Retinal Inflammation by Targeting of Microglial Activation. *Invest. Ophthalmol. Vis. Sci.* 52(14):1002. http://iovs.arvojournals.org/article.aspx?articleid=2350760

Liu, D.Z., Hu, C.M., Huang C.H., Wey S.P., Jan T.R. (2010)
Cannabidiol attenuates delayed-type hypersensitivity reactions via suppressing T-cell and macrophage reactivity. *Acta Pharmacol Sin*. (12):1611-7. doi: 10.1038/aps.2010.155.
https://www.ncbi.nlm.nih.gov/pubmed/21042286

Liu, W.M., Fowler, D.W., Dalgleish, A.G. (2010). Cannabis-derived substances in cancer therapy--an emerging anti-inflammatory role for the cannabinoids. *Curr Clin Pharmacol*. 5(4):281-7.
https://www.ncbi.nlm.nih.gov/pubmed/20925645

Liu, W.M., Scott, K.A., Shamash, J., Joel, S., Powles, T.B. (2008). Enhancing the in vitro cytotoxic activity of Delta9-tetrahydrocannabinol in leukemic cells through a combinatorial approach. *Leuk Lymphoma*. 49(9):1800-9. doi:10.1080/10428190802239188.
https://www.ncbi.nlm.nih.gov/pubmed/18608861

Lorente, M., Torres, S., Salazar, M., Carracedo, A., Hernández-Tiedra, S., Rodríguez-Fornés, F., García-Taboada, E., Meléndez, B., Mollejo, M., Campos-Martín, Y., Lakatosh, S.A., Barcia, J., Guzmán, M., Velasco, G. (2011). Stimulation of the midkine/ALK axis renders glioma cells resistant to cannabinoid antitumoral action. *Cell Death Differ.* 18(6):959-73. doi:10.1038/cdd.2010.170.
DOI:10.1038/cdd.2010.170
https://www.ncbi.nlm.nih.gov/pubmed/21233844

Lorenz, R., (2004). On the application of cannabis in paediatrics and epileptology. *Neuro Endocrinol Lett*. 25(1-2):40-4.
https://www.ncbi.nlm.nih.gov/pubmed/15159680

Lu, D., Kiran, V., Duclos, R.I. Jr., Makriyannis, A. (2006). The Cannabinergic System as a Target for Anti-inflammatory Therapies *Current Topics in Medicinal Chemistry,* Volume 6, Number 13, pp. 1401-1426(26)
http://www.ingentaconnect.com/content/ben/ctmc/2006/00000006/00000013/art00008

Ma, Y.-L., Weston, S. E., Whalley, B. J., & Stephens, G. J. (2008). The phytocannabinoid Δ9-tetrahydrocannabivarin modulates inhibitory neurotransmission in the cerebellum. *British Journal of Pharmacology*, *154*(1), 204–215. http://doi.org/10.1038/bjp.2008.57
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2438968/?tool=pubmed

Maccarrone, M., Lorenzon, T., Bari, M., Melino, G., Finazzi-Agro, A. (2000). Anandamide induces apoptosis in human cells via vanilloid receptors. Evidence for a protective role of cannabinoid receptors. *J Biol Chem*. 275(41):31938-45.
http://www.jbc.org/content/275/41/31938.full
https://www.ncbi.nlm.nih.gov/pubmed/10913156

Mach, F., Montecucco, F., & Steffens, S. (2008). Cannabinoid receptors in acute and chronic complications of atherosclerosis. *British Journal of Pharmacology*, *153*(2), 290–298.
http://doi.org/10.1038/sj.bjp.0707517
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2219535/?tool=pmcentrez

Mach, F., Montecucco, F., & Steffens, S. (2008). Cannabinoid receptors in acute and chronic complications of atherosclerosis. *British Journal of Pharmacology*, *153*(2), 290–298.
http://doi.org/10.1038/sj.bjp.0707517
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2219535/?tool=pmcentrez

Marcu1, J.P., Christian, R.T., Lau, D., Zielinski, A.J., Horowitz, M.P., Lee, J., Pakdel, A., Allison, J., Limbad, C. (2010). Cannabidiol Enhances the Inhibitory Effects of Δ9 -Tetrahydrocannabinol on Human Glioblastoma Cell Proliferation and Survival. *Mol Cancer Ther*; 9(1) January 2010 DOI: 10.1158/1535-7163.MCT-09-0407
https://www.ncbi.nlm.nih.gov/pubmed/20053780
http://www.letfreedomgrow.com/cmu/Brain_Cancer_Study.pdf p. 180

Martin-Moreno, A.M., Reigada, D., Ramirez, B.G., Mechoulam, R., Innamorato, N., Cuadrado, A., de Ceballos, M.L. (2011) Cannabidiol and other cannabinoids reduce microglial activation *in vitro* and *in vivo*: relevance to Alzheimers′ disease
Molecular Pharmacology. mol.111.071290; DOI:https://doi.org/10.1124/mol.111.071290
http://molpharm.aspetjournals.org/content/early/2011/02/24/mol.111.071290.long

Massi, P., Vaccani, A., Bianchessi, S., Costa, B., Macchi, P., Parolaro, D. (2006). The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells. *Cell Mol Life Sci.* 63(17):2057-66. DOI: 10.1007/s00018-006-6156-x
https://www.ncbi.nlm.nih.gov/pubmed/16909207?dopt=Abstract

Massi, P., Vaccani, A., Ceruti, S., Colombo, A., Abbracchio, M.P., Parolaro, D. (2004). Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther.* 308(3):838-45. Epub 2003 Nov 14. DOI:10.1124/jpet.103.061002
https://www.ncbi.nlm.nih.gov/pubmed/14617682

Massi, P., Valenti, M., Solinas, M., Parolaro, D. (2010). Molecular Mechanisms Involved in the Antitumor Activity of Cannabinoids on Gliomas: Role for Oxidative Stress. *Cancers*. *2*(2), 1013-1026; doi:10.3390/cancers2021013
http://www.mdpi.com/2072-6694/2/2/1013

Massi, P., Valenti, M., Vaccani, A., Gasperi, V., Perletti, G., Marras, E., Fezza, F., Maccarrone, M., Parolaro, D. (2008). 5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid. J *Neurochem*. 104(4):1091-100. Epub 2007 Nov 17. DOI: 10.1111/j.1471-4159.2007.05073.x
https://www.ncbi.nlm.nih.gov/pubmed/18028339

McAllister, S.D., Chan, C., Taft, R.J., Luu, T., Abood, M.E., Moore, D.H., Aldape, K., Yount, G. (2005). Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells. *J Neurooncol.* 74(1):31-40.
https://www.ncbi.nlm.nih.gov/pubmed/16078104?dopt=Abstract

McAllister, S. D., Murase, R., Christian, R. T., Lau, D., Zielinski, A. J., Allison, J., … Desprez, P.-Y. (2011). Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Research and Treatment*, *129*(1), 37–47.
http://doi.org/10.1007/s10549-010-1177-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3410650/

McAllister, S.D., Rigel, T., Christian, M.P., Horowitz, A. G., Desprez, P. (2007). Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. *molecular cancer therapeutics.* DOI**:** 10.1158/1535-7163.MCT-07-0371
http://mct.aacrjournals.org/content/6/11/2921.long

McKallip, R.J., Jia, W., Schlomer, J., Warren, J.W., Nagarkatti, P.S., Nagarkatti, M. (2006). Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in the regulation of p22phox and Nox4 expression. *Mol Pharmacol*.
https://www.ncbi.nlm.nih.gov/pubmed/16754784

McKallip, R.J., Lombard, C., Fisher, M., Martin, B.R., Ryu, S., Grant, S., Nagarkatti, P.S., Nagarkatti, M. (2002). Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. *BLOOD*. VOLUME 100, NUMBER 2 p. 627. DOI 10.1182/ blood-2002-01-0098. http://bloodjournal.hematologylibrary.org/cgi/reprint/100/2/627.pdf https://www.ncbi.nlm.nih.gov/pubmed/12091357

McLaughlin, R.J., Gobbi, G. (2012). Cannabinoids and emotionality: a neuroanatomical perspective. *Neuroscience*. 204:134-44. doi: 10.1016/j.neuroscience.2011.07.052. https://www.ncbi.nlm.nih.gov/pubmed/21827834

Mechoulam, R,. Panikashvili, D., Shohami, E. (2002). Cannabinoids and brain injury: therapeutic implications. *TRENDS in Molecular Medicine* Vol.8 No.2 http://www.ukcia.org/research/CannabinoidsAndBrainInjury.pdf

Medveczky, M.M., Sherwood, T.A., Klein, T.W., Friedman, H., & Medveczky, P.G. (2004). Delta-9 tetrahydrocannabinol (THC) inhibits lytic replication of gamma oncogenic herpesviruses in vitro. *BMC Medicine*, 2, 34. http://doi.org/10.1186/1741-7015-2-34 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC521080/?tool=pmcentrez

Melck, D., De Petrocellis, L., Orlando, P., Bisogno, T., Laezza, C., Bifulco, M., Di Marzo, V. (2000). Suppression of Nerve Growth Factor Trk Receptors and Prolactin Receptors by Endocannabinoids Leads to Inhibition of Human Breast and Prostate Cancer Cell Proliferation. *Endocrinology* 2000; 141 (1): 118-126. doi:10.1210/endo.141.1.7239

Michalski, C. W., Oti, F. E., Erkan, M., Sauliunaite, D., Bergmann, F., Pacher, P., … Kleeff, J. (2008). Cannabinoids in pancreatic cancer: Correlation with survival and pain. *International Journal of Cancer. Journal International Du Cancer*, *122*(4), 742–750. http://doi.org/10.1002/ijc.23114 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225529/?tool=pmcentrez

Mimeault, M., Pommery, N., Wattez, N., Bailly, C., Hénichart, J.P. (2003). Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. *Prostate.* 56(1):1-12. DOI: 10.1002/pros.10190 https://www.ncbi.nlm.nih.gov/pubmed/12746841?dopt=Abstract

Minocci, D., Massei, J., Martino, A., Milianti, M., Piz, L., Di Bello, D., Sbrana, A., Martinotti, E., Rossi, A.M., Nieri, P. (2011). Genetic association between bipolar disorder and 524A>C (Leu133Ile) polymorphism of CNR2 gene, encoding for CB2 cannabinoid receptor. *J Affect Disord*. Nov;134(1-3):427-30. doi:10.1016/j.jad.2011.05.023. https://www.ncbi.nlm.nih.gov/pubmed/21658778

Molina, P.E., Amedee, A., LeCapitaine, N.J., Zabaleta, J., Mohan, M., Winsauer, P., Vande Stouwe, C. (2011). Cannabinoid neuroimmune modulation of SIV disease. *J Neuroimmune Pharmacol.* 6(4):516–527. DOI: 10.1007/s11481-011-9301-8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208744/

Molina, P.E., Winsauer, P., Zhang, P., Walker, E., Birke, L., Amedee, A., Stouwe, C.V., Troxclair, D., McGoey, R., Varner, K., Byerley, L., LaMotte, L. (2011). Cannabinoid administration attenuates the

progression of simian immunodeficiency virus. *AIDS Res Hum Retroviruses.* 27(6). 585-92. DOI: 10.1089/AID.2010.0218
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131805/

Moreno, E., Andradas, C., Medrano, M., Caffarel, M.M., Perez-Gomez, E., Blasco-Benito, S., Gomez-Canas, M., Pazos, M.R., Irving, A.J., Lluis, C., Canela, E.I., Fernandez-Ruiz, J., Guzman, M., McCormick, P.J., Sanchez, C. (2014). Targeting CB2-GPR55 Receptor Heteromers Modulates Cancer Cell Signaling. *Journal of Biological Chemistry*. DOI:10.1074/jbc.M114.561761

Moss, D.E., McMaster, S.B., Rogers, J. (1981). Tetrahydrocannabinol potentiates reserpine-induced hypokinesia. *Pharmacol Biochem Behav*. 15(5):779-83.
https://www.ncbi.nlm.nih.gov/pubmed/6273940

Munson, A.E., Harris, L.S., Friedman, M.A., Dewey, W.L., Carchman, R.A. (1975). Antineoplastic activity of cannabinoids. Journal *of the National Cancer Institute*, Vol. 55, No. 3.
http://www.ukcia.org/research/AntineoplasticActivityOfCannabinoids/index.php

Munson, A.E., Harris, L.S., Friedman, M.A., Dewey, W.L., Carchman, R.A. (1975). Anticancer activity of cannabinoids. *Journal of the National Cancer Institute*. Vol. 55, No. 3, pp.597-602
http://drugpolicycentral.com/bot/pg/cancer/THC_cancer_sep_1975.htm

Murison, G. ; Chubb, C.B.H. ; Maeda, S. ; Gemmell, M.A. ; Huberman, E. (1987). Cannabinoids induce incomplete maturation of cultured human leukemia cells. *Proc. Natl. Acad. Sci*. (United States); Journal Volume: 84:15. DOI:10.1073/pnas.84.15.5414

Nagarkatti, P., Pandey, R., Rieder, S. A., Hegde, V. L., & Nagarkatti, M. (2009). Cannabinoids as novel anti-inflammatory drugs. *Future Medicinal Chemistry,* 1(7), 1333–1349. http://doi.org/10.4155/fmc.09.93
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2828614/?tool=pubmed

Nithipatikom, K., Gomez-Granados, A.D., Tang, A.T., Pfeiffer, A.W., Williams, C.L., Campbell, W.B. (2012). Cannabinoid receptor type 1 (CB1) activation inhibits small GTPase RhoA activity and regulates motility of prostate carcinoma cells. *Endocrinology*. 153(1):29-41. doi: 10.1210/en.2011-1144.
https://www.ncbi.nlm.nih.gov/pubmed/22087025

Oesch, S., Gertsch, J. (2009). Cannabinoid receptor ligands as potential anticancer agents--high hopes for new therapies? *J Pharm Pharmacol*. 61(7):839-53. doi:10.1211/jpp/61.07.0002.
https://www.ncbi.nlm.nih.gov/pubmed/19589225?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=14

Olea-Herrero, N., Vara, D., Malagarie-Cazenave, S., Díaz-Laviada, I. (2009). The cannabinoid R+ methanandamide induces IL-6 secretion by prostate cancer PC3 cells. J *Immunotoxicol*. 6(4):249-56. doi: 10.3109/15476910903241696.
https://www.ncbi.nlm.nih.gov/pubmed/19908944

Olea-Herrero, N., Vara, D., Malagarie-Cazenave, S., Díaz-Laviada, I. (2009). Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB_2. *British Journal of Cancer*. 101, 940–950. doi:10.1038/sj.bjc.6605248
http://www.nature.com/bjc/journal/v101/n6/full/6605248a.html

Pacher, P., & Steffens, S. (2009). The emerging role of the endocannabinoid system in cardiovascular disease. *Seminars in Immunopathology*, *31*(1), 63–77. http://doi.org/10.1007/s00281-009-0145-8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2791499/?tool=pmcentrez

Pacher, P., & Ungvári, Z. (2008). Pleiotropic effects of the CB2 cannabinoid receptor activation on human monocyte migration: implications for atherosclerosis and inflammatory diseases. *American Journal of Physiology. Heart and Circulatory Physiology*, *294*(3), H1133–H1134. http://doi.org/10.1152/ajpheart.00020.2008 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267750/?tool=pubmed

Parolaro, D., Massi, P. (2008). Cannabinoids as potential new therapy for the treatment of gliomas. *Expert Rev Neurother.* 8(1):37-49. http://safeaccess.ca/research/pdf/ParolaroCBasTherapyforGliomas2008.pdf https://www.ncbi.nlm.nih.gov/pubmed/18088200

Parolaro, D., Massi, P., Rubino, T., Monti, E. (2002). Endocannabinoids in the immune system and cancer. *Prostaglandins Leukot Essent Fatty Acids.* 66(2-3):319-32. DOI: 10.1054/plef.2001.0355 https://www.ncbi.nlm.nih.gov/pubmed/12052046

Patel, S., Shua-Haim, J.R,, Pass, M. (2003). Safety and efficacy of dronabinol in the treatment of agitation in patients with Alzheimer's disease with anorexia: A retrospective chart review. *Abstract, International Psychogeriatric Association, Eleventh International Congress.* http://www.cannabis-med.org/studies/ww_en_db_study_show.php?s_id=61

Patsos, H.A., Hicks, D.J., Dobson, R.R.H., Greenhough, A., Woodman, N., Lane, J.D., Williams, A.C., Paraskeva, C. (2005).The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase 2. *Gut* 54:1741-1750 doi:10.1136/gut.2005.073403 http://gut.bmj.com/content/54/12/1741.abstract

Patsos, H.A., Hicks, D.J., Greenhough, A., Williams, A.C., Paraskeva, C. (2005). Cannabinoids and cancer: potential for colorectal cancer therapy. *Biochem Soc Trans*. 33(Pt 4):712-4 (ISSN: 0300-5127) https://www.ncbi.nlm.nih.gov/pubmed/16042581

Phan, N.Q., Siepmann, D., Gralow, I., Ständer, S. (2010). Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia. *J Dtsch Dermatol Ges*. 8(2):88-91. doi: 10.1111/j.1610-0387.2009.07213.x.

Pisanti, S., Malfitano, A.M., Grimaldi, C., Santoro, A., Gazzerro, P., Laezza, C., Bifulco, M. (2009). Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. *Best Pract Res Clin Endocrinol Metab*. 23(1):117-31. doi:10.1016/j.beem.2009.02.001. https://www.ncbi.nlm.nih.gov/pubmed/14640910

Portella, G., Laezza, C., Laccetti, P., De Petrocellis, L., Di Marzo, V., Bifulco, M. (2003). Inhibitory effects of cannabinoid CB1 receptor stimulation on tumor growth and metastatic spreading: actions on signals involved in angiogenesis and metastasis. *FASEB J*. 17(12):1771-3. DOI: 10.1096/fj.02-1129fje https://www.ncbi.nlm.nih.gov/pubmed/12958205

Powles, T., Te Poele, R., Shamash, J., Chaplin, T., Propper, D., Joel, S., Oliver, T.,Liu, W.M. (2005). Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway. *Blood*. 105:1214-1221; doi:https://doi.org/10.1182/blood-2004-03-1182 http://www.bloodjournal.org/content/105/3/1214?sso-checked=true

Preet, A., R K Ganju, R.K., J E Groopman, J.E., (2008). Δ^9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration *in vitro* as well as its growth and metastasis *in vivo*. *Oncogene*. 27, 339–346; doi:10.1038/sj.onc.1210641; http://www.nature.com/onc/journal/v27/n3/full/1210641a.html

Preet, A., Qamri, Z., Nasser, M. W., Prasad, A., Shilo, K., Zou, X., … Ganju, R. K. (2011). Cannabinoid Receptors, CB1 and CB2, as Novel Targets for Inhibition of Non-Small Cell Lung Cancer Growth and Metastasis. *Cancer Prevention Research (Philadelphia, Pa.)*, *4*(1), 65–75. http://doi.org/10.1158/1940-6207.CAPR-10-0181 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025486/?tool=pubmed

Press Release: "New Synthetic Delta-9-THC Inhaler Offers Safe, Rapid Delivery" retrieved from: http://www.medicalnewstoday.com/releases/22937.php

Prociuk, M.A., Edel, A.L., Richard, M.N., Gavel, N.T., Ander, B.P., Dupasquier, C.M., Pierce, G.N. (2008). Cholesterol-induced stimulation of platelet aggregation is prevented by a hempseed-enriched diet. *Can J Physiol Pharmacol*. 86(4):153-9. doi: 10.1139/Y08-011. https://www.ncbi.nlm.nih.gov/pubmed/18418423

Raborn, E.S., Cabral,G.A. (2010). Cannabinoid Inhibition of Macrophage Migration to the Trans-Activating (Tat) Protein of HIV-1 Is Linked to the CB2 Cannabinoid Receptor. *J Pharmacol Exp Ther*. 333 (1). 319–327. DOI: 10.1124/jpet.109.163055 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2846023/?tool=pubmed

Rajesh, M., Mukhopadhyay, P., Bátkai, S., Haskó, G., Liaudet, L., Drel, V. R., … Pacher, P. (2007). Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. *American Journal of Physiology. Heart and Circulatory Physiology*, *293*(1), H610–H619. http://doi.org/10.1152/ajpheart.00236.2007 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2228254/?tool=pmcentrez

Rajesh, M., Mukhopadhyay, P., Bátkai, S., Patel, V., Saito, K., Matsumoto, S., Kashiwaya, Y., Horváth, B., Mukhopadhyay, B., Becker, L., Haskó, G., Liaudet, L., Wink, D.A., Veves, A., Mechoulam, R., Pacher, P. (2010). Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol*. 56(25):2115-25. doi:10.1016/j.jacc.2010.07.033. https://www.ncbi.nlm.nih.gov/pubmed/21144973

Raman, C., McAllister, S.D., Rizvi, G., Patel, S.G., Moore, D.H., Abood, M.E. (2004) Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. *Amyotroph Lateral Scler Other Motor Neuron Disord*. Mar;5(1):33-9. https://www.ncbi.nlm.nih.gov/pubmed/15204022

Ramer, R., Bublitz, K., Freimuth, N., Merkord, J., Rohde, H., Haustein, M., Borchert, P., Schmuhl, E., Linnebacher, M., Hinz, B. (2012). Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1. *FASEB J.* 26(4):1535-48. doi:10.1096/fj.11-198184. http://www.ncbi.nlm.nih.gov/pubmed/22198381

Ramer, R., Hinz, B. (2008). Inhibition of Cancer Cell Invasion by Cannabinoids via Increased Expression of Tissue Inhibitor of Matrix Metalloproteinases-1
J Natl Cancer Inst 100 (1): 59-69. DOI: https://doi.org/10.1093/jnci/djm268
https://academic.oup.com/jnci/article/100/1/59/2567700/Inhibition-of-Cancer-Cell-Invasion-by-Cannabinoids

Ramer, R., Merkord, J., Rohde, H., Hinz, B. (2010). Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. *Biochem Pharmacol.* 79(7):955-66. doi: 10.1016/j.bcp.2009.11.007. https://www.ncbi.nlm.nih.gov/pubmed/19914218

Ramer, R., Merkord, J., Rohde, H., Hinz, B. (2010). Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. *Biochem Pharmacol.* 79(7):955-66. doi: 10.1016/j.bcp.2009.11.007.
https://www.ncbi.nlm.nih.gov/pubmed/19914218

Ramer, R., Rohde, A., Merkord, J., Rohde, H., Hinz, B. (2010). Decrease of plasminogen activator inhibitor-1 may contribute to the anti-invasive action of cannabidiol on human lung cancer cells. *Pharm Res*. 27(10):2162-74. doi: 10.1007/s11095-010-0219-2. https://www.ncbi.nlm.nih.gov/pubmed/20668920

Ramírez, B.G., Blázquez, C., del Pulgar, T.G,. Guzmán, M., de Ceballos, M.L. (2005) Prevention of Alzheimer's Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation *Journal of Neuroscience*. 25 (8) 1904-1913; DOI:https://doi.org/10.1523/JNEUROSCI.4540-04.2005
http://www.jneurosci.org/content/25/8/1904

Reiman, A. (2009) Cannabis as a substitute for alcohol and other drugs.
Harm Reduct J. 6: 35. 10.1186/1477-7517-6-35
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2795734/?tool=pmcentrez

Richardson, D., Pearson, R. G., Kurian, N., Latif, M. L., Garle, M. J., Barrett, D. A., … Chapman, V. (2008). Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Research & Therapy*, *10*(2), R43.
http://doi.org/10.1186/ar2401
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2453762/?tool=pubmed

Rieder, S. A., Chauhan, A., Singh, U., Nagarkatti, M., & Nagarkatti, P. (2010). Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. *Immunobiology*, *215*(8), 598–605.
http://doi.org/10.1016/j.imbio.2009.04.001
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3005548/?tool=pubmed

Ringen, P.A., Vaskinn, A., Sundet, K., Engh, J.A., Jónsdóttir, H. et al.
(2009). Opposite relationships between cannabis use and neurocognitive functioning in bipolar disorder and schizophrenia. *Psychological Medicine* DOI:https://doi.org/10.1017/S0033291709991620

https://www.cambridge.org/core/journals/psychological-medicine/article/div classtitleopposite-relationships-between-cannabis-use-and-neurocognitive-functioning-in-bipolar-disorder-and-schizophreniadiv/0C444F4E22B46F43491A5C1AFDC4E4CD

Rodriguez-Leyva, D., & Pierce, G. N. (2010). The cardiac and haemostatic effects of dietary hempseed. *Nutrition & Metabolism*, *7*, 32. http://doi.org/10.1186/1743-7075-7-32 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868018/

Romero, J., Orgado, J.M. (2009). Cannabinoids and neurodegenerative diseases. *CNS Neurol Disord Drug Targets*. 8(6):440-50. https://www.ncbi.nlm.nih.gov/pubmed/19839933

Ruhaak, L.R., Felth, J., Karlsson, P.C., Rafter, J.J., Verpoorte, R., Bohlin, L. (2011). Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from Cannabis sativa. *Biol Pharm Bull.* 34(5):774-8. https://www.ncbi.nlm.nih.gov/pubmed/21532172

Ruiz, L., Miguel, A., Díaz-Laviada, I. (1999). Delta9-tetrahydrocannabinol induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism. *FEBS Lett*. 458(3):400-4. https://www.ncbi.nlm.nih.gov/pubmed/10570948

Ruiz-Llorente, L., Sánchez, M. G., Carmena, M. J., Prieto, J. C., Sánchez-Chapado, M., Izquierdo, A. and Díaz-Laviada, I. (2003), Expression of functionally active cannabinoid receptor CB1 in the human prostate gland. *Prostate*, 54: 95–102. doi:10.1002/pros.10165 http://onlinelibrary.wiley.com/doi/10.1002/pros.10165/abstract

Russo, E.B. (2011) Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 163(7):1344-64. doi: 10.1111/j.1476-5381.2011.01238.x. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/ https://www.ncbi.nlm.nih.gov/pubmed/2174936

Saghafi, N., Lam, D.K., Schmidt, B.L. (2011). Cannabinoids attenuate cancer pain and proliferation in a mouse model. *Neurosci Lett*. 488(3):247-51. https://www.ncbi.nlm.nih.gov/pubmed/21094209

Sagredo, O., García-Arencibia, M., de Lago, E., Finetti, S., Decio, A., Fernández-Ruiz, J. (2007). Cannabinoids and neuroprotection in basal ganglia disorders. *Mol Neurobiol.* 36(1):82-91. https://www.ncbi.nlm.nih.gov/pubmed/17952653

Saito, V.M., Wotjak, C.T., Moreira, F.A. (2010). Pharmacological exploitation of the endocannabinoid system: new perspectives for the treatment of depression and anxiety disorders? *Rev. Bras. Psiquiatr*. vol.32 supl.1 http://dx.doi.org/10.1590/S1516-44462010000500004 https://www.unboundmedicine.com/medline/citation/20512266/abstract/%5bPharmacological_exploitation_of_the_endocannabinoid_system:_new_perspectives_for_the_treatment_of_depression_and_anxiety_disorders%5d_

Salazar, M., Carracedo, A., Salanueva, Í. J., Hernández-Tiedra, S., Lorente, M., Egia, A., … Velasco, G. (2009). Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. *The Journal of Clinical Investigation*, *119*(5), 1359–1372. http://doi.org/10.1172/JCI37948

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2673842/?tool=pmcentrez

Salazar, M., Carracedo, A., Salanueva, I.J., Hernández-Tiedra, S., Egia, A., Lorente, M., Vázquez, P., Torres, S., Iovanna, J.L., Guzmán, M., Boya, P., Velasco, G. (2009). TRB3 links ER stress to autophagy in cannabinoid anti-tumoral action. *Autophagy*. 5(7):1048-9
DOI: 10.4161/auto.5.7.9508
https://www.researchgate.net/publication/26714808_TRB3_links_ER_stress_to_autophagy_in_cannabinoid_antitumoral_action

Sánchez, C., Galve-Roperh, I., Canova, C., Brachet, P., Guzmán, M. (1998). Delta9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. *FEBS Lett*. 436(1):6-10.

Sarfaraz, S., Afaq, F., Adhami, V.M., Malik, A., H. (2006). Cannabinoid Receptor Agonist-induced Apoptosis of Human Prostate Cancer Cells LNCaP Proceeds through Sustained Activation of ERK1/2 Leading to G_1 Cell Cycle Arrest. *The Journal of Biological Chemistry*. 281, 39480-39491. doi: 10.1074/jbc.M603495200
http://www.jbc.org/content/281/51/39480.full

Schicho, R., Storr, M. (2011). Alternative targets within the endocannabinoid system for future treatment of gastrointestinal diseases. *Can J Gastroenterol.* 25(7):377-83.
https://www.ncbi.nlm.nih.gov/pubmed/21876860

Shi, Y., Zou, M., Baitei, E.Y., Alzahrani, A.S., Parhar, R.S., Al-Makhalafi, Z., Al-Mohanna, F.A. (2008). Cannabinoid 2 receptor induction by IL-12 and its potential as a therapeutic target for the treatment of anaplastic thyroid carcinoma. *Cancer Gene Ther*. 15(2):101-7. doi: 10.1038/sj.cgt.7701101.
https://www.ncbi.nlm.nih.gov/pubmed/18197164

Shmist, Y.A., Goncharov, I., Eichler, M., Shneyvays, V., Isaac, A., Vogel, Z., Shainberg, A. (2006). Delta-9-tetrahydrocannabinol protects cardiac cells from hypoxia via CB2 receptor activation and nitric oxide production. *Mol Cell Biochem*. 283(1-2):75-83.
DOI: 10.1007/s11010-006-2346-y
https://www.ncbi.nlm.nih.gov/pubmed/16444588

Shrivastava, A., Kuzontkoski, P.M., Groopman, J.E., Prasad, A. (2011). Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther.* 10(7):1161-72. doi: 10.1158/1535-7163.MCT-10-1100.
https://www.ncbi.nlm.nih.gov/pubmed/21566064

Siniscalco, D., et al. (2013).
Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders.
J Autism Dev Disord. 43(11):2686-95. doi: 10.1007/s10803-013-1824-9.

Sofia, R.D., Nalepa, S.D., Harakal, J.J., Vassar, H.B. (1973). Anti-edema and analgesic properties of Δ9-tetrahydrocannabinol (THC). *Journal of Pharmacology and Experimental Therapeutics.* 186 (3) 646-655;
http://jpet.aspetjournals.org/content/186/3/646?maxtoshow=&hits=80&RESULTFORMAT=&fulltext=marihuana&searchid=1&FIRSTINDEX=2160&resourcetype=HWCIT

Sreevalsan, S., Joseph, S., Jutooru, I., Chadalapaka, G., Safe, S.H. (2011). Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent. *Anticancer Res.* 31(11):3799-807. https://www.ncbi.nlm.nih.gov/pubmed/22110202

Steffens, S. *et al*. (2005) Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature* 434: 782-786
https://www.ncbi.nlm.nih.gov/pubmed/15815632

Steffens, S., Mach, F. (2006). Cannabinoid receptors in atherosclerosis. *Curr Opin Lipidol.* 17(5):519-26.
https://www.ncbi.nlm.nih.gov/pubmed/16960500

Steffens, S., Mach, F. (2006). Towards a therapeutic use of selective CB2 cannabinoid receptor ligands for atherosclerosis. *Future Cardiol.* 2(1):49-53. doi:10.2217/14796678.2.1.49.
https://www.ncbi.nlm.nih.gov/pubmed/19804131

Steffens, S., Veillard, N.R., Arnaud, C., Pelli, G., Burger, F., Staub, C., Karsak, M., Zimmer, A., Frossard, J.L., Mach, F. (2005). Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature*. 434(7034):782-6. DOI:10.1038/nature03389
https://www.ncbi.nlm.nih.gov/pubmed/15815632/

Storr, M., Emmerdinger, D., Diegelmann, J., Pfennig, S., Ochsenkühn, T., Göke, B., … Brand, S. (2010). The Cannabinoid 1 Receptor (*CNR1*) 1359 G/A Polymorphism Modulates Susceptibility to Ulcerative Colitis and the Phenotype in Crohn's Disease. *PLoS ONE*, *5*(2), e9453.
http://doi.org/10.1371/journal.pone.0009453
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2829088/?tool=pmcentrez

Storr, M.A., Keenan, C.M., Emmerdinger, D., Zhang, H., Yüce, B., Sibaev, A., Massa, F., Buckley, N.E., Lutz, B., Göke, B., Brand, S., Patel, K.D., Sharkey, K.A. (2008). Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors. *J Mol Med (Berl)*. 86(8):925-36. doi:10.1007/s00109-008-0359-6. https://www.ncbi.nlm.nih.gov/pubmed/18493729

Storr, M. A., Keenan, C. M., Zhang, H., Patel, K. D., Makriyannis, A. and Sharkey, K. A. (2009), Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis. *Inflamm Bowel Dis*, 15: 1678–1685. doi:10.1002/ibd.20960
http://onlinelibrary.wiley.com/doi/10.1002/ibd.20960/full

Straus, S. E. (2000). Immunoactive cannabinoids: Therapeutic prospects for marijuana constituents. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(17), 9363–9364. doi: 10.1073/pnas.180314297

Szmitko, P.E., Verma, S. (2006). Does Cannabis Hold the Key to Treating Cardiometabolic Disease? *Nat Clin Pract Cardiovasc Med*. 3(3):116-117. doi:10.1038/ncpcardio0504
http://www.medscape.com/viewarticle/525040_print

Torres, S., Lorente, M., Rodríguez-Fornés, F., Hernández-Tiedra, S., Salazar, M., García-Taboada, E., Barcia, J., Guzmán, M., Velasco, G. (2011). A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Mol Cancer Ther.* 10(1):90-103. doi:10.1158/1535-7163.MCT-10-0688.
https://www.ncbi.nlm.nih.gov/pubmed/21220494 DOI: 10.1158/1535-7163.MCT-10-0688

Toth, C. C., Jedrzejewski, N. M., Ellis, C. L., & Frey, W. H. (2010). Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. *Molecular Pain*, *6*, 16. http://doi.org/10.1186/1744-8069-6-16 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2845559/?tool=pmcentrez

Tucker, A.N., Friedman, M.A. (1977). Effects of cannabinoids on L1210 murine leukemia. 1. Inhibition of DNA synthesis. *Res Commun Chem Pathol Pharmacol.* 17(4):703-14. https://www.ncbi.nlm.nih.gov/pubmed?Db=pubmed&Cmd=Retrieve&list_uids=897352&dopt=abstractplus

Vaccani, A., Massi, P., Colombo, A., Rubino, T., & Parolaro, D. (2005). Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism. *British Journal of Pharmacology*, *144*(8), 1032–1036. http://doi.org/10.1038/sj.bjp.0706134 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1576089/?tool=pmcentrez

Vara, D., Salazar, M., Olea-Herrero, N., Guzmán, M., Velasco, G., Díaz-Laviada, I. (2011). Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy. *Cell Death Differ*. 18(7):1099-111. doi:10.1038/cdd.2011.32. https://www.ncbi.nlm.nih.gov/pubmed/21475304

Velasco, G., Carracedo, A., Blázquez, C., Lorente, M., Aguado, T., Haro, A., Sánchez, C., Galve-Roperh, I., Guzmán, M. (2007). Cannabinoids and gliomas. *Mol Neurobiol.* 36(1):60-7. https://www.ncbi.nlm.nih.gov/pubmed/17952650

Velasco, G., Galve-Roperh, I., Sánchez, C., Blázquez, C., Guzmán, M. (2004). Hypothesis: cannabinoid therapy for the treatment of gliomas? *Neuropharmacology.* 47(3):315-23. https://www.ncbi.nlm.nih.gov/pubmed/15275820

Velasco, G., Sánchez, C., Guzmán, M. (2016). Anticancer mechanisms of cannabinoids. *Curr Oncol*. 23(2):S23-32. DOI: 10.3747/co.23.3080 https://www.ncbi.nlm.nih.gov/pubmed/27022311

Volicer, L., Stelly, M., Morris, J., McLaughlin, J., Volicer, B.J. (1997). Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*.12(9):913-919 http://www.cannabis-med.org/studies/ww_en_db_study_show.php?s_id=59

Von Bueren, A.O., Schlumpf, M., and W. Lichtensteiger, W. (2008). Delta(9)-tetrahydrocannabinol Inhibits 17,-Estradiol-induced Proliferation and Fails to Activate Androgen and Estrogen Receptors in MCF7 Human Breast Cancer Cells A. O. *ANTICANCER RESEARCH* . 28: 85-90 http://ar.iiarjournals.org/content/28/1A/85.long

Walker, E.M., Amedee, A., Birke, L., Vande Stouwe, C., LaCour, N., Winsauer, P., Molina,P. (2010). Chronic cannabinoid administration lowers viral replication in lymph nodes of SIV infected Rhesus macaques. *FASEB.* vol. 24 no. 1 Supplement 752.6 http://www.fasebj.org/content/24/1_Supplement/752.6

Wallace, R. (2004). Cannabinoids: Defending the Epileptic Brain. *Epilepsy Currents*, *4*(3), 93–95. http://doi.org/10.1111/j.1535-7597.2004.43003.x
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1176332/?tool=pmcentrez

Walsh, S. K., Hepburn, C. Y., Kane, K. A., & Wainwright, C. L. (2010). Acute administration of cannabidiol *in vivo* suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion. *British Journal of Pharmacology*, *160*(5), 1234–1242. http://doi.org/10.1111/j.1476-5381.2010.00755.x
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2936031/?tool=pubmed

Weber, J., Schley, M., Casutt,M., Gerber, H., Schuepfer,G., Rukwied, R., Schleinzer, W., Ueberall, M., Konrad, C. (2009) Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey. *Anesthesiology Research and Practice*. Article ID 827290. Doi:10.1155/2009/827290
https://www.hindawi.com/journals/arp/2009/827290/

Weiss, L., Zeira, M., Reich, S., Slavin, S., Raz, I., Mechoulam, R., & Gallily, R. (2008). Cannabidiol Arrests Onset of Autoimmune Diabetes in NOD Mice. *Neuropharmacology*, *54*(1), 244–249. http://doi.org/10.1016/j.neuropharm.2007.06.029
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2270485/?tool=pmcentrez

Weydt, P., Hong, S., Witting, A., Möller, T., Stella, N., Kliot, M. (2005) Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 6(3):182-4.
https://www.ncbi.nlm.nih.gov/pubmed?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=16183560

Whyte, D.A., Al-Hammadi, S., Balhaj, G., Brown, O.M., Penefsky, H.S., Souid, A.K. (2010). Cannabinoids Inhibit Cellular Respiration of Human Oral Cancer Cells. *Pharmacology*. 85:328–335. DOI:10.1159/000312686
http://content.karger.com/Article/Abstract/312686

Wu, H.Y., Chang, A.C., Wang, C.C., Kuo, F.H., Lee, C.Y., Liu, D.Z., Jan, T.R. (2010). Cannabidiol induced a contrasting pro-apoptotic effect between freshly isolated and precultured human monocytes. *Toxicology and applied pharmacology* 246:3 pg 141-7
https://www.unboundmedicine.com/medline/citation/20471992/abstract/Cannabidiol_induced_a_contrasting_pro_apoptotic_effect_between_freshly_isolated_and_precultured_human_monocytes

Xu, X., Liu, Y., Huang, S., Liu, G., Xie, C., Zhou, J., Fan, W., Li, Q., Wang, Q., Zhong, D., Miao, X. (2006). Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma. *Cancer Genet Cytogenet.* 171(1):31-8. DOI: 10.1016/j.cancergencyto.2006.06.014
https://www.ncbi.nlm.nih.gov/pubmed/17074588

Zutt, M., Hänssle, H., Emmert, S., Neumann, C., Kretschmer, L. (2006). Dronabinol for supportive therapy in patients with malignant melanoma and liver metastases. *Hautarzt*. 57(5):423-7. DOI: 10.1007/s00105-005-1063-x https://www.ncbi.nlm.nih.gov/pubmed/16408219

References, List Three:

Baker, M. E. 1997. Steroid receptor phylogeny and vertebrate origins. *Mol Cell Endocrinol* 135:101-7.

Chen, S., Cai, D., Pearce, K., Philip, Y. W., Sun P. Y. W., Roberts A. C., Glanzman D. L. (2014). Reinstatement of long-term memory following erasure of its behavioral and synaptic expression in Aplysia. *eLife:* http://dx.doi.org/10.7554/eLife.03896

Chiu, J., R. DeSalle, H. M. Lam, L. Meisel, and G. Coruzzi. 1999. Molecular evolution of glutamate receptors: A primitive signaling mechanism that existed before plants and animals diverged. *Mol Biol Evol* 16:826-38.

Clark, I. E., Dodson, M. W., Jiang, C., Cao, J. H., Huh, J. R., Seol, J. H., Yoo, S. J., Hay, B. A., & Guo, M. (2006). Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. *Nature.* 441(7097):1162-6.

Davis, M., Rainnie, D., & Casell, M. (1994).
Neurotransmission in the rat amygdala related to fear and anxiety.
Trends neurosci. 17: 208-214.

De Lanerolle, N. C., & Lang, F. F. (1988).
Functional neural pathways for vocalization in the domestic cat.
In *The physiological control of mammalian vocalization* (J. D. Newman ed.).
pp. 21-41 NY.: Plenum Press.

Dias, B. G., & Ressler, K. J. (2014).
Parental olfactory experience influences behavior and neural structure in subsequent generations.
Nature Neuroscience **17**, 89–96 doi:10.1038/nn.3594

Di Marzo, V., C. S. Breivogel, Q. Tao, D. T. Bridgen, R. K. Razdan, A. M. Zimmer, A. Zimmer, and B. R. Martin. (2000). Levels, metabolism, and pharmacological activity of anandamide in CB(1) cannabinoid receptor knockout mice: evidence for non-CB(1), non-CB(2) receptor-mediated actions of anandamide in mouse brain. *J Neurochem* 75:2434-44.

Feng, D. F., and R. F. Doolittle. 1996. Progressive alignment of amino acid sequences and construction of phylogenetic trees from them. *Methods Enzymol* 266:368-82.

Gadzicki, D., K. Muller-Vahl, and M. Stuhrmann. 1999. A frequent polymorphism in the coding exon of the human cannabinoid receptor (CNR1) gene. *Mol Cell Probes* 13:321-323.

Greer E. L. et al. (2014).
A Histone Methylation Network Regulates Transgenerational Epigenetic Memory in *C. elegans.*
Cell Reports, Volume 7, Issue 1, 113 - 126.

Harteneck, C., T. D. Plant, and G. Schultz. 2000. From worm to man: Three subfamilies of TRP channels. *Trends Neurosci* 23:159-66.

Jurgens, U., & Ploog, D., (1988). On motor coordination of monkey calls. In *The physiological control of mammalian vocalization* (J. D. Newman ed.). pp. 7-19. NY.: Plenum Press.

Lee, M. S. 1999. Molecular clock calibrations and metazoan divergence dates. *J Mol Evol* 49:385-91.

McPartland, J. M., V. Di Marzo, L. De Petrocellis, A. Mercer, and M. Glass. 2001. Cannabinoid receptors are absent in insects. *J Comparative Neurol* 434:

McPartland, J. and Pruitt, P. (2002) Sourcing the Code Searching for the Evolutionary Origins of Cannabinoid Receptors, Vanilloid Receptors, and Anandamide. *Journal of Cannabis Therapeutics*, Vol. 2(1) http://dx.doi.org/10.1300/J175v02n01_04 http://www.tandfonline.com/doi/abs/10.1300/J175v02n01_04

Miczek, K. A. (1987). The psychopharmacology of aggression. In *Handbook of psychopharmacology*. Vol 19. *New directions in behavioral pharmacology.* (L. L. Iverson, S. D. Iverson & S. H. Snyder eds.) pp. 183-328. NY.: Plenum Press.

Miczek, K., Haney, M., Tidey, J., Vivian, J., & Weerts E. (1994). Neurochemistry and pharmacotherapeutic management of aggression and violence. In *Understanding and preventing violence. Vol. 2 Biobehavioral influences.* (A. Reiss, K. Miczek, and J. Roth eds.) pp. 245- 514 Washington D.C.: National Academy Press.

Morais, V. A., Verstreken, P., Roethig, A., Smet, J., Snellinx, A., Vanbrabant, M., Haddad, D., Frezza. C., Mandemakers, W., Vogt-Weisenhorn, D., Van Coster, R., Wurst, W., Scorrano. L., & De Strooper, B. (2009). Parkinson's disease mutations in PINK1 result in decreased Complex I activity and deficient synaptic function. *EMBO Mol Med*. (2):99-111. doi: 10.1002/emmm.200900006.

Munro, S., K. L. Thomas, and M. Abu-Shaar. 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365:61-5.

Nakane, S., T. Tanaka, K. Satouchi, Y. Kobayashi, K. Waku, and T. Sugiura. 2000. Occurrence of a novel cannabimimetic molecule 2-sciadonoylglycerol (2-eicosa-5_, 11_,14_-trienoylglycerol) in the umbrella pine Sciadopityl verticillata seeds. *Biolog Pharmaceut Bull* 23:758-61.

Norman, R. (2015). Modern Man: of phylogeny, guilt, obedience and consequence—an answer to old problems. *Mind magazine.* Retrieved from:

http://www.mindmagazine.net/
http://www.mindmagazine.net/#!new-ideas/czpl

Norman, R. (2015*a*).
Mnemic Psycho-Epigenetics: the foundational basis of depth,
archetype and synthesis in psychology.
Mind magazine. Retrieved from:
http://www.mindmagazine.net/
http://www.mindmagazine.net/#!new-ideas/czpl

Norman, R. (2015*b*).
The Epigenetic Unconscious pt. 1.
Mind magazine. Retrieved from:
http://www.mindmagazine.net/
http://www.mindmagazine.net/#!new-ideas/czpl

Norman, R. (2015*c*).
The Epigenetic Unconscious pt. 2.
Mind magazine. Retrieved from:
http://www.mindmagazine.net/
http://www.mindmagazine.net/#!new-ideas/czpl

Norman, R. (2015*d*) Our Primordial Recipe… and other delights. *Mind magazine. New ideas section*. www.mindmagazine.net
http://docs.wixstatic.com/ugd/cf8614_90bd211a4f7a4d208c682ce9232fa96e.pdf

Panksepp, J., Herman B. J., Vilberg, T., Bishop, P., & De Eskinazi, F. G. (1980).
Endoginous opioids and social behavior. *Neurosci. Biobehav. Revs. 4: 473-487.*

Panksepp, J. (1990).
The psychoneurology of fear: Evolutionary perspectives and the role
of animal models in understanding anxiety. In *Handbook of anxiety*. Vol. 3.
The neurobiology of anxiety (G. D. Burrows, M. Roth, & R. Noyes, Jr., eds.). pp. 3-58
Amsterdam: Elsevier.

Panksepp, J. (1998). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. New York, NY.: Oxford Press.

Panksepp, J. (2012).
The Archaeology of Mind: Neuroevolutionary origins of human emotions.
NY/London: W.W. Norton and Company.

Panksepp J., & Panksepp, J. B. (2013).
Toward a cross-species understanding of empathy.
Trends in neurosciences. 36:8 pp. 439-496.

Peroutka, S. J., and T. A. Howell. 1994. The molecular evolution of G protein-coupled receptors: Focus on 5-hydroxytryptamine receptors. *Neuropharmacology* 33:319-24.

Robinson, B. W. (1967). Vocalization evoked from forebrain in *Macaca mulata*. *Physiol. Behav.* 2: 345-354.

Salzet, M., C. Breton, T. Bisogno, and V. Di Marzo. 2000. Comparative biology of the endocannabinoid system. *Eur J Biochem* 267:1-12.

Shire, D., C. Carillon, M. Kaghad, B. Calandra, M. Rinaldi-Carmona, G. Le Fur, D. Caput, and P. Ferrara. 1995. An amino-terminal variant of the central cannabinoid receptor resulting from alternative splicing. *J Biol Chem* 270:3726-31.

Soderstrom, K., T. F. Murray, H. D. Yoo, S. Ketchum, K. Milligan, W. Gerwick, M. J. Ortega, and J. Salva. 1997. Discovery of novel cannabinoid receptor ligands from diverse marine organisms. *Adv Exper Med Biol* 433:73-7. https://www.ncbi.nlm.nih.gov/pubmed/9561107

Szolcsanyi, J. 2000. Anandamide and the question of its functional role for activation of capsaicin receptors. *Trends Pharmacol Sci* 21:203-4.

Tamulis A., Berteska L., Grigalavicius, M., & Baltrusaitis, J. (2016). Quantum Dynamics of Self-Assembly of Minimal Photosynthetic Cells. *Quantum Matter*. 5, 5 DOI: http://dx.doi.org/10.1166/qm.2016.1248

Tsai, S. J., Y. C. Wang, and C. J. Hong. 2000. Association study of a cannabinoid receptor gene (CNR1) polymorphism and schizophrenia. *Psychiatr Genet* 10:149-151.

van Zadelhoff, G., G. A. Veldink, and F. G. Vliegenhart. 1998. With anandamide as substrate plant 5-lipoxygenases behave like 11-lipoxygenases. *Biochemical & Biophysical Research Communications* 248:33-8.

Watanabe, Y., Stone, E., & McEwen, B. S. (1994). Induction and habituation of C-fos and zif/268 by acute and repeated stressors. *Neuroreport*. 5: 1321-1324

Yehuda, R., Daskalakis N. P., Bierer L. M., Bader H. N., Klengel T., Holsboer, F., & Binder, E. B. (2015). Holocaust Exposure Induced Intergenerational Effects on *FKBP5* Methylation. *Biological Psychiatry,* 8:5 DOI: http://dx.doi.org/10.1016/j.biopsych.2015.08.005

Yun, J., Yang H., Lizzio M. A., Wu C., Sheng Z-H., & Guo M. (2014). MUL1 acts in parallel to the PINK1/parkin pathway in regulating mitofusin and compensates for loss of PINK1/parkin. eLife, 3 DOI: http://dx.doi.org/10.7554/elife.01958

Zhu, X. O., Brown, M. W., McCabe, B. J., & Aggleton, J. P. (1995). Effects of the novelty or familiarity of visual stimuli on the expression of the immediate early c-fos in rats. *Neuroscience*. 69: 821-829

References, List Four:

Abel, E. (1980). *Marijuana: The first 12,000 years*. Plenum Press: NY.

Allen, J.L. (1900) *The reign of law, a tale of the Kentucky hemp fields*. MacMillan NY.

Americans for Safe Access. (2016). Medical access to cannabis for pain treatment. Retrieved January 3, 2017, from http://www.safeaccessnow.org/medical_cannabis_access_for_pain_treatment.

Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M et al. (2008). Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. J Nat Prod 71: 1427–1430.

Atakan, Z. (2012). Cannabis, a complex plant: different compounds and different effects on individuals. *Therapeutic Advances in Psychopharmacology*, *2*(6), 241–254. http://doi.org/10.1177/2045125312457586

Aulde, J. (1890). Studies in therapeutics-Cannabis indica. Therapeutic Gazette, 14, 523-526.

Batho, R. (1883, May 26). Cannabis indica. British Medical Journal, I, 1002.

Biruni, M.I.A., & Said, H.M. (1973). al-Biruni's book on pharmacy and materia medica. Karachi: Hamdard Academy.

Boehnke, K.F., Litinas E., Clauw, D. J. (2016) Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain *The Journal of Pain* Volume 17, Issue 6, https://doi.org/10.1016/j.jpain.2016.03.002 http://www.sciencedirect.com/science/article/pii/S1526590016005678

Bonnie, R., Whitebread, C. (1974) *The Marijuana Conviction*. U. of Virginia press.

Brown, J. (1883). Cannabis indica: A valuable remedy in menorrhagia. British Medical Journal, (May 26), 1002.

Campbell, W.E., D.W. Gammon, P. Smith, M. Abrahams, and T.D. Purves. 1997. Composition and antimalarial activity in vitro of the essential oil of Tetradenia riparia. Planta Med 63(3):270-2.

Carlini EA, Karniol IG, Renault PF, Schuster CR. (1974) Effects of marihuana in laboratory animals and in man. *Br J Pharmacol*. ;50:299–309. [PMC free article] [PubMed]

Carson, C.F., and T.V. Riley. 1995. Antimicrobial activity of the major components of the essential oil of Melaleuca alternifolia. J Appl Bacter 78(3):264-9.

Chen, W., Liu, Y., Li, M., Mao, J., Zhang, L., Huang, R., et al. (2015). Anti-tumor effect of alpha-pinene on human hepatoma cell lines through inducing G2/M cell cycle arrest. *Journal of Pharmacological Sciences*, 127(3), 332–338. https://doi.org/10.1016/j.jphs.2015.01.008

Chomel, P.J.B. (1782). Abrege de I'histoire des plantes usuelles. Paris: Libraires Associes.

Chopra, I.C., & Chopra, R.W. (1957). The use of cannabis drugs in India. Bulletin on Narcotics, 9, 4-29.

Christison, A.. (1851). On the natural history, action, and uses of Indian hemp. Monthly Journal of Medical Science of Edinburgh, Scotland, 13, 26-45,117-121,

Clark, V.S. (1929) *History of manufacture in the United States*. McGraw Hill NY.

Clendinning, J. (1843). Observation on the medicinal properties of Cannabis sativa of India. Medico-Chirurgical Transactions, 26, 188-2 10.

Cohen, S. and Stillman R. (1976) *Therapeutic potential of marijuana*. Plenum press, NY.

Crowell, P.L. 1999. Prevention and therapy of cancer by dietary monoterpenes. J Nutr 1999; 129:775S-8S.

Daaka, Y., W. Zhu, H. Friedman, and T.W. Klein. 1997. Induction of interleukin-2 receptor α gene by Δ9-tetrahydrocannabinol is mediated by nuclear factor κB and CB1 cannabinoid receptor. DNA Cell Biol 16:301-9.

Dach, J., Moore, E.A., Kander, J. (2015) *Cannabis extracts in medicine*. McFarland health topics; McFarland and co. Inc. publishers. North Carolina. p. 165

De Petrocellis L, Di Marzo V (2010). Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. J Neuroimmune Pharmacol 5: 103–121.

De Petrocellis L, Ligresti A, Moriello AS, Allara M, Bisogno T, Petrosino S et al. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol DOI:10.1111/j.1476-5381.2010.0166.x

Dioscorides, P. (1968). The Greek herbal of Dioscorides. London: Hafner Publishing.

Dixon, WE. (1899). The pharmacology of Cannabis indica. British Medical Journal, 2, 1354-1357.

Donovan, M. (1845). On the physical and medicinal qualities of Indian hemp (Cannabis indica); With observations on the best mode of administration, and cases illustrative of its powers. Dublin Journal of Medical Science, 26, 368^02, 459-461.

Douthwaite, A.H. (1947). Choice of drugs in the treatment of duodenal ulcer. British Medical Journal, 43, 43-47.

Dwarakanath, C. (1965). Use of opium and cannabis in the traditional systems of medicine in India. Bulletin on Narcotics, 17, 15-1 9.

Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T (2006a). The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. J Mol Med 84: 253–258.

Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T (2006b). Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. Neurosci Lett 399: 91–95.

Eubanks LM, Rogers CJ, Beuscher AE 4th, Koob GF, Olson AJ, Dickerson TJ et al. (2006). A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm 3: 773–777.

Evans, A.T., E.A. Formukong, and F.J. Evans. 1987. Actions of cannabis constituents on enzymes of arachidonate metabolism: anti-inflammatory potential. Bioch Pharmacol 36:2035-7.

Fairbairn JW, Pickens JT. Activity of cannabis in relation to its delta'-trans-tetrahydro-cannabinol content. *Br J Pharmacol*. 1981;72:401–409. [PMC free article] [PubMed]

Farlow, J.W. (1889). On the use of belladonna and Cannabis indica by the rectum in gynecological practice. Boston Medical and Surgical Journal, 120, 507-509.

Fellermeier M, Eisenreich W, Bacher A, Zenk MH (2001).

Biosynthesis of cannabinoids. Incorporation experiments with (13)C-labeled glucoses. Eur J Biochem 268: 1596–1604.

Frazier, J. (1972) The marijuana farmers. Solar Age Press. New Orleans LA.

Ghalioungui, P. (1987). The Eberspapyrus: A new English translation, commentaries and glossaries. Cairo: Academy of Scientific Research and Technology.

Grigor, J. (1852). Indian hemp as an oxytocic. Monthly Journal aft Medical Sciences, 14, 124.

Grinspoon, L., Bakalar J.B. (1997). Marihuana, the forbidden medicine, revised edition. New Haven, CT: Yale University Press.

Hardcastle, I.R., M.G. Rowlands, A.M. Barber, R.M. Grimshaw, M.K. Mohan, B.P. Nutley, and M. Jarman. 1999. Inhibition of protein prenylation by metabolites of limonene. Biochem Pharmacol 57:801-9.

Hare, HA. (1887). Clinical and physiological notes on the action of Cannabis indica. Therapeutic Gazette, 2, 225-228.

Hare, HA. (1922). A text-book of practical therapeutics, with especial reference to the application oft remedial measures to disease and their employment upon a rational basis (18th ed.). Philadelphia: Lea & Febiger.

Herer, J. (1990) *The emperor wears no clothes*. Hemp/queen of clubs publishing. Van Nuys, Ca. Newer version here: http://www.actuarialoutpost.com/actuarial_discussion_forum/archive/index.php/t-56220.html

Herndon, G.M. (1963) Hemp in Colonial Va. *Agricultural History* 37 93.

Hoechstetter, S.S. (1930). Effects of alcohol and cannabis during labor. Journal of the American Medical Association, 94(15), 1165.

Iseger T.A., Bossong M.G. (2015) A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophr Res. 162(1-3):153-61.* https://www.ncbi.nlm.nih.gov/pubmed/25667194

Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA (2004). Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. J Neurochem 89: 134–141.

Jones, C.L.A. 1999. Monoterpenes: Essence of a cancer cure. Nutr Sci News 4 (4):190.

Julien, M.S. (1849). Chirugie chinoise-Substance anesthetique employee en Chine, dans le commencement du III-ieme

siecle de notre ere, pour paralyser momentanement la sensibilite. Comptes Rendus Hebdomadaires de I'Academie des Sciences, 28, 223-229.

Kahl, 0. (1994). Sabur ibn Sahl: Dispensatorium parvum (al-Aarabadhin al-Sughir). Leiden, The Netherlands: E.J. Brill.

Komori, T., R. Fujiwara, M. Tanida, J. Nomura, and M.M. Yokoyama. 1995. Effects of citrus fragrance on immune function and depressive states. Neuroimmunomod 2:174-80.

Lewis, B., Menage, V.L., Pellat, C.H., & Schacht, J. (1971). The encyclopedia of Islam. Leiden, The Netherlands: E.J. Brill.

Li H. (1973) An archaeological and historical account of cannabis in China. *Economic Botany* 28: 437–448

Lichtman, A. H., Sheikh, S. M., Loh, H. H., & Martin, B. R. (2001). Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice. Journal of Pharmacology and Experimental Therapeutics, 298(3), 1007–1014.

Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L et al. (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther 318: 1375–1387.

Lilly (1898). Lilly's Handbook of Pharmacy and Therapeutics. Indianapolis: Lilly and Company.

Linne, C.A. (1772). Materia medica per regna tria naturae. Lipsiae et Erlangae: Wolfgang Waltherum.

Lorenzetti, B.B., G.E.P. Souza, S.J. Sarti, D. Santos Filho, and S.H. Ferreira. 1991. Myrcene mimics the peripheral analgesic activity of lemongrass tea. J Ethnopharmacol 34:43-8.

Mackenzie, S. (1894). Therapeutique medicale: De la valeur therapeutique speciale du chanvre indien dans certains Ctats morbides. Semaine Medicale, 14, 399400.

Malfait, A.M., R. Gallily, P.F. Sumariwalla, A.S. Malik, E. Andreakos, R. Mechoulam, and M. Feldman. 2000. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci 97:9561-6.

Marcandier, M. (1764). Treatise on hemp. London: T. Becket

and P. A. de Hondt.

Mannische, L. (1989). An ancient Egyptian herbal. Austin: University of Texas.

Mattison, J.B. (1891). Cannabis indica as an anodyne and hyp-
notic. St. Louis Medical and Surgical Journal, 61,
265-27 1.

McPartland, J.M., and P.P. Pruitt. (1997). Medical marijuana and its use by the
immunocompromised. Altern Therap 3(3):39-45.
McPartland, J. M., and Russo, E. B. (2001) Cannabis and Cannabis Extracts:
Greater Than the Sum of Their Parts? Co-published simultaneously in Journal of Cannabis Therapeutics
Vol. 1, No. 3/4, pp. 103-132; and:
Cannabis Therapeutics in HIV/AIDS (ed: Ethan Russo) The Haworth Integrative
Healing Press, an imprint of The Haworth Press, Inc., 2001, pp. 103-132.

McPartland, J. and Pruitt, P. (2002) Sourcing the Code
Searching for the Evolutionary Origins of Cannabinoid Receptors, Vanilloid Receptors, and Anandamide.
Journal of Cannabis Therapeutics, Vol. 2(1)
http://dx.doi.org/10.1300/J175v02n01_04
http://www.tandfonline.com/doi/abs/10.1300/J175v02n01_04

Michel, L. (1880). Proprietes medicinales de l'lndian hemp ou
du Cannabis indica. Montpellier Medical, 45, 103-1 16.

Mikuriya, T. (1973) Marijuana medical papers (1839-1972). Edited by
Tod H. Mikuriya, M.D. (1973) 465 pages
Medi-Comp Press, 2633 E. 27th St., Oakland, CA 94601.
Library of Congress Catalog Card Number 72-87736
http://www.marijuanalibrary.org/Dr_Mikuriya.html

Moldzio, R., Pacher, T., Krewenka,C.,Kranner, B., Novak, J.,Duvigneau, J.C., et al. (2012).
Effects of cannabinoids Δ(9)-tetrahydrocannabinol, Δ(9)-tetrahydrocannabinolic acid and
cannabidiol in MPP+ affected murine mesencephalic cultures. Phytomedicine, 19(8–9),
819–824. http://doi.org/10.1016/j.phymed.2012.04.002.

Moreno-Sanz, G. (2016). Can you pass the acid test? Critical review and novel therapeutic
perspectives of Δ 9-tetrahydrocannabinolic acid A. *Cannabis and Cannabinoid Research*,
1(1), 124–130. http://doi.org/10.1089/can.2016.0008.

Naef, M., Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L., Zbinden, A., &
Brenneisen, R. (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol
(THC), morphine, and a THC-morphine combination in healthy subjects under
experimental
pain conditions. Pain, 105(1–2), 79–88.

Nakao, T., Okada, K. and Kanba, S. (2014), Neurobiological model of
obsessive–compulsive disorder:
Evidence from recent neuropsychological and neuroimaging findings.

Psychiatry Clin Neurosci, 68: 587–605.
doi:10.1111/pcn.12195 http://onlinelibrary.wiley.com/doi/10.1111/pcn.12195/full

Norman RL, Dunning-Davies J, Heredia-Rojas JA, Foletti A (2016). Quantum Information Medicine: Bit as It—The Future Direction of Medical Science: Antimicrobial and Other Potential Nontoxic Treatments. World Journal of Neuroscience. 6: 193-207. http://dx.doi.org/10.4236/wjns.2016.63024

Nunes DS, Linck VM, da Silva AL, Figueiro M, Elisabetsky E (2010). Psychopharmacology of essential oils. In: Baser KHC, Buchbauer G (eds). Handbook of Essential Oils: Science, Technology, and Applications. CRC Press: Boca Raton, FL, pp. 297–314.

Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M et al. (2008). Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. J Nat Prod 71: 1427–1430.

Nunn, J. F. (1996). Ancient Egyptian medicine. Norman: University of Oklahoma Press.

Ortiz de Urbina, A.V., M.L. Martin, M.J. Montero, A. Moran, and L. San Roman. 1989. Sedating and antipyretic activity of the essential oil of Calamintha sylvatica subsp. ascendens. J Ethnopharmacol 25(2):165-71.

O'Shaughnessy, W.B. (1838-1840). On the preparations of the Indian hemp, or gunjah (Cannabis indica); Their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. Transactions of the Medical and Physical Society of Bengal, 71-102, 421^161.

Osier, W., & McCrae, T. (1915). The principles and practice of medicine. New York: Appleton and Company.

Parkinson, J., & Cotes, T. (1640). Theatrum botanicum: The theater of plants. London: Tho. Cotes.
Marcandier, M. (1758). Traite du chanvre. Paris: Chez Nyon.

Pertwee, R. G., Howlett, A. C., Abood, M. E., Alexander, S. P. H., Di Marzo, V., Elphick, M. R., et al. (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacological Reviews, 62(4), 588–631. http://doi.org/10.1124/pr.110.003004.

Pertwee, R. (Editor) (2014) *The cannabis handbook*. Oxford press. UK.

Pliny (1951). Pliny: Natural history. Cambridge, MA: Harvard University.

Popular Mechanics magazine Feb (1938 prepared in 1937) *New Billion Dollar crop*.

Rennie, S.J. (1886). On the therapeutic value of tinctura Can-

nabis indica in the treatment of dysentery, more particularly in its sub-acute and chronic forms. I ndian M edical Gazette, 21, 353-354.

Reynolds, J.R. (1868). On some of the therapeutical uses of Indian hemp. Archives of Medicine, 2, 154-160.

Roffman, R. (1982) *Marijuana as medicine*. Mendrone books. WA.

Rumpf, G.E., & Beekman, E.M. (1981). The poison tree: Selected writings of Rumphius on the natural history of the Indies. Amherst: University of Massachusetts Press.

Russo, E.B. (2002) *The Role of Cannabis and Cannabinoids in Pain Management*.
In: *PAIN MANAGEMENT A Practical Guide for Clinicians SIXTH EDITION*
Editor Richard S. Weiner AMERICAN ACADEMY OF PAIN MANAGEMENT CRC PRESS
Boca Raton London New York Washington, D.C.
https://archive.org/stream/TheRoleOfCannabisAndCannabinoidsInPainManagement/The%20Role%20of%20Cannabis%20and%20Cannabinoids%20in%20Pain%20Management_djvu.txt

Russo EB, Guy GW, Robson PJ (2007). Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chem Biodivers 4: 1729–1743.

Russo EB (2011) Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 163(7):1344-64. doi: 10.1111/j.1476-5381.2011.01238.x.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/
https://www.ncbi.nlm.nih.gov/pubmed/21749363

Russo, E.B., Marcu J. (2017) in press, article in book: *Advances in Pharmacology*
Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads; Article Number: 111.
Elsevier Press, http://dx.doi.org/10.1016/bs.apha.2017.03.004

Ryan D, Drysdale AJ, Pertwee RG, Platt B. (2006) Differential effects of cannabis extracts and pure plant cannabinoids on hippocampal neurones and glia. *Neurosci Lett*. 408:236–241. [PubMed]

Setzer, W.N., M.C. Setzer, D.M. Moriarity, R.B. Bates, and W.A. Haber. 1999. Biological activity of the essential oil of Myrcianthes sp. nov. “black fruit” from Monteverde, Costa Rica. Planta Med 65(5):468-9.

Sharma, C., Al Kaabi, J. M., Nurulain, S. M., Goyal, S. N., Kamal, M. A., & Ojha, S. (2016). Polypharmacological properties and therapeutic potential of β-caryophyllene: A dietary phytocannabinoid of pharmaceutical promise. *Current Pharmaceutical Design*, 22(21), 3237–3264

Shoemaker, J.V. (1899). The therapeutic value of Cannabis indica. Texas Medical News, 8(10), 477-488.

Silver, A. (1870). On the value of Indian hemp in menorrhagia

and dysmenorrhoea. Medical Times and Gazette, 2,
59-61.

Sloman, L. (1979). *Reefer Madness: The History of Marijuana in America*. Bobbs-Merrill.
ISBN 978-0-672-52423-3.

Stein DJ, Arya M, Pietrini P, Rapoport JL, Swedo SE. (2006)
Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: a positron emission
tomography study.*Metab Brain Dis. 21(2-3):267-77. Epub 2006 Jul 19.*
https://www.ncbi.nlm.nih.gov/pubmed/26301829
https://link.springer.com/article/10.1007/s11011-006-9021-6

Suckling, C. (1891). On the therapeutic value of Indian hemp.
British Medical Journal, 2, 12.

Thompson, R.C. (1924). The Assyrian herbal. London: Luzac
and Co.

Thompson, R.C. (1949). A dictionary of Assyrian botany. London: British Academy

Wagner H, Ulrich-Merzenich G (2009). Synergy research:
approaching a new generation of phytopharmaceuticals. Phytomed
16: 97–110.

Waring, E. (1874). Practical Therapeutics. Philadelphia: Lindsay and Blackiston.

Wilkinson JD, Whalley BJ, Baker D, Pryce G, Constanti A, Gibbons S, et al. (2003) Medicinal cannabis:
is delta9-tetrahydrocannabinol necessary for all its effects? *J Pharm Pharmacol*. 55:1687–
1694. [PubMed]

Williams, C.S., Mann, M. and Raymond N DuBois, R.N.
(1999) The role of cyclooxygenases in inflammation, cancer, and development *Oncogene*,
Volume 18, Number 55, Pages 7908-7916
http://www.nature.com/onc/journal/v18/n55/full/1203286a.html

Williamson EM (2001). Synergy and other interactions in
phytomedicines. Phytomed 8: 401–409.

Zias, J., Stark, H, Sellgman, J., Levy, R., Werker, E., Breuer,
A., & Mechoulam, R. (1993). Early medical use of
cannabis. Nature, 363(6426), 215.

Zuardi AW, Rodrigues JA, Cunha JM (1991). Effects of cannabidiol
in animal models predictive of antipsychotic activity.
Psychopharmacol 104: 260–264.

Zuardi AW, Guimaraes FS (1997). Cannabidiol as an anxiolytic and

antipsychotic. In: Mathre ML (ed.). Cannabis in Medical Practice: A Legal, Historical and Pharmacological Overview of the Therapeutic Use of Marijuana. McFarland: Jefferson, NC, pp. 133–141.

Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimaraes FS (2006). Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res 39: 421–429.

Web References:

1. **https://blogs.scientificamerican.com/scicurious-brain/knocking-5-ht1a-down-to-bring-mood-up/**

2. http://www.theweek.co.uk/65464/when-was-cannabis-made-illegal-in-the-uk

3. https://www.the-mha.org/treating-breast-cancer-with-cannabis/

4. http://www.cannabiscure.info/cannabis-breast-cancer/

5. **https://www.cancer.org/latest-news/10-must-know-2015-global-cancer-facts.html**

6. https://www.youtube.com/watch?v=fQwwGPiyW9M

7. http://phoenixtears.ca/producing-the-oil/

8. http://phoenixtears.ca/dosage-information/

Appendix: reprinted from:
Beyond the Veil: Deception, Truth and the Hidden Promise of Science (2016) written by Jeremy Dunning-Davies and Richard Lawrence Norman, Standing Dead Publications). Section below written by Rich Norman.

Monetary priority and medical practice: the 'patentable molecule.'

There are two sides to the conundrum of greed in medicine: the 'patentable molecule.' On one side, the drugs produced, just as Pasteur's lucrative yet deadly vaccines, carry with them a monetary incentive which affects bias toward confirmation of drug efficacy. That implies that drugs may be produced and sold which are ineffective and/or harmful so as to make money. The other side to this dirty coin, is the lack of incentive to bring forward treatment strategies or specific options which although effective and healthful, are not patentable and so, cannot extract money from the health of mankind.

Parkinson's and profit, un-patentable molecules and studies:

Parkinson's Disease (PD) is a common cause of neuro-degeneration in the geriatric population. This prolific and dread affliction may be ameliorated with a variety of substances which are unavailable for patent. This is not an assertion based in a soft-headed holistic naturopathic daydream. The following facts are extracted from detailed studies which are in the main available on the single most conservative source of modern mainstream orthodox science, the U.S. National Library of Medicine National Institutes of Health's archive at PubMed. Other sources below, are also from trustworthy peer reviewed journals. Please investigate the sources which I will reference with a simple link in the text, and assure yourself with a click as to the quality and reliability of the science. In place of the traditional reference list I will include a bibliography.

It should be noted that among the many compounds which are included below are some derived from cannabis, the international and local laws concerning which being quite arbitrary and various. In England doctors are legally and, I believe rightly, permitted to prescribe heroin in cases of severe pain, yet are not permitted to prescribe the much less dangerous drug cannabis, under any circumstance. One constituent in the highly complex assemblage of active compounds in cannabis, namely CBD, may well be efficacious in the amelioration of various pathologies from Parkinson's to seizure disorders, and causes no intoxicating side effects. It appears logical to reexamine the laws concerning cannabis and the rights of doctors to prescribe it, and/or its constituents. (The cannabis based pharmaceutical drug Sativex [GW pharmaceuticals] is the lone exception permitted for prescription in England to treat spasticity in multiple sclerosis). I do not recommend or advise any treatment strategy which does not adhere to the laws and legal codes where you reside.

Condensed facts [Cannabis/THC/CBD, Pregnenolone, Cinnamon, Thiamine, K2, D, Glutathione]:

Cannabis/THC/CBD and the uninvestigated role of pregnenolone:

a. From, Modifications of neuroactive steroid levels in an experimental model of nigrostriatal degeneration: potential relevance to the pathophysiology of Parkinson's disease. Melcangi et al.
"Among the neuroactive steroid levels assessed (i.e., pregnenolone, progesterone, dihydroprogesterone, tetrahydroprogesterone, isopregnanolone, testosterone, dihydrotestosterone, 3α-diol, dehydroepiandrosterone, 17α-estradiol, and 17β-estradiol), we observed a significant decrease of pregnenolone in the striatum."

b. From, Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Lotan et al.
"RESULTS: Mean (SD) total score on the motor Unified Parkinson Disease Rating Scale score improved significantly from 33.1 (13.8) at baseline to 23.2 (10.5) after cannabis consumption ($t = 5.9$; $P < 0.001$). *Analysis of specific motor symptoms revealed significant improvement after treatment* in tremor ($P < 0.001$), rigidity ($P = 0.004$), and bradykinesia ($P < 0.001$). CONCLUSIONS: *There was also significant improvement of sleep and pain scores. No significant adverse effects of the drug were observed. The study suggests that cannabis might have a place in the therapeutic armamentarium of PD.* [Emphasis added].

c. From, Pregnenolone Can Protect the Brain from Cannabis Intoxication. Vallee et al.
"Pregnenolone is considered the inactive precursor of all steroid hormones, and its potential functional effects have been largely uninvestigated. The administration of the main active principle of *Cannabis sativa* (marijuana), Δ^9-tetrahydrocannabinol (THC), substantially increases the synthesis of pregnenolone in the brain via activation of the type-1 cannabinoid (CB_1) receptor." [Emphasis added].

d. There are antioxidant effects and others ascribed to CBD as well. From, Prospects for cannabinoid therapies in basal ganglia disorders. Fernandez-Ruiz et al.
"This CB(2) receptor up-regulation has been found in many neurodegenerative disorders including HD and PD, which supports the beneficial effects found for CB(2) receptor agonists in both disorders. In conclusion, the evidence reported so far supports that *those cannabinoids having antioxidant properties and/or capability to activate CB(2) receptors may represent promising therapeutic agents in HD and PD, thus deserving a prompt clinical evaluation." [Emphasis added]*.

e. From, Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. García-Arencibia et al.
"In summary, our results indicate that those cannabinoids having antioxidant cannabinoid receptor-independent properties provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons occurring in PD. In addition, the activation of CB2 (but not CB1) receptors, or other additional mechanisms, might also contribute to some extent to the potential of cannabinoids in this disease."

f. From, Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and

in vitro: relevance to Parkinson's disease. Lastres-Becker et al.
"In summary, our results support the view of a potential neuroprotective action of cannabinoids against the in vivo and in vitro toxicity of 6-hydroxydopamine, which might be relevant for PD. Our data indicated that these neuroprotective effects might be due, among others, to the antioxidant properties of certain plant-derived cannabinoids, or exerted through the capability of cannabinoid agonists to modulate glial function, or produced by a combination of both mechanisms."

We may conclude that Cannabis/THC/CBD may be helpful in the treatment of Parkinson's.

K2 and Mitochondrial function:

a. Parkinson's is a disease of energetic deficiency stemming from mitochondrial dysfunction. From, PINK1 Loss-of-Function Mutations Affect Mitochondrial Complex I Activity via NdufA10 Ubiquinone Uncoupling. Morais et al.
“A second hypothesis suggests that PINK1 has a direct effect on mitochondrial complex I, affecting the maintenance of the electron transport chain (ETC) resulting in decreased mitochondrial membrane potential and dysfunctional mitochondria.”
And from Mitochondrial Biology and Parkinson's Disease. Perier and Vila. "Whether a primary or secondary event, mitochondrial dysfunction holds promise as a potential therapeutic target to halt the progression of dopaminergic neurodegeneration in PD."

b. Mitochondrial electron carrier, vitamin K2, rescues Parkinson's disease models based on this theory. From, Vitamin K2 is a mitochondrial electron carrier that rescues pink1 deficiency. Vos et al.
"We found that vitamin K(2) was necessary and sufficient to transfer electrons in Drosophila mitochondria. Heix mutants showed severe mitochondrial defects that were rescued by vitamin K(2), and, similar to ubiquinone, vitamin K(2) transferred electrons in Drosophila mitochondria, resulting in more efficient adenosine triphosphate (ATP) production. Thus, mitochondrial dysfunction was rescued by vitamin K(2) that serves as a mitochondrial electron carrier, helping to maintain normal ATP production."

We may conclude that K2 may be helpful in the treatment of Parkinson's.

Vitamin D:

Vitamin D has been demonstrated to slow the physical deterioration associated with Parkinson's. From, Randomized double blind placebo controlled trial of vitamin D supplementation in Parkinson disease. Suzuki M, et al.
"Compared with the placebo, vitamin D3 significantly prevented the deterioration of the HY stage in patients [difference between groups: P = 0.005; mean ± SD change within vitamin D3 group: +0.02 ± 0.62 (P = 0.79); change within placebo group: +0.33 ± 0.70 (P = 0.0006)]."

We may conclude that Vitamin D may be helpful in the treatment of Parkinson's.

Glutathione:

According to Dr. Julian Whitaker, from his newsletter of September, 2014:

"Glutathione is the major antioxidant produced in neurons and cells throughout the body. Oxidative stress and inflammation are implicated in the dysfunction and ultimate death of dopamine-producing cells. Restoring depleted glutathione stores slows this destructive process and improves symptoms in patients with Parkinson's. IV administrations helps ensure it gets into the brain.

I'll never forget one of the first patients we treated at the clinic with IV Glutathione. He had a significant tremor in his left arm and arrived in a wheelchair. After his second IV treatment, his tremor decreased and he was up and walking, albeit with an unsteady gait and his arms stiff at his sides. After his third infusion, he was walking more or less normally, with a confident stride, arms swinging—and no tremor."

Also see: Reduced intravenous glutathione in the treatment of early Parkinson's disease. Sechi G, et al.
"All patients improved significantly after GSH therapy, with a 42% decline in disability. Once GSH was stopped the therapeutic effect lasted for 2-4 months. 4. Our data indicate that in untreated PD patients GSH has symptomatic efficacy and possibly retards the progression of the disease."

Also see: Glutathione and Parkinson's disease: is this the elephant in the room? Zeevalk et al.

Nasal administration may also be effective. See Central nervous system uptake of intranasal glutathione in Parkinson's disease. Mischley et al.

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We may conclude that Glutathione may be helpful in the treatment of Parkinson's.

Thiamine:

From, Long-Term Treatment with High-Dose Thiamine in Parkinson Disease: An Open-Label Pilot Study. Costantini et al.

"CONCLUSIONS:
Administration of parenteral high-dose thiamine was effective in reversing PD motor and non-motor symptoms. The clinical improvement was stable over time in all the patients. From our clinical evidence, we hypothesize that a dysfunction of thiamine-dependent metabolic processes could cause selective neural damage in the centers typically affected by this disease and might be a fundamental molecular event provoking neurodegeneration. Thiamine could have both restorative and neuroprotective action in PD."

From, High-dose thiamine as initial treatment for Parkinson's disease. Costantini et al.

"Injection of high doses of thiamine was effective in reversing the symptoms, suggesting that the abnormalities in thiamine-dependent processes could be overcome by diffusion-mediated transport at supranormal thiamine concentrations."

From, The Beneficial Role of Thiamine in Parkinson's Disease: Preliminary Report. Luong et al.
"Five PD patients presented with stone face, right-hand tremors, Parkinsonian gait and bradykinesia with occasional freezing. Two patients presented with sialorrhea and the plasma transkelosase activity was low in one patient. All of the patients received 100 - 200 mg daily doses of parenteral thiamine. Within days of thiamine treatment, the patients had smiles on their faces, walked normally with longer steps, increased their arm swings, and experienced no tremors or sialorrhea."

We may conclude that Thiamine may be helpful in the treatment of Parkinson's.

Cinnamon:

From, Cinnamon treatment upregulates neuroprotective proteins Parkin and DJ-1 and protects dopaminergic neurons in a mouse model of Parkinson's disease. Khasnavis and Pahan.
". . . However, oral treatment of MPTP-intoxicated mice with cinnamon powder and NaB reduced the expression of iNOS and protected Parkin/DJ-1 in the nigra. These findings paralleled dopaminergic neuronal protection, normalized striatal neurotransmitters, and improved motor functions by cinnamon in MPTP-intoxicated mice. *These results suggest that cinnamon may be beneficial for PD patients." [Emphasis added]*.

We may conclude that Cinnamon may be helpful in the treatment of Parkinson's.

Conclusion:

In the case of Parkinson's disease a safe, inexpensive, nontoxic, efficacious supplement might easily be developed based in this science. It may well offer substantial prophylactic protection against the onset of full blown symptomatology, and aid in the curtailment of disease processes when symptoms are evident. Those without active symptoms who have the dread LRRK2 mutation, or those with a family history of Parkinson's may be wise to take it, and those who display symptoms as well. Clearly, a diet rich in these pharmacologically active nontoxic compounds, may provide substantial benefit. I hypothesize as these studies are well known, that the only reason this obvious benefit has yet to be brought to fruition and these ideas are not in current clinical practice, is due to the fact that they are natural molecules and hence, cannot be patented. When money dictates medical practice, people remain ill and *pay*. Inexpensive effective treatments which do not benefit a large drug company or industry, are simply left to wither. This is why those effective treatments which are currently available are toxic and costly.

Oxytocin:
The category of 'unprofitable but safe' molecular constituents is large. I will choose very quickly oxytocin (OT) as an additional example. With antidepressant properties (Panksepp, 1998) and possible benefits extending from neurosis and sexual dysfunction to schizophrenia, alongside clear effects in creating neural plasticity, there are a great many who might benefit from different modes of treatment. I have constructed several such treatments but am unable to fund the studies to advance them. Why is this safe neuropeptide not already in clinical practice after years of detailed study?

"Although intranasal OT appears quite safe and tolerable, there are several practical barriers to its therapeutic drug development in humans. These include the lack of intellectual property ownership of the actual hormone, lack of US Food and Drug Administration (US FDA) approval for any psychiatric indication and challenges around the actual availability of the drug." [MacDonald and Feifel, 2012]—Oxytocin in schizophrenia: a review of evidence for its therapeutic effect.

The list of stated practical "clinical hurdles" articulated in that study is painfully weak. Only money has prevented this substance from serving the greater good and health of man.

Profit from poison:

The other face of the 'patentable molecule', this dirty coin of the realm in for-profit medical science, is to be found in toxic harmful compounds which although of little or no clinical use, do cause harm to those who take them and yield profit for the companies which develop and pedal them to consumers and physicians.

Statin drugs (such as Lipitor or Crestor), are not heart protective, they are a money making racket. They do lower cholesterol, but the benefits have been falsified. These drugs can CAUSE heart failure, and sabotage the energy production mechanisms of the cell. They cause the problems they are supposed to prevent. These deadly pills are, however, some of the very best selling drugs of all time.

An enzyme is blocked by statins which thereby suppresses the production of a coenzyme: CoQ10––that harms the ATP production process. The drugs are toxic to mitochondria. They interfere with K2 production. That leads to hardening of the arteries. These drugs can *cause* heart failure! Glutathione is interfered with leading to oxidative stress. As is known, statins are associated with cataracts, liver damage, kidney disease, cancer, sexual dysfunction, depression, memory loss, and diabetes. How have we citizens and many doctors been fooled?

"Relative Risk Reduction" statistical analysis has been falsely applied to create the impression that, what are ~one/two percent benefits…revealing a worthless treatment, which harms a great many, are "in fact" 30 and 50 percent gains in the amelioration of pathology. With annual lobbying for the pharmaceutical/health giants amounting to ~$235,107,261 in 2015, it appears, *the government*

is in bed with the corporations. The modern system of money and scientific advancement is flawed, ugly and dangerous. An entirely new way to fund science is required.

From an important PubMed paper on the topic (Okuyama et al., 2015), we can see what this means for each of us:

"An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency. **Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs**. We propose that current statin treatment guidelines be critically reevaluated." [Emphasis added]. [Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms. Okuyama et al.]

Just in case you imagine that to be a fluke, a simple mistake from our benevolent and protective monetary-based authoritarian government and for-profit scientific and medical industries…please note the following: It is official that the top grossing drug in America (in 2014) was ***an anti-psychotic***: Abilify. Complete with the usual anti-psychotic profile of side-effects, such as *permanent ticks and motor symptoms*: Tardive Dyskinesia. Now, prescribed for depression, typically with an SSRI (such as Prozac or Zoloft), which are themselves potentially associated with suicide upon withdrawal, and their own permanent condition, Tardive Dysphoria. Let's be clear: these "nonaddictive" SSRI drugs, do not themselves cause death upon withdrawal. SSRI drugs (used for depression and OCD) are only correlated with death via one of the most certain findings in all of psychiatry: low 5-HT is associated with suicide. Withdrawal therefore, may lead to death. Not an addictive drug. Simply know, if you stop from high doses, you may die by suicide. Taper very gradually, and only attempt withdrawal under a doctor's supervision, knowing, there may or may not be permanent damage. Now Abilify with its anti-psychotic profile of damage is also handed out like anti-psychotic candy for depression. American medicine...is a racket...nearly as lucrative as war. These drugs do most assuredly have a valid place in medicine, they are indispensable for those few who need them. Please do understand: using them as high dollar substitute jelly beans is not it. ~7 billion dollars in sales from Abilify, in one year (2014). Money makes for deadly, toxic medicine.

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For a sample of Richard's scientific and creative work please enjoy the entire of *Mind Magazine* www.mindmagazine.net. The "New Ideas" section contains some of his papers and articles detailing potential new medical treatments without toxicity; affective analysis of quantum Clifford algebraic theory; analysis of relativistic theory; analysis of subjective quantum theory; analysis of aqueous systems; analysis of objective reality; analysis of wave/particle duality and light; analysis of quantum unconscious isomorphism; examination of relativity; psycho-ontology and fractal dimension; temporal field theory; Bohmian mechanics; quantitative approaches to the human unconscious; new approaches to pharmacology; mnemic connectionist modeling as a holographic paradigm; ontological calculus; semi-regressive plastic attachment therapy; temporal process as tripartite pre-temporal simultaneity; quantitative unconscious theory; re-polarization theory; homeostatic conductance and parasympathetic basis alteration (new approaches to Parkinson's; OCD; Depression); the hard problem of consciousness (new solution); informational pleomorphism; somatic adaptivity and ego process; new methods proposed to treat degenerative nerve disease and others, some utilizing quantum information mediated through aqueous systems in place of drugs.

Other papers are available here:
https://www.researchgate.net/profile/Rich_Norman/publications