Cannabis and Its Place in Modern Medicine

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"The contrary qualities of the plant, its stimulant and sedative effects, are prominently dwelt on. They at first exhilarate the spirits, cause cheerfulness, give color to the complexion, bring on intoxication, excite the imagination into the most rapturous ideas, produce thirst, increase appetite, and excite concupiscence. Afterwards the sedative effects begin to preside, the spirits sink, the vision darkens and weakens; and madness, melancholy, fearfulness, dropsy, and such like distempers, are the sequel-and the seminal secretions dry up. These effects are increased by sweets, and combated by acids…. It produces a ravenous appetite and constipation, arrests the secretions except that of the liver, excites wild imagining, especially a sensation of ascending, forgetfulness of all that happens during its use, and such mental exaltation, that the beholders attribute it to supernatural inspiration."

-Description of Cannabis effects, *via* translation of ***Mukzun-ul-Udwieh***, an ancient Persian text

INTRODUCTION

The sages and healers of antiquity were the intellectual cornerstones of their communities. Possessed with insatiable curiosity toward the world around them, they soon discovered a relationship with the plant kingdom. Wild edible plants have always been plentiful. From the cacti of the deserts to the flowers of the Himalayas to the herbs of the Caribbean, plant "consumption" by humans often takes the obvious form of food. The Cannabis plant has been found all over the world, but thought to originate in what is now mid and West Asia. Ancient medical writings ranging from Egypt and Persia to China and India have words and symbols in their respective languages describing the Cannabis plant and its medicinal properties. [1]

Fast forward over 4500 years, and the Cannabis plant has stood the test of time. Extinction is not part of its story. It has propagated itself and possesses innate knowledge of how to interact with its environment. The plant secretes an oily resin, containing cannabinoids, a class of molecules specific to this plant. Metaphorically, cannabinoids are like keys that insert into locks. Over 400 "keys" have been discovered since the 1940's.[2-4] What is relatively new (30 years) within the scientific community is the evidence that humans and other animals have already been programmed to interact with the cannabis plant. The discovery of the human endocannabinoid system of receptors has proved to be one of the more interesting discoveries of the 21st century.[5] Research continues to be prolific in this area, but it is not without conflict. Up against longstanding federal statute and a legislative environment that began with a provision of the Uniform Narcotic Drug Act proposed in 1932 and subsequently with the Marihuana Tax Act of 1937, only 26 states have legalized "medical marijuana" to date. Coupled with the financial lobbying potential of the trillion dollar pharmaceutical industry, medicinal Cannabis has plenty of hoops to jump before being embraced as a viable phytopharmaceutical, or plant-derived medication. Can the Cannabis plant and the human world at large coexist? The purpose of this article is threefold: to review our current knowledge of this natural, living organism called the Cannabis plant; to understand how it can advance medical treatment of chronic pain, cancer, immunity, and various other health maladies; and the potential as medical marijuana makes the transition from "taboo" into a highly regulated and profitable pharmaceutical arena.

ETHNOBOTANY

The original natural habitat of Cannabis encompassed mid and Western Asia in what is now India, China, and the Middle East, but varying species of the plant is now found ferally in North America and Canada. The Cannabis plant grows very tall and erect, often times reaching 20 feet (6 m) within its natural life cycle of 4-6 months.[1] What has been discovered within these plants are a group of chemicals called **cannabinoids**, the most well-known of which is **delta-9 tetrahydrocannabinol (THC)**, the chemical responsible for the psychoactive effects of the Cannabis plant.[6]

All living organisms belong to a certain taxonomy, or classification. Taxonomy follows the common nomenclature of Family, Genus, and Species. For example, humans are in the Family *Hominadae*, Genus *Homo* and Species *Homo sapiens*. The cannabis plant belongs to the Family *Cannabaceae*, or "a family of flowering plants." This *Cannabaceae* Family includes two prominent Genus members: **Cannabis** (hemp, marijuana), and **Humulus** (hops). [1] The *Cannabaceae* Family takes on different morphologies or shapes, including trees (e.g. *Celtis*), erect herbs (e.g. *Cannabis*), or climbing plants (e.g. *Humulus*). [6-7]

As we move further down the taxonomy, the Cannabis genus has 3 prominent species***: Cannabis sativa, Cannabis indica, and Cannabis ruderalis***. *Cannabis sativa* is generally found at higher sunnier altitudes. This species has long slender leaves, grows better outdoors with a longer flowering period, and the plants produce a predominance of the molecule THC (more energetic, euphoric feeling). *Cannabis indica* has shorter, more broad leaves, has better yields when growing indoors with a shorter flowering period (i.e., more yield), and the plants produce more of the cannabinoid molecule called CBD (a relaxing, sleepy feeling). *Cannabis indica* is thought to have originated in Afghanistan, Morocco, and Tibet-countries that produce most of the world's hashish, a concentrated form of Cannabis. *Cannabis ruderalis* originated in Central Russia, and survives in more harsh conditions. This species flowers based on its age, not on the light cycle as with the other two species. Ruderalis is known to be lower in THC content but higher in another type of molecule called CBD, similar to *Cannabis indica*. [7-9]

HISTORY OF CANNABIS: From Textiles to Medicine

Various part of the plants are used for different purposes, including the stems, leaves, seeds, flowers, and buds. Traditionally, parts of the Cannabis plant have been used as fiber, fuel, timber, animal feed and medicine. The hemp fiber found in stalk is considered some of the strongest in the plant kingdom. Historically, hemp was introduced into Europe in the 12th century and was used for paper, oil, and sails. Although the seedlings are believed to have rooted in mid and West Asia, Cannabis spread to the New World as European explorers set sail; hemp seeds were brought to the US by the Jamestown settlers in 1611. Hemp fibers were replaced eventually by wood pulp, influenced both by the politics of the time and by advances in textile manufacturing. [9]

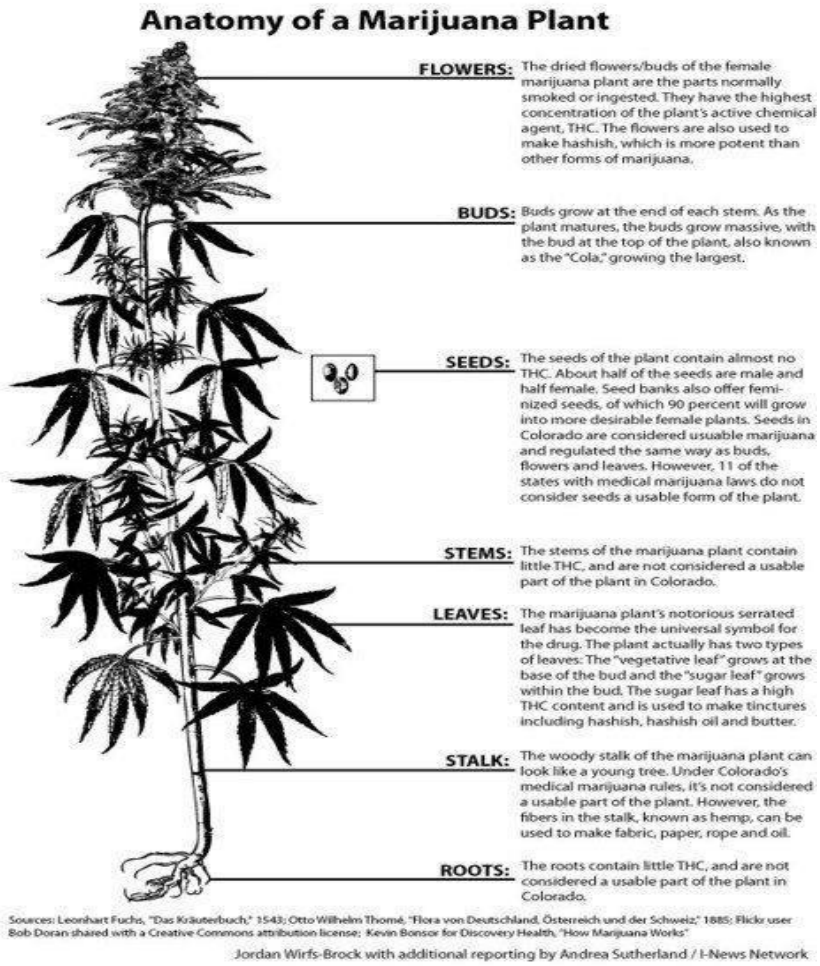


Figure: Anatomy of a Cannabis Plant [10]

Recorded writings from all over the world have included Cannabis for medicinal purposes. The most concentrated area for THC in the Cannabis plant is found in the "cola," the flower at the top of the plant. The ancient Chinese emperor, Shen Nung (2700 BC), was considered to be the father of Chinese medicine. He wrote of the healing properties of ginseng, ephedra, and marijuana. Some anthropologists and Biblical scholars claim to find evidence of Cannabis plants, called kaneh-bosem (or calamus) in Hebrew, in the preparation of holy anointing oil in the book of Exodus (30: 22-25) in older translations of the Bible. US Presidents George Washington and Thomas Jefferson both grew hemp; diary entries by President Washington show that he used it for medicinal purposes.[11]

A turning point in contemporary medical applications of the Cannabis plant occurred in the 19th century. Dr. William Brooke O'Shaughnessy was a physician and scientist who graduated from the University of Edinburgh (Scotland), and a professor of chemistry at the Medical College of Calcutta, India. Dr. O'Shaughnessy traveled extensively throughout India, exploring and learning from indigenous medical doctors and traditional healers. In 1839, he introduced the Western world to the medicinal uses of Cannabis indica, or "Indian hemp," after his time in Calcutta, India. In his seminal paper entitled "**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**," he describes for the first time an herb that was unknown to the Western world. He eludes: *"The narcotic effects of hemp are popularly known in the South of Africa, South America, Turkey, Egypt, Asia Minor, India, and the adjacent territories of the Malays, Burmese, and Siamese. In all these countries hemp is used in various forms, by the dissipated and depraved, as the ready agent of a pleasing intoxication. In the popular medicine of these nations, we find it extensively employed for a multitude of affections, especially those in which spasm or neuralgic pain are the prominent symptoms. But in Western Europe its use, either as a stimulant or as a remedy, is equally unknown. "* [11-12]

It is apparent that Dr. O'Shaughnessy spent much time learning from the Indian healing community. In his writings, he ventures to describe the anatomy of the plant, its chemical properties, and its popular uses. Even then, a similar harvesting procedure occurred as does today: "the natives cut the plant when in flower, allow it to dry for three days, and then lay it in bundles averaging two pounds weight each, which are distributed to the licensed dealers. " Dr. O'Shaughnessy was studious of other scientific texts by Arabian and Persian writers, one of which was called the Mukzun-ul-Udwieh. While other accounts of the time alluded only to the historical and botanical context of Cannabis, these ancient texts explain the plant properties from the perspective of ancient physicians: *"The contrary qualities of the plant, its stimulant and sedative effects, are prominently dwelt on. They at first exhilarate the spirits, cause cheerfulness, give color to the complexion, bring on intoxication, excite the imagination into the most rapturous ideas, produce thirst, increase appetite, and excite concupiscence. Afterwards the sedative effects begin to preside, the spirits sink, the vision darkens and weakens; and madness, melancholy, fearfulness, dropsy, and such like distempers, are the sequel- and the seminal secretions dry up. These effects are increased by sweets, and combated by acids…. It produces a ravenous appetite and constipation, arrests the secretions except that of the liver, excites wild imagining, especially a sensation of ascending, forgetfulness of all that happens during its use, and such mental exaltation, that the beholders attribute it to supernatural inspiration."* [11-12]

The influence of the Cannabis plant was immense. The Royal Physician of England Sir Robert Russell used Cannabis to treat Queen Victoria's menstrual cramps. By mid-1800's, Cannabis use was widespread in the Western medical field, indicated for headaches, appetite stimulation, and insomnia. [11, 13] In 1850, medical Cannabis was found in the US Pharmacopeia, the official authority for all prescription and over-the-counter medications. Indications for use included "neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding, among others. Patented marijuana tinctures were sold..." [14]

Sir John Russell Reynolds, the president of the British Medical Association and another physician to the royal household, wrote a paper in Lancet in 1890 reviewing 30 years of personal experience in prescribing cannabis. He was a staunch advocate for its legitimate medicinal usages. [15] In 1915, the father of modern medicine, Sir William Osler, advocated for cannabis use in migraine, which he published in his textbook **The Principles and Practice of Medicine**. He stated that when treating migraine, "Cannabis indica is probably the most satisfactory remedy." [9, 15]

The utility of Cannabis in various medical disorders continues to be documented. Examples of these disorders include: chronic pain, inflammatory bowel disease, epilepsy, headaches, spasticity of muscles, nausea and vomiting from chemotherapy, appetite stimulation in cachexia,

glaucoma, and various autoimmune diseases. [15] However, scientific study of and contemporary medical acceptance of this plant has been limited by a multitude of factors, especially by the politics of the 20th century's War on Drugs.

WHAT ARE CANNABINOIDS?

The active ingredient of the poppy plants *Papaver somniferum* are opiate alkaloids and were isolated in the late 1800's. This discovery led to the eventual development of the narcotic pain medicines, first introduced by the German company Bayer in 1898.[17] Despite widespread usage, the mechanism of action of the Cannabis plant was not discovered until 1964 when the identification, isolation, and synthesis of THC as the active ingredient in Cannabis was achieved.

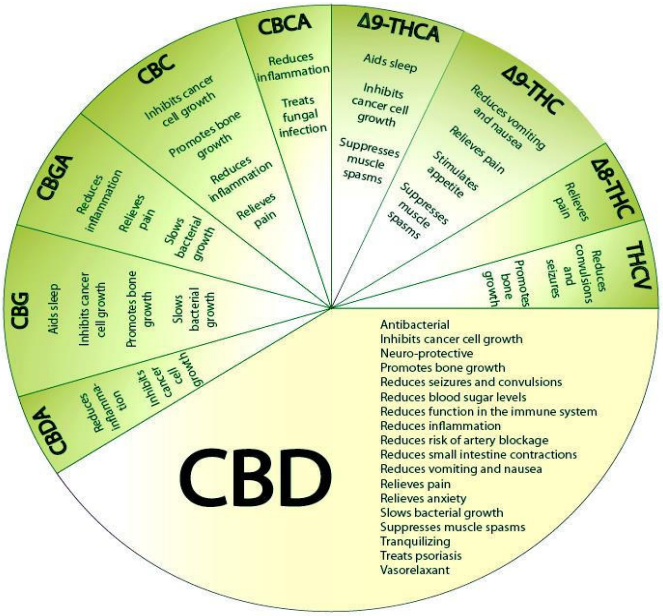
Cannabinoids is a term used to describe the active ingredient(s) in Cannabis. We now know that there are 3 types of cannabinoids known to man: **phytocannabinoids** (found in plants), **endocannabinoids** (found in the humans and other mammals, birds, fish, and reptiles), and **synthetic cannabinoids** (made in the lab). The Cannabis plant has been found to contain over 500 chemical compounds, including over 60 phytocannabinoids, which are chemical molecules unique to this plant. Cannabis also contains other chemical compounds, including proteins, sugars, enzymes, terpenoids (produce the notorious odor of the plant), flavonoids, esters and essential fatty acids (found in seeds as nutrients).[18]

A group of Israeli pharmacology researchers led by Dr. Raphael Mechoulam in 1964 were the first to isolate and discover the most well-known cannabinoid **delta-9 tetrahydrocannabinol (THC)**.[4] THC, however, does not act alone to cause the psychoactive effects of Cannabis. The effects are modulated by other types of cannabinoids and the other chemicals within the plants. This whole plant concept is a cornerstone of herbal medicine and has been called the "**entourage effect**," another phenomenon discovered by Dr. Mechoulam's team in 1988. [19] This effect describes the idea that there is more than one active cannabinoid that effects the body; these cannabinoids, along with other chemical constituents in the plant, exert their effect on the human body. They theorized that cannabinoids within the Cannabis plant possess synergy and work together, affecting the body in a mechanism similar to the body's own **endocannabinoid system**, discovered by the same team in 1992.[2-3] Pharmaceutical companies, on the other hand, often look to isolate a single active ingredient and manufacture it into a drug, or a synthetic cannabinoid. Examples of synthetic drugs include Marinol (used for appetite stimulation and anti-nausea) and Sativex (used for cancer pain and the spasticity of multiple sclerosis). Many herbal medicines are superior to the isolated chemical constituents, both pharmacologically and therapeutically. Current scientists have built onto this theory of the entourage effect, stimulating a novel way of studying the therapeutic potential of herbal medicine. By using state-of-the-art technology, these researchers are advancing the understanding of the entourage effect, thereby spurring the development of a new generation of "**phytopharmaceuticals**," or plant based medicine.

The main **phytocannabinoids** have been named and separated into other classes:

- Cannabigerols (CBG)
- Cannabichromenes (CBC)
- Cannabidiols (CBD)
- Tetrahydrocannabinols (THC)
- Cannabinol (CBN) and cannabinodiol (CBDL)
- Other cannabinoids (such as cannabicyclol (CBL), cannabielsoin (CBE), cannabitriol (CBT) and other miscellaneous types

While THC was the initial cannabinoid that garnered international attention, contemporary scientific research has begun to proliferate on **cannabidiol (CBD).** This cannabinoid gives Cannabis its sedative effect. CBD has been the subject of intense research due to a multitude of evidence that suggests benefit for various medical conditions (migraine headaches, rheumatoid arthritis, autoimmune diseases, diabetes, epilepsy, nausea, bowel disorders, and schizophrenia).[18, 21] The discovery of THC and others as phytocannabinoids, along with the discovery of the endocannabinoid receptor system in 1988, laid the scientific foundation that has facilitated the re-emergence of Cannabis as a modern medicine. The table below [21] summarizes some of the known biological effects of the phytocannabinoids.



THE PHYTOCANNABINOID SYSTEM

Wild edible plants have always been plentiful. From the cacti of the deserts to the flowers of the Himalayas to the herbs of the Caribbean, plant "consumption" by humans often takes the obvious form of food. Let's remember that the Cannabis species are flowering plants. Each possesses a life cycle which differs from male to female plants. What attracts the pollinators is the magical ingredient, a group of molecules called the phytocannabinoids, and these molecules live within their special home, called the **trichome**. [22] These appendages are like finger-shaped mushrooms, simple extensions of the epidermis, or skin, of the plant.

http://cdn5.theweedblog.com/wp-content/uploads/Trichomes-are-milky-white-.jpg

The female plant produces more trichomes than the male, and the cannabinoids are chemically activated once the trichomes are exposed to UV-B rays from sunlight. As the plant flowers, the oily liquid resin that develops within the tips of the trichome eventually becomes ready for harvest, to be used topically or via ingestion and inhalation. These chemical cannabinoid *keys*, when released from the trichome are called **ligands**; they possess an innate intelligence to seek out the *locks*, or **receptors**, on various cells.

THE ENDOCANNABINOID SYSTEM

The endocannabinoid system, although recently discovered in 1992, is thought to have evolved 600 million years ago in the sea squirt. The main purpose of this system is to provide homeostasis, or in other words, a stable internal environment despite changes in the outside environment. The endocannabinoid system helps different cells to communicate and works in concert with other chemicals in the body called neurotransmitters. [23] It is postulated that some diseases emerge when the endocannabinoid system is dysfunctional.

Dr. Mechoulam and team dedicated their life research to advancing the understanding of the Cannabis effect of animal cells. Twenty-five years after discovering THC in the Cannabis plant, this team discovered the cannabinoid receptors and the endocannabinoid system in the rat brain. Four short years later in 1992, 2 endocannabinoid ligands were discovered in animals that were chemically similar to THC, named anandamide (Sanskrit for "supreme joy") and 2-AG (2-Arachidonoylglycerol). These ligands bind to 2 different types of receptors in animals, aptly named CB1 and CB2.[2, 3, 5, 23]

CB1 receptors are found primarily in the brain, spinal cord, peripheral nerves, and reproductive system; activation of these receptors regulate motor control, cognition, and emotional responses; provide neuroprotection, and modulate pain and memory. These CB1 receptors preferentially bind the THC ligand (and the endogenous Anandamide ligand which is quite similar in structure) and are responsible for the euphoric and anticonvulsive effects of Cannabis. Because these receptors are absent from the lungs and heart is why Cannabis is considered non-toxic; no fatal overdoses have been reported. [24]

CB2 receptors are found outside of the brain mainly in the immune system and also in the gut. Once activated, these receptors help to control inflammation, immunity, and programmed cell death. Echinacea augustifolia and Echinacea purpura are 2 popular herbal medicines long considered for their antibacterial properties. Certain components of this plant species have been identified as ligands that bind the CB2 receptors. [24]

A summary of the abundant research on the medicinal benefits of Cannabis is shown below:

Table 1 Medicinal use of Cannabis Sativa [25]

Medicinal Use	Reference
Anthelmintic	Bhattarai, 1992
Anticancer activity against cancer cell lines	Tariq and Reyaz, 2012a
Antimicrobial activity	Tariq and Reyaz, 2012b
Anti-nausea and Anti-vomiting	Sallan et al., 1975
Antispasmodic, anodyne and narcotic	Anon, 1931
Aphrodisiac	Waddell et al., 1980
Apoptosis	Lee et al., 2008
As a hallucinogen and for rheumatism	Saha et al., 1961
As a parturifacient	Ahmad, 1957
As an abortifacient	Saha et al., 1961
As an antiseptic and to treat swelling of sprained joints	Bhattarai, 1993
As an antispasmodic and anodyne	Asprey and Thornton, 1955
As an aphrodisiac	Lewis and Elvin-Lewis, 1977
As an emmenagogue	Saha et al., 1961; Berhault, 1974
As an insect repellant	Nayar, 1955
As a narcotic, antispasmodic and analgesic	Anon, 1898
Decoction of the seed used for migraine and cancer	Duke and Ayensu, 1985
Decrease fertilizing capacity	Schuel et al., 1987
Decrease testosterone metabolism	Watanabe et al., 2005
For asthma	Simon and Lamla, 1991
For burns	Jain and Puri, 1984
For cuts, boils and blisters	Singh and Maheshwari, 1994
For diabetes	Tucakov, 1978; Morrison and West, 1982
For diabetes, hysteria and sleeplessness	Rajurkar and Pardeshi, 1997

For dysentery	Bhattarai, 1992
For inflammation	Rana and Datta, 1997
Fresh leaves used for hemorrhoids	Singh et al., 1996
Fruit used externally for skin diseases	Rao, 1981
Hallucinogen	Diaz, 1977
In diarrrhea	Manandhar, 1993
In indigestion	Sahu, 1984
In rheumatoid arthritis, epilepsy and cholera	Zagari, 1992
Increase amorous prowess of women	Nahas, 1981
Induce abortion	Hunte, 1975
Narcotic	Bellakhdar, et al., 1991
Psychotropic	Anon, 1946
Reduce abdominal pain, neuralgia and coughing	Zagari, 1992
Relieve menstrual pain	Tatkon, 1976
Relieve pain of dysmenorrhea	Lockmi, 1982
To clear the blood and for rheumatism	Li, 1974
To eliminate cough and bronchitis	Lal and Yadav, 1983
To induce abortion, labor and menstruation	Woo et al., 1981
To relieve muscular pain	Giron et al., 1991
Treatment of dyspepsia and gonorrhea	Sahu, 1984
Treatment of malaria	Asprey and Thornton, 1955
To induce sleep	Shah, 1982
To treat headaches	Baron, 2015 [15]
To treat tumors of cancer	Whiting et al., 2015 [26]; McAllister et al., 2015 [27]
To treat chronic pain and spasticity	Hill, 2015 [28]

THE POLITICS OF CANNABIS

Cannabis shifted from widespread medical usage, including standardized tinctures developed by pharmaceutical giants Eli-Lilly (Humulin, Cialis) and Parke-Davis (Lipitor, Dilantin), to association with the hippie era of the 1960's and 1970's. There were numerous Acts ratified by the US Congress that propagated this shift. [11] These legal precedents included the Harrison Act (1914), the Uniform Narcotic Drug Act (1932), the Marihuana Tax Act (1937), the Boggs Act (1951), and culminating with the Controlled Substances Act (1970), where Cannabis was classified (felt erroneous by most medicinal cannabis advocates) into Schedule 1 by the DEA. This class includes LSD, ecstasy and heroin states that there is "no known medical use, and that there is high potential for abuse with potentially severe psychological and physical dependence." [16] Detailed discussion of these Acts is beyond the scope of my article, but I suggest readers to take time to understand the political backdrop that moved Cannabis from the medical arena into the criminal and legal arena. Time has come to move it back.

CONCLUSION

It is apparent both through historical anecdotal evidence and scientific studies that medicinal Cannabis is generally safe and able to provide some medical benefit in various disorders. Physicians, the sages of our time, have prescribed medicinal cannabis until the early 20th century (and recreational use also persisted up until this time). However, once threatened by excessive taxation, imprisonment, and negative/false propaganda generated during the 20th century War on drugs (some with racial bias against Blacks and Mexicans), the medical community quickly

abandoned medicinal cannabis as it was inappropriately exiled in 1970 to the category of Schedule 1 under the DEA classification. Nonetheless, interest in cutting edge methods to treat old diseases is full-fledged. The current scientific literature on medicinal Cannabis speaks for itself; there are over 14,000 published studies referenced on PubMed, the home for all biomedical literature online. [29] Some recent studies cite low to moderate quality evidence of benefit in some conditions, but few cite FATAL adverse events.[26-28] On the contrary, as recently as 2013, there were over 117,000 deaths from prescription medications, and over 700,000 serious adverse side effects (one of which was death) to these same medications.[30] Given Cannabis' low side effect profile combined with historical precedent and state-of-the-art scientific discoveries, Cannabis (and its cannabinoid constituents) is a phytopharmaceutical poised to reenter the field and to capture a piece of the trillion-dollar pharmaceutical market, providing medicinal relief to many who suffer from chronic disease. There are many within the scientific, medical, and business community who support a change in the DEA classification of Cannabis from Schedule 1 to Schedule 2. This simple act would allow in-depth research on phytocannabinoids thereby advancing scientific knowledge of our ancient endocannabinoid system and pioneering novel treatments for most diseases of the 21st century.

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