A Plant is NOT Medicine: Plant vs. Constituent Element

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Short Communication

A quagmire exists for scientists and health care providers when discussing the issue of any alkaloid or constituent element contained within a given plant species. The language we use within the research community and, by extension, journal editors and reviewers appear to control or fuel the direction, goal or regulatory involvement of the IND pathway to drug approval. To put the cart before the horse, the clear take-home message of this article is:

There remains only one, legally-competent, authority in the United States that determines and establishes if a substance has medical use—the Department of Health and Human Services (HHS, i.e. Food and Drug Administration). In spite of repeated federal regulatory announcements published in the Federal Register by HHS that marijuana is NOT medicine many researchers reveal their own personal bias and subjectivity on the control status of marijuana. Physicians, researchers and journal editors need to improve their precision and accuracy of the statutory language regarding what is and what is not medicine.

Many plant-derived drugs are common in modern medicine. In man's search for edible plants, we have come across numerous species of plants with non-nutritive benefits, intoxication. Siegel has suggested that throughout our entire history as a species, intoxication has functioned like the basic drives of hunger, thirst or sex, sometimes overshadowing all other activities in life [1]. Siegel further suggested "intoxication is the fourth drive". Individual and group survival depends on the ability to understand and control this basic motivation to seek out and use intoxicants. Plants are the oldest and perhaps still the most commonly used therapeutic. Modern day "Svengali-like" colleagues in the medical profession have added angst to the process of drug development of new therapeutic cannabinoids, knowing the strict legal road to product approval required to minimize the risks to public health. Good laboratory (GLP) and manufacturing (GMP) practices remain the bulwark for a common defense of public health and safety guaranteed by the constitution and the Controlled Substances Act.

Raw materials of Cannabis sativa and other botanicals, do not meet the minimal standards for pharmaceutical-grade medicines.

The distinction between drug substance and nutrient is generally based on their innate necessity. A nutrient is a substance that is essential to processes of life and growth. A drug substance is any chemical- or naturally-derived alkaloid that alters biological processes with the connotation that it has some therapeutic or recreational use. An "approved drug" or "medicinal" within the meaning of section 201(g) (1) (B) of the Act [21 U.S.C. § 321 (g) (1) (B)], means they are approved for the intention to use in the diagnosis, cure, mitigation, treatment or prevention of disease in man and under section 201(g) (1) (C) of the Act [21 U.S.C. § 321 (g) (1) (C)], that they are intended to affect the structure or any function of the body. A poison or toxin, in contrast, is a substance with predominantly harmful effects on biological processes. For those of us in the drug development industry, hundreds of years of experience have confirmed that calling something a "natural product" does NOT mean "safe product".

The definition of "drug" in section 201 (g) (1) of the Food, Drug and Cosmetic Act [21 U.S.C. § 321 (g) (1)] includes articles recognized in the official Homeopathic Pharmacopeia of the United States (HPUS) or any supplement to it. Homeopathic drugs are subject to the same regulatory requirements as other drugs; nothing in the Act exempts homeopathic drugs from any of the requirements related to approval. We acknowledge that many homeopathic drugs are manufactured and distributed without FDA approval under enforcement policies set out in the Agency's Compliance Policy Guide titled "Conditions Under Which Homeopathic Drugs May be Marketed (CPG 7132.15)" (the CPG). As its title suggests, the CPG identifies specific conditions under which homeopathic drugs may ordinarily be marketed; thus, in order to fall under the enforcement policies set forth in the CPG, a homeopathic product must meet the conditions set forth in the CPG. The CPG defines a homeopathic drug as "Any drug labelled as being homeopathic which is listed in the Homeopathic Pharmacopoeia of the United States (HPUS), an addendum to it or its supplements".

One significant difference between herbal and pharmaceutical drugs is that pharmaceutical drugs most often consist of a purified single active constituent. Botanical medications, on the other hand, may have multiple active constituents. When it comes to botanical dosage forms
it is generally recognized that the reported pharmacological action is due to more than one chemical component acting synergistically with other components present in the raw plant material [2]. Therefore, no assay procedure for any single chemical constituent is specified in the U.S. Pharmacopeia monographs on botanicals and their preparation. According to Srinivasan quantitative test procedures for more than one chemical constituent, commonly termed in the botanical world as a “marker compound” are specified [2]. The USP’s approach is to require dissolution of only one marker compound for which a quantitative test procedure is specified in the dosage form monograph.

The World Health Organization (WHO) has repeatedly emphasized the fact that “safety” should be the overriding criterion in the selection of botanical medicines for use in healthcare [3]. The policy of the WHO is that proof of safety should take precedence over establishing efficacy. For some, there is no doubt regarding the value of marijuana remedies. What is difficult is the conversion of these remedies into modern therapeutic agents in a sustainable, accurate and safe manner.

As described by Brielman, there are numerous types of phytochemical components of plants including 1) hydrocarbons (saturated and unsaturated), 2) terpenes, 3) the aromatics: tetrapyrroles, phenols, phenylpropanoids, flavonoids, quinones, 4) carbohydrates: mono-, oligo- and poly-saccharides and alkaloids from the poppy plant material for analgesia will diminish the effects, this we generally do not discuss “medical poppy” with patients. For example, extracting and purifying morphine alkaloids from the poppy plant and are standard medications used to treat pain (Papaver somniferum). The third major poppy alkaloid, thebaine, has also been the progenitor of many other synthetic analgesics. In spite of this, we generally do not discuss “medicinal poppy” with patients.

The opium poppy contains more than 30 alkaloids. The active chemical constituents of a plant may each have different individual effects, so that the effects of the total plant material is a summary combination (entourage substance) of the effects of several different component elements. In regards to drug development, it is preferable to purify only one component for use, thus avoiding any extraneous effects of others. For example, extracting and purifying morphine alkaloids from the poppy plant material for analgesia will diminish the vasodilator effects of another poppy alkaloid, papaverine or the proconvulsant effects of thebaine, which is also present in raw plant materials.

Digoxin is a cardiac pharmaceutical that is derived from the herbaceous perennial foxglove plant. The flowers of the plant are cone shaped that easily fit over the finger; thus the shape is often called “finger-like” which translates in Latin to “Digitalis purpurea”. The garden plant is highly toxic to humans and their pets. There is doubt that cardiologists, in general, discuss “medicinal foxglove” with their patients. Through the millennia of human experiences with plant materials it has been clearly and repeatedly demonstrated that “calling something a natural product does NOT mean safe product”.

Kratom is a CNS active botanical product with a history of addiction, dependence, death and abuse. As a plant, there is no quality control or genetic limitations to the variations in alkaloid content from harvest to harvest. Kratom is not medicine and has no accepted medical use in the United States. Consuming kratom has varying concentrations of over 30 alkaloids; it by definition is an entourage herb.

Kratom is an indigenous plant to Thailand. According to the United Nations Office on Drugs and Crime, market gardeners, peasants and laborers often become addicted to kratom leaf use [6]. In certain respects kratom addiction resembles addiction to a drug with narcotic; mu opioid, properties, except long-term use of kratom induces the development of darkened pigmentation of facial skin (cheeks). Kratom is a large tropical tree of the genus, Rubiaceae, cultivated in Thailand, especially in the central and southern regions; it has been reported to be rare in the northern or north-eastern parts of the country.

The overall processing of plant materials for human consumption is not a simple process and is fraught with difficulties. Errors in the plant harvesting and botanical processing can affect the final end-product that enters into the retail market that will be consumed by the human purchaser of the product. For example:

1. During the collection of a plant in Thailand (Kratom) or Colorado (Cannabis) it should be of critical importance to ensure that the specimens are healthy, since microbial and other botanical-based infections may change the metabolites produced by the plant specimens, e.g. by phytoalexin formation [7]. Variations in harvest-site altitude, plant age, climate, soil type and genetic seed stocks can all influence the concentration levels of secondary metabolites and even the kinds of compounds biosynthesized in certain cases. Different organs in the plant are known to produce and/or accumulate different profiles of secondary metabolites, e.g. flavonoids may be present in flowers and leaves of a particular species, whereas tropane alkaloids occur in the roots and sesquiterpene lactones and essential oils may be restricted to glandular hairs or other glands. The fact that plant-secondary metabolite profiles may vary both qualitatively and quantitatively among different batches of the same plant collected at different times has important consequences to the end-human-consumer.

2. Harvested plant materials must be kept away from direct sunlight because ultraviolet radiation may produce chemical reactions giving rise to compound artifacts. Compacted samples of fresh plant materials with little air circulation may experience fungal infestation and elevated temperatures of the local environments may induce fermentation [7].

3. Decomposition or rearrangements by pH changes may occur, leading to hydrolysis of constituents such as iridoid and flavonoid glycosides [7].

Under an open unregulated and non-government monitored growth and harvest cycle there is no security, oversight or inspection process in place to ensure the kratom- or cannabis-based products that enters the human food/herit/nutrient chain is safe and free of contaminants.

Fraser and Tibbits drew attention to agricultural/industrial contaminants of cultivated marijuana as a significant source of concern to the health status of marijuana users [8]. Main risks may come from pesticide residues on plants, cultivation infrastructure and materials; left-over plant growth-promoting substances; mycotoxins from fungal pathogens on harvested plants; and/or high levels of cannabinoids in cannabis plant parts for consumption. In 2016, Nathan Russo reported 22 out of 26 marijuana samples were positive when analyzed for pesticide contamination in cultivation plots from the State of Washington (USA) [9]. Many harbored multiple contaminants attaining levels 10's of thousands of parts per billion (ppb) and exceeding the upper limit of quantitation. These included 45 distinct agents from every class of insecticides, miticides, fungicides, synergists.
and growth regulators, including organophosphates and organochlorides. In a more recent review, Cuypers et al. reported on pesticides found in indoor cannabis plantations in Belgium to identify pesticides that are hazardous to human consumers [10]. Cuypers et al. found pesticides in 64.3% of 72 cannabis plant samples and in 65.2% of 46 carbon filter cloth samples taken from the air supply of the fruticetum. Overall, 19 pesticides belonging to different chemical classes were identified, including o-phenylenediamine, bifenthrin, cypermethrin, imidacloprid, propamocarb, propiconazole and tebuconazole, which are consistent with the commonly reported pesticides in the literature. In only a few cases, pesticides found in bottles with a commercial label, were also identified in plant or stagnant water samples collected from the growth rooms where the bottles had been collected. Further revealed was the fact that, even though most pesticides have a low volatility, they could be detected from the carbon filters hanging at the ceiling of cultivation rooms. As a result, it is likely that pesticides also prevail in the plantation atmosphere during and after cultivation. The risk of inhaling the latter pesticides increases when plants sprayed with pesticides are intensively manipulated during dismantling activities. In a 2015 report by Raber et al. California grown patient-advocate grown marijuana was submitted by the end users requesting analysis for contaminants [11]. Thirty-three percent of all submitted samples were found to be contaminated with pesticides. The most commonly found pesticide in the California samples was paclobutrazol, a plant growth regulator. This is of great concern because this pesticide is not registered by the U.S. Environmental Protection Agency (EPA) for use on food crops. Sullivan et al. has previously reported that up to 70% of paclobutrazol is transferred into the smoke stream [12]. Two other pesticides identified in the US samples were bifenthrin (an pyrathroid insecticide) and myclobutanil (a systemic fungicide). In 2015, myclobutanil was found in Colorado-grown marijuana by the Colorado Department of Agriculture [13]. In the health alert it was noted that the Colorado Department of Agriculture had identified and published a list of “minimum risk pesticides” that pose little or no risk to human health and are allowable for use on marijuana during cultivation. The myclobutanil is not on this list, but the absence of regulatory oversight has contributed to its widespread use in marijuana cultivation in Colorado. These data strongly support the conclusion that pesticides pose an underestimated and under-documented health risk for the marijuana user.

It is clear that plant materials do not provide consistent concentrations of alkaloid content which vary as a function of age of plant, environmental influences such as ambient temperatures, sunlight and soil quality, as well as time of year. Kratom and marijuana are not a single source botanical. This, alone, is a staggering fact: there are at least 554 identified compounds in cannabis; the World Health Organization (2016) has put this number as high as 650 [14-17]. There are 113 known phytocannabinoids and 120 terpenes [18,19] in the plant material, as well. There are no neutral cannabinoids found in fresh plants [19]. Natural does not mean neutral or benign.

The eminent Professor Mahmoud ElSohly from the University of Mississippi has been conducting “finger-print” DNA testing of marijuana for over 35 years and has concluded that environmental factors have a greater effect on constituent element concentrations (i.e. cannabinoids, terpenes, etc.) when compared to DNA of the plant [20]. Therefore, free market exchange of unregulated psychoactive and biologically active chemicals remains a significant risk to the health and well-being of patients.

The simplest way to consume a plant is to eat it or smoke it. However many plants are unpalatable and pyrolysis may neutralize the alkaloids if smoked. To avoid these issues, plants can be dried and ground and administered in capsule forms. This method still supplies the entire entourage of behaviourally- or psychoactive alkaloids in the plant material. Alternatively, the dried plant material can be made into a decoction or an infusion. An infusion is when boiling water is poured over the plant material and its chemical constituents steep into the water, which is then drunk: common for tea or coffee. A decoction is similar, except the water is boiled with the plant actually in it. The length of time steeping or boiling is significant, as it determines how much of the alkaloids and chemicals will enter into the water [21-23].

An additional risk to human safety comes from “edible cannabinoid” foodstuffs produced from home-based cultivated marijuana, that also fall under FDA control. Gourdet et al. report that state laws governing recreational marijuana edibles have evolved in Alaska, Colorado Oregon and Washington where they now require edible product labels to disclose a variety of product information, including risk factors associated with consumption, a federally-mandated responsibility of the FDA [24]. While all four states prohibit the manufacture or packaging of edibles that appeal to youth no state-mandate requires the analysis of harvested cannabinoids to identify or quantify the levels of agricultural industrial contaminants in these foodstuffs in the human food chain.

Pokeweed (*Phytolacca americana*) is a common perennial garden weed in the United States. It is often harvested in spring throughout Appalachia and boiled several times, each time pouring off the hot water. All parts of the plant above ground contain toxic triterpene saponins. The ritual of kitchen boiling is to make sure that the green leaves are rendered edible by removing low amounts of toxic saponins. Pokeweed poisonings were commonplace prior to the FD&C Act, but the medicinal decoction is still in use for achy muscles and joints (rheumatism); swelling of the nose, throat and chest; tonsilitis; hoarse throat (laryngitis); swelling of lymph glands (adenitis); swollen and tender breasts (mastitis); mumps; skin infections including scabies, tinea, scysis, ringworm and acne; fluid retention (edema), skin cancers, menstrual cramps (dysmenorrhea) and syphilis [25]. “Medicinal pokeweed” has lost some of its favor among the residents of Appalachia.

The South American tradition of preparing ayahuasca [26], a decoction from two key plant materials, the vine *Banisteriopsis caapi* (*B. caapi*) and the bark material from *Psychotria viridis* (*P. viridis*) to produce a hallucinogenic drink containing dimethyltryptamine (DMT). Active constituents may have cooperative effects and together act in an additive or synergistic (supra-additive) manner. Therefore, to blindly advocate either the use of whole herb or refined single constituents is naive, to say the least.

“Natural” does not mean “safe”, “effective” or “curative”. Current plant constituents and biological entities already controlled as Schedule I (dangerous, with no acceptable medical use in the US) or Schedule II substances (high potential for abuse, but has been approved by FDA as “medicine” with therapeutic efficacy), under International treaties and US statutes are:

- Bufotenine-hallucinogenic substance secreted by the buffo frog;
- Dimethyltryptamine (DMT)-hallucinogenic plant material;
- Ibogaine-hallucinogenic plant material;
- Marijuana-hallucinogenic, intoxicating plant material;
- Mescaline-hallucinogenic fungus (mushroom) material;
Cannabidiol is one of many constituent elements of cannabis and has been reported to functionally block or reduce the intoxication induced by smoked marijuana [28,29]. A concentrated extract of cannabidiol manufactured by GW Research, Ltd. [30] was used in this study. Marijuana was NOT administered to any patient in the controlled environment, yet professionals tout the overall plant material as “medicine”.

As shown in Figure 1, today’s marijuana is not the “pot of the 1960s”. A recent paper by ElSohly et al. characterized the changing cannabinoid concentrations in forensic laboratory samples of marijuana from 1995 through 2014 in the United States (Figure 1) [31]. During the 10 year interval of analysis of seized marijuana samples the THC content increased from ~4% to ~12% with a correlated decrease in CBD content from 0.28% to 0.15%. Guy Pharmaceuticals has defined “medical marijuana” as Use of cannabis or cannabis products in an attempt to treat disease or alleviate symptoms by patient choice, understanding that there is a lack of placebo-controlled trials supporting the favourable efficacy and safety of these products [32].

Using the 2014 concentrations of these two cannabinoids, a legal “standard dose” of 1 g paper rolled marijuana “joint” would provide 120 mg of Δ9-tetrahydrocannabinol (THC) and 1.5 mg of CBD. In the recent CBD-seizure study, the standard dose administered to children was 20 mg/kg of concentrated extracted CBD. Using standard weights for a 5 year (17.7 kg) and 10 year old male (32 kg) pediatric patient to deliver 20 mg/kg dose of CBD using pyrolyzed marijuana the 5 year old child would have to smoke 235 joints and the 10 year old patient would have to smoke 426 joints in order to titrate to the terminal therapeutic daily dose of 20 mg/kg. This would also require the 5 year old to consume 236 g of raw material and the 10 year old male patient would need to consume almost half a kilogram of raw material in order to achieve the therapeutic window. The major intoxicating chemical entity, THC, in the consumed bulk raw material would be 51 g in the 10 year old and 28.2 g in the 5 year old male patient. There is no single report appearing in any peer-reviewed scientific journal listed in the National Library of Medicine that has investigated the controlled administration of these astronomical THC concentrations to any living animal for research purposes. Is this even a reasonable expectation for dosing strategies in the 21st Century?

What happened to science, accuracy and integrity? Health care professionals need to clean up the language, stop serving as a “pied piper” on either side of this political issue-remain objective and unbiased. The fact is that any determination of “medical use” by the FDA must be based on legally-defensible, scientifically accurate and contemporary data. “Medicinal THC” is a reality (Marinol®), “medicinal cannabidiol” may be in our future, however, “medical marijuana” will not.

There remains a paucity of well-designed controlled studies of cannabinoids conducted under the FDA’s Good Laboratory Practice Guidelines (GLP) and the production of natural cannabinoids or their extraction do not seem to meet the FDA’s Good Manufacturing Practice Guideline (GMP) requirements. The “legalization” of marijuana is not advanced by physicians and health care professionals who deviate from established IND-enabling methodologies or attempt to substitute popular opinion for the submission of a “New Drug Application (NDA) for formal review and approval by the FDA.

The most notable pharmacological effect associated with marijuana use, the increase in appetite, was a rallying call for medical use of plant material to stimulate the appetites of AIDS or chemotherapy patients

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**Figure 1:** The quantitative changes in THC concentrations in marijuana samples over the last 2 decades in the United States from the analytical laboratories at the University of Mississippi under contracts with the National Institute on Drug Abuse and/or Drug Enforcement Administration. The subjective and physiological effects of a given amount of bulk cultivated material in today’s market, far exceeds those of the early 1990s. Drug safety evaluations must be contemporary to current escalating THC concentrations.

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- Peyote-hallucinogenic plant (cactus) material containing mescaline;
- Psilocybin and psilocin-hallucinogenic material from "magic mushrooms";
- Coca Leaves, Ecgonine-cocaine precursors used in cocaine production;
- Opium extracts, opium fluid extracts-entourage materials containing morphine, codeine and thebaine;
- Opium poppy, opium raw-precursors for opiate analgesics;
- Poppy straw, poppy straw-precursors for opiate analgesics;
- Thebaine-precursor for many opiate analgesics.

The sad state of current affairs of health care professionals and journal editors that contribute to the hotly debated topic of “medical marijuana” need to tone down the rhetoric, stop the vitriol and select their language carefully. The free market exchange of unregulated psychoactive and biologically active chemicals remains a significant risk to the health and well-being of patients regardless of the “celebrity status” of physicians who kindle the vitriol for the anti-prohibition policies of drug control in the United States.

A recent report suggesting therapeutic efficacy for the treatment of a variant of childhood seizure disorder (Dravet Syndrome) by cannabidiol may serve as a good example [27]. The study report included the results of 120 human pediatric patients using extracts of the single entity cannabinoid, cannabidiol (CBD). The results reported no significant reduction in non-convulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo. Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhoea, vomiting, fatigue, pyrexia, somnolence and abnormal results on liver-function tests. The world-wide press, anti-marijuana prohibitionist groups and scientific organizations have publicly referred to these miraculous effects of “medical marijuana”.

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Nabiximols (Sativex™) as an agonist replacement therapy during cannabis withdrawal [34]. In that study participants could not reliably differentiate between cannabinoid-treatment and placebo. Interestingly, the number and severity of adverse events did not differ significantly between cannabinoid and placebo treatment groups. Both groups showed reduced cannabis use at follow-up, with no advantage of nabiximols over placebo for self-reported cannabis use, cannabinoid-related problems or cannabis dependence. The authors concluded that placebo was as effective as nabiximols in promoting long-term reductions in cannabis use following medication cessation.

In a recent review investigating the efficacy of cannabinoids in inflammatory bowel diseases (IBD), Hasenohrl et al. concluded there is still a lack of clinical studies to prove efficacy, tolerability and safety of cannabinoid-based medication for IBD patients, leaving medical professionals without evidence and guidelines [35].

It is time for the pharmaceutical industry itself to stake claim to what is and what isn't good science when it comes to those who push the political agenda on medicinal cannabinoids. Medicines are not determined by politics, state legislatures or popular vote. Individual states do not have the legal authority to supersede federal mandates ratified by the U.S. Congress. Colleagues who serve as "pied pipers" or modern day Svengali's for the sake of a political agenda or personal notoriety do not serve the best interest of public health. Nomenclature is important. Believe it or not, accept it or not, in 2017 Cannabis sativa, kratom and ayahuasca are NOT medicine.

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