HHS Public Access

Author manuscript

Int Rev Psychiatry. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Int Rev Psychiatry. 2018 June ; 30(3): 277–284. doi:10.1080/09540261.2018.1474730.

Cannabis and Cannabinoid Drug Development: Evaluating Botanical Versus Single Molecule Approaches

Marcel O. Bonn-Miller[1], **Mahmoud ElSohly**[2,3,4], **Mallory J. E. Loflin**[5], **Suman Chandra**[2], and **Ryan Vandrey**[6]

[1]University of Pennsylvania Perelman School of Medicine, Department of Psychiatry, Philadelphia, PA 19104, USA

[2]National Center for Natural Product Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, MS 38677, USA

[3]Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, University, MS 38677, USA

[4]ElSohly Laboratory Inc., 5 Industrial Park Drive, Oxford, MS 38655, USA

[5]San Diego Healthcare System, Center of Excellence for Stress and Mental Health, San Diego, CA 92161, USA

[6]Johns Hopkins University School of Medicine, Baltimore MD, 21224, USA

Abstract

Accumulating evidence suggests that the endocannabinoid system is a promising target for the treatment of a variety of health conditions. Two paths of cannabinoid drug development have emerged. One approach is focused on developing medications that are directly derived from the cannabis plant. The another utilizes a single molecule approach whereby individual phytocannabinoids or novel cannabinoids with therapeutic potential are identified and synthesized for pharmaceutical development. This commentary discusses the unique challenges and merits of botanical versus single molecule cannabinoid drug development strategies, highlights how both can be impacted by legalization of cannabis via legislative processes, and also addresses regulatory and public health considerations that are important to consider as cannabinoid medicine advances as a discipline.

Introduction.

Cannabis has a long history of use in medicine, dating back thousands of years, and has been used historically to treat a variety of ailments such as asthma, depression, epilepsy, fatigue, glaucoma, insomnia, migraine, nausea, pain, rheumatism and tetanus (Doyle and Spence, 1995; Zuardi, 2006). However, a wide-spread political movement in the early 20th century resulted in prohibition of cannabis use throughout the developed world. Subsequent to this

Conflict of Interest: Dr. Vandrey has served as a paid consultant for Zynerba Pharmaceuticals and Insys Therapeutics, and several small businesses operating in U.S. states where cannabis has been legalized. Dr. Bonn-Miller is an employee of Zynerba Pharmaceuticals.

prohibition, western medical practices transitioned from reliance on botanical extracts and tinctures to a pharmacopeia predominantly comprised of single molecule therapeutics and the establishment of rigid regulations regarding the review and approval of new medications in a highly competitive and lucrative drug marketplace.

In the time since cannabis prohibition, a lot has been discovered with regards to the chemical constituents of the cannabis plant and their pharmacology. Researchers in Israel identified Δ^9-Tetrahydrocannabinol (Δ^9-THC) as the primary psychoactive agent in the cannabis plant in the mid-1960s (Mechoulam and Gaoni, 1967). This discovery led to extensive research on cannabinoids in the 1970s, which also coincided with renewed interest in potential therapeutic effects of cannabinoids. In 1985, a synthetic formulation of THC (dronabinol) and a synthetic analog of THC (nabilone) were approved by the U.S. Food and Drug Administration for the treatment of nausea and vomiting associated with cancer chemotherapy. They were subsequently also approved for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). This progression followed the established model of western medicine in which individual chemical constituents of plants historically used in medicine are isolated and then developed into proprietary medications.

In 1996, however, a twist in this saga began when the U.S. state of California legalized the medicinal use of botanical cannabis by its residents. Over the past 20 years, an increasing number of countries, states, and territories have followed suit, legalizing the medicinal use of cannabis for a variety of health conditions. This is important because it is a unique example in medicine where: (1) a new medication is introduced to the market via legislation rather than through formal drug development practices, and (2) we see a reversal of the trend towards single molecule drug development in favor of the use of raw botanical products. The caveat here is that cannabis has long been used as an intoxicating drug in the absence of medical need, and most of the organizations that successfully lobbied to legalize medicinal use of cannabis have since acknowledged that medical cannabis legalization was a stepping stone to getting cannabis legalized for non-medicinal purposes as well. However, at the time of this writing, a British pharmaceutical company (GW Pharmaceuticals) has successfully brought a medication derived from raw cannabis (Sativex®; a blend of extracts high in THC and high in cannabidiol (CBD) in a roughly 1:1 ratio) to market in several countries through the currently accepted drug development process, rather than via legislation, and a second product (Epidiolex®; a botanically derived CBD extract) is currently in review for U.S. regulatory approval as a new therapeutic in the treatment of rare seizure disorders. Thus, it seems clear that both cannabis and isolated cannabinoids hold tremendous therapeutic promise, but it also begs the question: Should medication development efforts be focused on botanical or single molecule drug development?

This question is of interest because there are several important nuances to each approach that complicate the answer from both regulatory and scientific perspectives. Moreover, in conversations related to the medicinal use of cannabis/cannabinoids there seem to be strong ideological beliefs among patients, physicians, and caregivers where there is a heavy bias towards only considering use of either botanical cannabis products or pharmaceutical cannabinoids. There are also a number of popular misconceptions (detailed below)

associated with the two approaches that require better public education as cannabinoid medicines becomes more commonplace.

The aim of this paper is to provide a broad commentary on cannabinoid drug development. It is not intended to serve as a systematic review, nor will we be making recommendations for the use of cannabinoids for specific health conditions. Rather, we will detail why we believe there is renewed interest in cannabis as a botanical medication, as well specific discussion of the merits and drawbacks of both single molecule and botanical drug development approaches as means of maximizing the promise of therapeutics targeting the cannabinoid system in medicine. To achieve this, contributors on this paper include world experts in cannabinoid drug development. Dr. Marcel Bonn-Miller and Dr. Mallory Loflin contributed from the perspective of clinical development of single molecule cannabinoid medications. Dr. Bonn-Miller is a cannabinoid researcher at the University of Pennsylvania Perelman School of Medicine with expertise in single molecule cannabinoid drug development. Dr. Loflin is a clinical psychologist and cannabinoid researcher at the San Diego Veterans Affairs Healthcare System. From the perspective of botanical drug development, Dr. Mahmoud ElSohly and Dr. Suman Chandra of the National Center for Natural Products Research at the University of Mississippi have contributed, each of whom have spent decades researching the cannabis plant and its therapeutic potential. As editor of the issue, Dr. Vandrey conceptualized this paper, helped integrate the input of the other contributors, and also contributed to content related to both perspectives.

Cannabis vs. cannabinoids.

This section provides an important background with respect to important definitions, nomenclature, and pharmacology that will be referenced later. The cannabis plant has been shown to be chemically rich, with 565 known constituents belonging to 23 classes of compounds (ElSohly and Slade, 2005; ElSohly and Gul 2014; Radwan et al. 2017). Perhaps the most recognized class of compounds in cannabis are the namesake cannabinoids. At the time of this writing, 120 different phytocannabinoids, plant-derived molecules unique to cannabis, have been identified in the cannabis plant, many of which directly modulate the endogenous cannabinoid system. These naturally occurring cannabinoids are distributed among ten subclasses, including Δ^9- and Δ^8-THC, cannabidiol (CBD), cannabigerol (CBG), cannabinol (CBN), Cannabinodiol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), cannabitriol (CBT) and miscellaneous type (30 known). THC is produced as an acid (Δ^9-Tetrahydrocannabinolic acid, Δ^9-THCA) in the glandular trichomes of the leaves and inflorescence bracts of the plant and undergoes decarboxylation with age or heating to form Δ^9-THC (Turner et al., 1980). THC is typically the most abundant chemical constituent of the cannabis flower, and is by far the most studied and well-understood cannabinoid. However, cannabinoids are not the only active components of cannabis. Other constituents that might contribute in some way to the effects of cannabis include Terpenes (120 known); Nitrogenous compounds (33 known); Amino acids (18 known); Proteins, enzymes and glycoproteins (11); Sugars and related compounds (34); Hydrocarbons (50 known); Simple alcohols (7 known); Simple aldehydes (12 known); Simple ketones (13 known); Simple acids (20 known); Fatty acids (27 known); Simple esters and lactones (13 known); Steroids (15 known); Non-cannabinoid phenols (25 known); Flavonoids (27 known); Vitamins (1

known); Pigments (2 known); Elements (9 known); Phenanthrenes (4 known); Spiroindans (2 known); Xanthones (1 known) and Biphenyls (1 known).

In addition to plant-derived phytocannabinoids, hundreds of exogenous synthetic cannabinoids have been synthesized and characterized. These include pharmaceutical-grade synthetically derived substances that are chemically identical to the phytocannabinoids found naturally in the cannabis plant (e.g. dronabinol, an oral formulation of synthetically derived Δ^9-THC, and ZYN002, a transdermal synthetic CBD gel produced by Zynerba Pharmaceuticals), in addition to novel molecules not found in nature (e.g., WIN 55,212–2, JWH-018, AM-2201, AMB-FUBINACA). There are two common misconceptions we often hear related to synthetic versus naturally occurring phytocannabinoids. One is that there are differences in the effects of a single molecule phytocannabinoid (e.g. CBD) based on whether it is synthetic versus plant derived. This should not be the case as chemistry is an exact science with respect to chemical composition and structure. The circumstances under which this could be true with respect to botanical cannabinoid products versus synthetic products would be limited to cases in which one of the two substances contains impurities that contribute to the overall pharmacological or toxicological effect, or due to inappropriate designation of synthetically derived isomers as being true replications of naturally derived cannabinoids. In these cases, the differences would be due to impure extraction of botanically sourced cannabinoids or missteps in the synthesis of the cannabinoid.

The other common misconception is that synthetic cannabinoids not found naturally in cannabis are more harmful than phytocannabinoids. This largely stems from the ongoing problems associated with illicit sales of synthetic CB1 full agonists (Fattore and Fratta, 2011; Vandrey et al., 2012). The potential harm associated with any newly synthesized drug is directly tied to its pharmacological effects (pharmacology, receptor specificity and affinity, potency) in the body. Indeed, one advantage of pursuing drug development of botanical cannabis or synthesized phytocannabinoids is that the cannabis plant has a very well established and positive safety profile.

Both phytocannabinoids and synthetic cannabinoids can directly impact the endocannabinoid system via a variety of pharmacological mechanisms, including agonism, antagonism, and allosteric modulation (for detailed reviews of cannabinoid pharmacology see Pertwee, 2008; Pertwee et al., 2010). Though 120 phytocannabinoids have been identified, they are finite and somewhat limited with respect to pharmacological interaction with the endocannabinoid system. Because of this, there are clear advantages of focusing on single molecule synthetic cannabinoid drug development, simply due to the fact that medicinal chemists are able to systematically modify known cannabinoid molecules in order to target very specific pharmacological effects. This type of “fine tuning” has the potential to yield medications that have a very specific mechanism of action (e.g. full agonism of CB1 receptors outside the CNS), which might both improve therapeutic efficacy and reduce adverse effects compared with phytocannabinoids such as THC, which is neither selective to a specific cannabinoid receptor subtype nor limited with respect to crossing the blood-brain barrier.

The major rejoinder to using single molecule and synthetic preparations of cannabinoids is the possibility of unique therapeutic benefit from a dynamic interaction between the myriad chemicals found in the cannabis plant. Referred to as the “entourage effect,” unique therapeutic effects of cannabis are hypothesized to be achieved through a complex synergy between phytocannabinoids and the many other secondary constituents of the plant (Ben-Shabat et al., 1998; Russo & McPartland, 2003). The term “entourage effect” was coined by Raphael Mechoulam (Ben-Shabat et al., 1998; Mechoulam & Hanus, 2000) as he elaborated on the fact that the presence of glycerol fatty acid esters, alongside 2-arachidonoyl glycerol (2-AG), an important endocannabinoid, reduced the rate of hydrolysis of 2-AG, which enhanced its activity. The term was later used by others (Fowler, 2003; Sanchez-Ramos, 2015) to highlight the contribution of other cannabinoids and non-cannabinoid constituents to the activity of cannabis preparations. Carlini et al. (1974) provided an early example of the entourage effect by demonstrating that 2 of 3 cannabis extracts, administered in multiple species, including humans, produced effects 2–4 times greater than what was observed after administration of pure THC at the same doses contained in the extracts.

The limitations of the entourage effect are that, at this time, it is not clear which compounds drive the effect, which pharmacodynamic effects of cannabis are impacted, or whether this can be harnessed for improved cannabinoid therapeutics. Ethan Russo has proposed very clear hypotheses about how select terpenes contribute to the cannabis entourage effect, but the empirical research required to test these hypotheses with cannabis has yet to be completed (Russo, 2011). Moreover, evidence for an entourage effect has not been consistently observed, and very few controlled studies have examined it systematically (Hazekamp, Ware, Muller-Vahl, Abrams, & Grotenhermen, 2013). In one study, Wachtel and colleagues (Wachtel, ElSohly, Ross, Ambre, & De Wit, 2002) directly compared oral and smoked cannabis to dronabinol (oral synthetic THC) and found that dronabinol produced similar subjective effects as herbal cannabis. Similarly, three appropriately powered randomized control trials all failed to find differences in medicinal effects between synthetic and herbal cannabis preparations when compared to placebo (Haney et al., 2007; O’Neil et al., 2017; Strasser et al., 2006). Using these findings to dismiss the potential for an entourage effect, however, is premature, and admittedly is arguing from the null hypothesis. Additional controlled research in this area is needed.

Quality control and experimental design considerations.

One of the key tenets of modern medicine is that one must be able to define medications chemically to the highest degree possible. A botanical drug such as cannabis requires definition of its chemical profile and the ratio of all components to one another. The ability to fully characterize, define, and demonstrate consistency in chemical composition is one of the greatest challenges to botanical drug development. This requires highly regimented and controlled agricultural practices under conditions that would guarantee consistency in the chemistry of the final product, be it raw plant material or manufactured extracts. It also requires that the developer be able to select a single variety of cannabis, or chemovar, for which to evaluate efficacy for a specific health condition. Due to interactions between constituent chemical components of the cannabis plant, a positive clinical outcome for one defined botanical cannabis product cannot be generalized to other chemovars, or to cannabis

more broadly. Similarly, lack of efficacy for one cannabis chemovar cannot be used to establish lack of efficacy because the interactive effects of individual components of the botanical may negate effects that would otherwise be observed if cannabis with a different chemical profile was utilized.

Though these issues make it difficult to develop a botanical drug from cannabis, it is not an impossible task. The most notable example to date is GW Pharmaceuticals, a United Kingdom-based company that has developed a botanical drug (Sativex®), which is a combination of extracts from a high CBD producing variety of cannabis and a high THC producing variety of cannabis, combined to create a final product that contains roughly equal amounts of CBD and THC. GW Pharmaceuticals has obtained regulatory approval for Sativex® in several countries, indicating that they have been able to demonstrate a consistent chemical profile of the biomass (drug substance) and the drug product (Sativex®) both within and across batches.

Another example of botanical cannabis preparations in clinical use are those produced by Bedrocan, a medicinal cannabis company based in The Netherlands. The company produces cannabis for medical use in the form of a standardized biomass (dried female flowers). Based on defined THC, CBD, and terpene content, the company has five different biomass products: Bedrocan®, Bedica® and Bedrobinol® (all high THC varieties); Bediol® (Intermediate variety, THC~CBD) and Bedrolite® (high CBD and low THC variety). Their process from propagation, harvesting, processing and storage is “ISO 9001”-certified and meets the European standard of good agricultural practice (GAP). These products, however, have not been subjected to the stringent regulatory requirements in the USA, nor have they been clinically tested for specific disease conditions. Therefore, they are still not considered botanical drugs per se.

In contrast, quality control for synthetically derived, single molecule medications is much easier, and is the norm for the pharmaceutical industry. There are clear standards to follow and established methods for manufacturing, testing, and quality control from start to finish. Single molecule medications also have major advantages in clinical testing. In single molecule studies, the study drug represents only one independent variable and one direct effect being tested. The simplicity of design makes it easier to ensure that clinical trials are well powered to find effects, and interpretation of results is relatively straightforward and concise. That being said, identification of target molecules, especially novel synthetic molecules, requires a rigorous and lengthy pre-clinical screening process that is entirely different than what is required for botanical cannabis products.

Regulatory considerations.

Pharmaceutical drug development is a complex and often misunderstood arena, and there are unique considerations with respect to cannabinoid medications. Currently, in the U.S. and many other countries, cannabis and several of its constituent components remain controlled substances. This requires extra regulatory approvals, security, and a substantial regulatory burden for any level of botanical drug development, as well as for single molecule drug development for which local regulations consider that molecule (e.g. THC, CBD) a

controlled substance. For *novel* synthetic cannabinoids (e.g., analogues), it is possible that this additional regulatory limitation may not apply.

In some circumstances, regulations may completely sequester cannabinoid drug development. For example, in the U.S., individual states have legalized the medicinal use of cannabis through legislation, but cannabis remains illegal at the federal level. This regulatory quagmire is harmful to cannabinoid drug development because businesses that are manufacturing and selling botanical cannabis products for medicinal use legally at the state level are prohibited from obtaining federal regulatory approvals to conduct clinical trials to evaluate the safety and efficacy of their products. Moreover, the mere fact that they can sell these products without having to meet the standards of product definition, quality control, safety, and efficacy is a disincentive for any of these businesses to actually engage in proper drug development methods. The result of this is a hazardous environment for consumers of these products. It also places treatment providers in the difficult position of trying to engage in clinical decision making related to patient use of these products in the absence of reliable information typically found in a medication package insert such as recommended dose, dose frequency, expected adverse effects, contraindications, comparative efficacy to alternative therapeutics, etc.

To date, two single molecule cannabinoid medications (dronabinol and nabilone), but no botanical cannabinoid products, have been approved by the U.S. Food and Drug Administration (FDA). This is likely due to the complexity of the approval process for botanical drugs. Specifically, the FDA notes that one must demonstrate that a multiple molecule compound is associated with improved efficacy above and beyond its individual components. Similarly, one must demonstrate that the safety and tolerability of the combination compound is not significantly worse than that of each individual component (U.S. Food & Drug Administration). These considerations for botanical cannabinoid preparations extend from toxicology through pre-clinical and clinical development.

Public/global health considerations.

A number of the above-mentioned regulatory considerations also have global public health ramifications. As the current regulatory requirements provide a barrier to the FDA-approval of plant-derived full-spectrum cannabinoid preparations, a plethora of companies have circumvented the FDA and sold their products directly to consumers within state medical cannabis marketplaces. Unsurprisingly, there is documentation of ongoing quality issues with these non-FDA approved products. These quality issues include inaccuracies in product labeling, products containing potentially toxic manufacturing byproducts, and product inconsistency (Bonn-Miller et al., 2017; Vandrey et al., 2015; Wilcox, Jacyno, Marcu, & Neal-Kababick, 2016). Beyond the regulatory concerns, non-FDA-approved cannabis preparations are not eligible for insurance reimbursement, which can prove to be cost prohibitive for consumers given requisite dosages of CBD that have been demonstrated as efficacious within clinical trials (Devinsky et al., 2016).

Another common public health concern related to botanical cannabis drug development relates to formulation and dose delivery. There is almost universal agreement that there is no

place in medicine for a therapeutic that is smoked. Though a number of sophisticated devices are being marketed as reduced-risk (e.g. vaporizers) or as able to deliver precise pulmonary doses, these products have not been developed with integrated botanical or single molecule cannabinoid products using standard clinical trials methodology. Device development and exploration of alternative routes of administration that are tailored to clinical needs is an area for future development for both botanical and single molecule cannabinoid medications.

Although it does not appear to have been systematically evaluated, there may be confusion and misperceptions related to medicinal cannabis/cannabinoids. Most products sold in legislatively sanctioned medicinal cannabis programs are products with heterogeneous chemical composition that do not meet standards for modern medicine. Results from research studies on synthetic/single molecule cannabinoid products or botanical cannabinoids that are being developed in accordance with established regulations may be mistakenly generalized to other products inappropriately. As described above, botanical cannabinoid drugs seeking regulatory approval must undergo rigorous testing and standardization procedures that most cannabis-based products sold in dispensaries are not subject to, and FDA-approved cannabis medications are not sold in dispensaries. The mismatch between consumer and research products is an enduring problem for both single molecule and botanical cannabinoid drugs.

Another public health consideration relates to potential scalability issues with plant-derived botanical drugs relative to synthetic, single molecule cannabinoids. While synthetic cannabinoids can be manufactured in bulk within a laboratory, the complexities of manufacturing botanical medications have been described in detail above. Clinical trials of plant-derived cannabinoid preparations have largely focused on populations with rare and orphan diseases (e.g., Dravet Syndrome), for which demand for medication is limited to the small populations affected by these conditions. Cannabinoids such as CBD, however, are purported to have a wide array of therapeutic applications, including health conditions that impact large segments of the population, such as anxiety, sleep disturbances, and inflammation (Whiting et al., 2015). It is unclear whether botanical medications could scale up to meet potential wide-spread global demand and still meet stringent quality control standards. The environmental impact of producing botanical cannabis medicines at such a scale is also unknown.

Discussion.

Accumulating biomedical discoveries about the endocannabioid system clearly indicate that it is an important drug development target for a variety of health conditions. Due to the truly unique and fluctuating regulatory space in which cannabis and cannabinoids currently reside, however, there are several important considerations with respect to navigating different drug development pathways. Botanical drug development offers the promise of synergy amongst the diverse chemical characteristics of the cannabis plant, for which there are some examples of increased magnitude of select effects in some studies. There is also the advantage of a massive natural history experiment that is currently under way for which data can (and should) be collected to evaluate the impact of cannabis use amongst the millions of

individuals currently using botanical cannabis products to help treat a variety of ailments. However, there are substantial challenges in determining the right balance of constituent components in the cannabis plant in order to establish a defined product with which to move forward in clinical development. There remain many constituents of the cannabis plant for which the human behavioral pharmacology and toxicology are poorly understood. Moreover, with each increase in the number of "active" substances in a medicine, the challenges with respect to clinical evaluation and manufacturing precision increase exponentially. Obtaining the level of precision in manufacturing that is expected for modern medicine must be achieved for the botanical drug development approach to be successful.

Pursuit of single molecule cannabinoid medications has merit over botanical drugs mainly because this pathway is consistent with how most other medications are currently developed. There are clear guidelines for drug discovery, evaluation of pharmacology and toxicology, quality control, and both pre-clinical and clinical research methods. Further, synthetic drug development simply offers more choices, thus, there is potential for greater precision than what is available with respect to naturally occurring phytocannabinoids. One challenge for single molecule cannabinoid drug development is that there seems to be growing sentiment, though unfounded in published scientific studies, that "natural" cannabis is safer and better than pharmaceuticals. Another, somewhat related complicating factor in cannabinoid drug development is the existence and structure of the legislatively approved medicinal, and more recently "recreational," cannabis industries. From an economic standpoint, there is little incentive for the businesses able to sell cannabis products through legislatively sanctioned mechanisms to invest tens of millions of dollars into clinical research, because they are not currently required to do so. At the same time, pharmaceutical companies face the financial uncertainty of whether any drug (botanical or single molecule) brought to market through traditional drug development methods would be able to compete with the existing cannabis industry. From a regulatory standpoint, traditional drug development also faces significant challenges. Given that cannabis and many single molecule cannabinoids are still tightly regulated in most countries, there are substantial challenges with importing/exporting products, arduous requirements for conducting research, and few sources of raw botanical or synthetic materials that meet the quality standards needed for medicinal drug development.

In sum, while there appears to be tremendous therapeutic potential for cannabinoid medicines, there is a need for the development of defined, consistent, and targeted products. Independent of whether these are botanical or single molecule substances, these products must pass established standards for quality, safety, and efficacy before being approved for use. Currently, there is a need for government agencies to ease the regulatory hurdles associated with cannabinoid pharmaceutical drug development, including those currently required to conduct proper clinical evaluation of both botanical and single molecule products.

Acknowledgments

Funding: U.S. Department of Health and Human Services >

National Institutes of Health >

National Institute on Drug Abuse

R01-DA043475

REFERENCES

Ben-Shabat S, Fride E, Sheskin T, Tamiri T, Rhee M-H, Vogel Z, … Mechoulam R. (1998). An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. European Journal of Pharmacology, 353(1), 23–31. https://doi.org/10.1016/S0014-2999(98)00392-6 [PubMed: 9721036]

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, & Vandrey R (2017). Labeling accuracy of cannabidiol extracts sold online. JAMA - Journal of the American Medical Association, 318(17). https://doi.org/10.1001/jama.2017.11909

Carlini EA, Karniol IG, Renault PF, Schuster CR (1975) Effects of marihuana in laboratory animals and in man, British Journal of Pharmacology, 50: 299–309.

Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, … Cilio MR. (2016). Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. The Lancet Neurology, 15(3), 270–278. https://doi.org/10.1016/S1474-4422(15)00379-8 [PubMed: 26724101]

Doyle E and Spence AA (1995) Cannabis as a medicine? British Journal of Anesthesia 74, 359–361.

ElSohly MA and Gul W (2014) Costituents of cannabis sativa, In: Pertwee RG (Ed.) Handbook of cannabis, Oxford University press, 3–22.

ElSohly MA, & Slade D (2005). Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sciences, 78, 539–548. [PubMed: 16199061]

Fantegrossi WE, Moran JH, Radominska-Pandya A, & Prather PL (2014). Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Δ9-THC: Mechanism underlying greater toxicity? Life Sciences, 97(1), 45–54. https://doi.org/10.1016/J.LFS.2013.09.017 [PubMed: 24084047]

Fattore L, & Fratta W (2011). Beyond THC: The new generation of cannabinoid designer drugs. Frontiers in Behavioral Neuroscience, 5, 1–12. [PubMed: 21267359]

Fowler CJ (2003). Plant-derived, synthetic and endogenous cannabinoids as neuroprotective agents. Non-psychoactive cannabinoids, ‘entourage’ compounds and inhibitors of N-acyl ethanolamine breakdown as therapeutic strategies to avoid psychotropic effects. Brain Research. Brain Research Reviews, 41, 26–43. [PubMed: 12505646]

Haney M, Gunderson EW, Rabkin J, Hart CL, Vosburg SK, Comer SD, & Foltin RW (2007). Dronabinol and marijuana in HIV-positive marijuana smokers: Caloric intake, mood, and sleep. Journal of Acquired Immune Deficiency Syndromes, 45(5), 545–554. https://doi.org/10.1097/QAI.0b013e31811ed205 [PubMed: 17589370]

Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, & Grotenhermen F (2013). The Medicinal Use of Cannabis and Cannabinoids—An International Cross-Sectional Survey on Administration Forms. Journal of Psychoactive Drugs, 45(3), 199–210. https://doi.org/10.1080/02791072.2013.805976 [PubMed: 24175484]

Mechoulam R, & Gaoni Y (1967). The absolute conturation of delta-1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Letters, 12, 1109–1111. [PubMed: 6039537]

Mechoulam R, & Hanus L (2000). A historical overview of chemical research on cannabinoids. Chemistry and Physics of Lipids, 108, 1–13. [PubMed: 11106779]

O’Neil ME, Nugent SM, Morasco BJ, Freeman M, Low A, Kondo K, … Kansagara D. (2017). Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder. Annals of Internal Medicine, 167(5), 332 https://doi.org/10.7326/M17-0477 [PubMed: 28806794]

Pertwee RG (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. British Journal of Pharmacology, 153, 199–215. [PubMed: 17828291]

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA, 2010 International Union of Basic and Clinical

Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). Pharmacological Reviews, 62, 588–631. [PubMed: 21079038]

Radwan MM, Wanas AS, Chandra S and ElSohly MA (2017) Natural Cannabinoids of Cannabis and Methods of Analysis, In: Chandra Suman, Lata Hemant, and ElSohly Mahmoud A. (Eds.) Cannabis Sativa L.: Botany and Biotechnology, Springer Publication, 161–182.

Russo EB (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology, 163(7), 1344–1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x [PubMed: 21749363]

Russo EB, & McPartland JM (2003). Cannabis is more than simply Δ9-tetrahydrocannabinol. Psychopharmacology, 165(4), 431–432. https://doi.org/10.1007/s00213-002-1348-z [PubMed: 12491031]

Sanchez-Ramos J The entourage effect of the phytocannabinoids. Annals of Neurology, 77, 1083.

Strasser F, Luftner D, Possinger K, Ernst G, Ruhstaller T, Meissner W, … Cerny T. (2006). Comparison of orally administered cannabis extract and delta-9- tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannab. Journal of Clinical Oncology, 24(21), 3394–3400. https://doi.org/10.1200/JCO.2005.05.1847 [PubMed: 16849753]

Turner CE, ElSohly MA, Boeren EG (1980) Constituents of C. sativa L. XVII. A review of the natural constituents. J Nat Prod 43:169–234 [PubMed: 6991645]

U.S. Food & Drug Administration (FDA). Search for FDA Guidance Documents - Early Development Considerations for Innovative Combination Products Retrieved March 2, 2018, from https://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm

Vandrey R, Dunn KE, Fry JA, Girling ER, 2012 A survey study to characterize use of Spice products (synthetic cannabinoids). Drug and Alcohol Dependence, 120, 238–241. [PubMed: 21835562]

Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, & Bonn-Miller MO (2015). Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. JAMA, 313(24), 2491 https://doi.org/10.1001/jama.2015.6613 [PubMed: 26103034]

Wachtel S, ElSohly M, Ross S, Ambre J, & De Wit H (2002). Comparison of the subjective effects ofDelta9-tetrahydrocannabinol and marijuana in humans. Psychopharmacology, 161(4), 331–339. https://doi.org/10.1007/s00213-002-1033-2 [PubMed: 12073159]

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, … Kleijnen J. (2015). Cannabinoids for Medical Use. JAMA, 313(24), 2456 https://doi.org/10.1001/jama.2015.6358 [PubMed: 26103030]

Wilcox M, Jacyno M, Marcu J, & Neal-Kababick J (2016). Improving Quality Control Methods For Cannabis-Infused Products Using Automated Flash Chromatography. Planta Medica, 82(5), PA32 https://doi.org/10.1055/s-0036-1578647

Zuardi AW (2006) History of Cannabis as a medicine: a review. Brazilian Journal of Psychiatry 28,153–157. [PubMed: 16810401]