Review article **Bimonthly published scientific journal**

INTERNATIONAL JOURNAL of Indigenous Herbs and Drugs

Phytochemical and pharmacological profile of *Cannabis sativa* L.

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Abstract

Plants have always been a common source of medicaments, either in the form of traditional preparations or as pure active principles. The Cannabis plant (*Cannabis sativa* L.) has a long history as a recreational drug, but also as part of traditional medicine in many cultures. The cannabis plant and products thereof (such as marijuana, hashish and hash oil) have a long history of use both as a medicinal agent and intoxicant. Over the last few years there have been an active debate regarding the medicinal aspects of cannabis. It contains about 60 different cannabinoids including tetrahydrocannabinol (THC, dronabinol), cannabinol, cannabidiol, cannabigerol and cannabichromene. Its therapeutic potential is still in the area of muscle relaxation and cannabinoids are currently advocated for the treatment of anorexia, bronchial asthma, epilepsy, glaucoma, hypertension, muscle spasticity, nausea, vomiting and pain. There are two cannabinoids currently licensed for medicinal use. The first is THC (Marinol) which is made synthetically and licensed in the USA for the treatment of nausea following cancer chemotherapy and appetite enhancement in patients with AIDS. The second is nabilone, which is a completely synthetically derived cannabinoid. It is licensed in the UK for the treatment of nausea caused by chemotherapy. A third synthetic cannabinoid, dexanabinol, is in phase III clinical trials. Cannabis medicinal use and much research still need to be undertaken to provide patients with a medicine that is safe, efficacious and of the appropriate quality.

Keywords: Cannabis plant, *Cannabis sativa* L., Cannabinoids, Phytochemical profile, Pharmacological profile

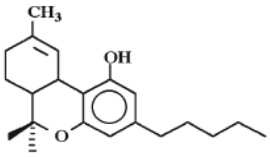
Introduction

Cannabis is considered to be the most widely used illegal drug in the world, and it was estimated that 4% of the world's adult population (160 million) were using cannabis in 2005 [1]. Marijuana is the crude drug derived from the plant *Cannabis sativa* L., a plant that is currently accepted as belonging to a family (Cannabaceae) that has only one genus (Cannabis) with only one species (sativa) that is highly variable. There are several species of cannabis. The most relevant are *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. *Cannabis sativa*, the largest variety, grows in both tropical and temperate climates. The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco but referring today to the dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant [2]. The plant Cannabis sativa grows in temperate and tropical climate. Its seeds, flowering tops, leaves and stalks contain a cocktail of chemicals termed cannabinoids that causes psychoactive manifestations following ingestion or inhalation of smoke [3]. Though the special significance of this plant was first recorded in allopathic medical literature at the turn of the last century, the oriental physicians have been using it as a medicinal plant for many millennia [4]. Dried leaves and flowering tops (grass, marijuana, joint, weed, ganja, hashish), resinous extracts from flowering tops and cannabis oil (hash oil) are different formulations with psychoactive chemicals that are used for medicinal and recreational purposes [5]. These are largely derived from the female plant of *Cannabis sativa*. Cannabis has been used recreationally for millennia and is the third most commonly used drug after tobacco and alcohol. Cannabis may be smoked in a joint, which is the size of a cigarette, and tobacco may be added to assist burning. Smokers typically inhale deeply and hold their breath to maximize absorption via the lungs. Although marijuana and hashish may be eaten, they are more usually smoked because titration of blood levels in order to achieve a given psychoactive effect is easier [6]. The acute effects of cannabis use are well recognized; it induces a psychoactive, mildly euphoric, relaxing intoxication or "high", which leads to slight changes in psychomotor and cognitive function. In some limited cases, cannabis can also induce unpleasant effects including anxiety, panic, and paranoia, and very rarely it may lead to acute psychosis involving delusions and hallucinations. Frequent users may develop a motivational syndrome. Cannabis also induces an increase in heart rate, a lowering of blood pressure due to vasodilatation (which causes the classic "red eye"), appetite stimulation (known as "the munchies"), dry mouth, and dizziness [7].

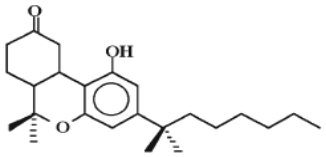
Phytochemical profile

The term cannabinoids is used for a number of chemicals found in the extracts of Cannabis sativa. Cannabis sativa produces unique secondary metabolites consisting of alkyl resorcinol and monoterpene groups. The plant Cannabis sativa contains more than 60 terpenophenolic compounds,

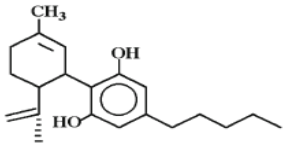
named phytocannabinoids (Figure 1). The best-studied phytocannabinoid is Δ^9-tetrahydrocannabinol (TCH) which binds specific G-protein-coupled receptors named cannabinoid (CB1 and CB2) receptors, it is the main active component which has been shown to induce acute transient psychotic reactions in previously well individuals when administered as an isolated compound [8]. Δ^9-tetrahydrocannabinolic acid (THCA), a product of the cannabinoid class, is the primary psychoactive agent. This compound is produced as an acid in the glandular trichomes of inflorescence bracts and undergoes decarboxylation with age or heating to Δ^9-tetrahydrocannabinol (THC) [9, 10]. Still there are other components in this chemical mixture, such as cannabidiol (CBD) and cannabigerol, which may also play a role in modulating the effects of TCH [11]. A number of cannabis components that do not activate the receptors are often called cannabinoids.



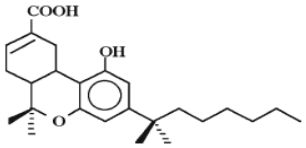
Δ^9-tetrahydrocannabinol (TCH)



Nabilone



Cannabidiol (CBD)



Ajulemic acid (AJA)

Figure 1: Phytocannabinoids: Δ^9-tetrahydrocannabinol (TCH), nabilone, cannabidiol (CBD) and ajulemic acid (AJA)

Phytocannabinoids

Cannabis may contain over 60 "classical" cannabinoid (tricyclic dibenzopyran) compounds and some, such as cannabidiol, may modulate the response to THC [12-14]. Cannabinoids (cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabicyclol (CBL), cannabielsoin (CBE), cannabinol (CBN), cannabinodiol (CBND), cannabitriol (CBT)) nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, sugars, hydrocarbons, simple alcohols, simple aldehydes, simple ketones, simple acids, fatty acids, simple esters, lactones, steroids, terpenes, non-cannabinoid phenols, flavonoids, vitamins, pigments and elements are the chemical classes compounds of *Cannabis sativa* which has been identified [15-17].

Δ^9-tetrahydrocannabinol (TCH)

The cannabis plant (*Cannabis sativa*) contains many compounds, but Δ^9-tetrahydrocannabinol (THC) is the main psychoactive ingredient. THC breaks down to produce cannabinol and was identified along with cannabidiol (the main non-psychoactive component) [12, 13]. However, THC was not isolated, synthesised, and stereochemically defined until the 1960s [12]. THC is concentrated in the flowering head of the female plant and selective growing in the past 5–10 years has substantially increased THC content from 1-3% THC in the "flowerpower" era to 6–13% and above.

Cannabidiol (CBD)

Cannabidiol (Figure 2) was isolated in 1940 [18] and its absolute configuration established by synthesis of (-)-CBD as (-)-trans-(1R, 6R) [19]. The optical rotation of cannabidivarin was reported as [α] D-139.5-(chloroform) [20]. All of the known CBD-type cannabinoids (Table 1) have trans-(1R, 6R) (Figure 3) absolute configuration and presumably also negative optical rotation.

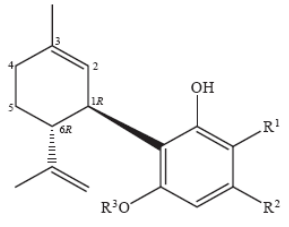


Figure 2: CBD type cannabinoids

Table 1: CBD-type cannabinoids

COMPOUND	R^1	R^2	R^3
Cannabidiolic acid (CBDA-C5)	COOH	n-C_5H_{11}	H
(⁻)-Cannabidiol (CBD-C5)	H	n-C_5H_{11}	H
Cannabidiol monomethyl ether (CBDM-C5)	H	n-C_5H_{11}	Me
Cannabidiol-C4 (CBD-C4)	H	n-C_4H_9	H
Cannabidivarinic acid (CBDVA-C3)	COOH	n-C_3H_7	H
(⁻)-Cannabidivarin (CBDV-C3)	H	n-C_3H_7	H
Cannabidiorcol (CBD-C1)	H	CH_3	H

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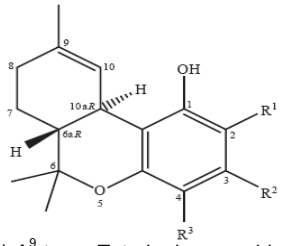
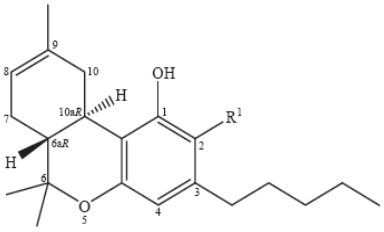


(-)-Δ^9-trans-Tetrahydrocannabinol (Δ^9-THC)



(-)-Δ^8-trans-Tetrahydrocannabinol (Δ^8-THC)

Figure 3: Δ^9-THC and Δ^8-THC type cannabinoids

Nabilone

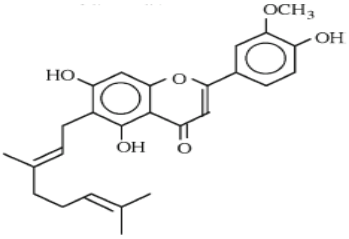
Nabilone turned out to be significantly superior to prochlorperazine, domperidone and alizapride for treating nausea and vomiting associated with cancer chemotherapy. On the other hand, the patients clearly favoured nabilone for continuous use. The results led Health Canada to approve the marketing of this product. Marketed under the name Cesamet®, nabilone has been available in Canada since 1982. It is presented in the form of 1 mg pulvules. The recommended dosage is 2-6 mg/day [21].

Ajulemic Acid (AJA, CT3, IP751)

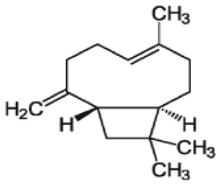
Numerous compounds have been synthesized with the goal of separating psychotropic activity from analgesic, antiinflammatory action. Among the most promising is 1', 1'-dimethylheptyl-THC-11-oic acid (Figure 1. Ajulemic acid). The synthesis, chemistry and biological activity of AJA have been the subjects of several reviews [22, 23]. The oral administration of low dose (0.1 mg/kg/day) AJA suppresses joint inflammation and tissue injury in rats with adjuvant arthritis led to further investigation of its mechanisms of action [24]. Addition of AJA to human cells in vitro reduces production of interleukin (IL) - 1b but not TNFα, suppresses matrix metalloproteinases [25] and increases apoptosis of human T lymphocytes. More recently, it has been reported [26] that AJA reduces production of IL-6 by human monocyte-derived macrophages.

Noncannabinoid

Noncannabinoid, the geranylated flavone cannflavin A (Figure 4), is 30 times more potent than aspirin as an inhibitor of prostaglandin E2 [27, 28].



Cannflavin-A



β-Caryophyllene

Figure 4: Structures of noncannabinoid plant constituents

Six new non-cannabinoid constituents were isolated from a high potency *Cannabis sativa* L. variety, namely 5-acetoxy-6-geranyl-3-n-pentyl-1,4-benzoquinone, 4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene, 4,7-dimethoxy- 1,2,5-trihydroxyphenanthrene, cannflavin C and b-sitosteryl-3-O-b-D-glucopyranoside-20- O-palmitate, 4-hydroxy-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene. In addition, five known compounds, a-cannabispiranol, chrysoeriol, 6-prenylapigenin, cannflavin A and b-acetyl cannabispiranol were identified. Non-cannabinoid constituents isolated from cannabis include flavonoids, spiroindans, dihydrostilbenes, dihydrophenanthrenes, sterols and alkaloids, among others [28, 30].

Pharmacological profile

The clinical potential of the cannabinoids is large; some people suggest that cannabis could be the "aspirin of the 21st century" [31]. However, much of the evidence for the use of cannabinoids is anecdotal and is too broad in scope to review. To date, there are a multitude of anecdotal reports and a certain number of clinical trials evaluating the therapeutic applications of cannabis and its derivatives.

Antiemetic effect

Cancer chemotherapy frequently causes nausea and vomiting which vary in intensity, but which can sometimes be severe and prolonged. Various controlled studies evaluating the antiemetic effects of nabilone and dronabinol described the efficacy of these two cannabinoids. Nabilone (Cesamet®) is a synthetic analog of THC and dronabinol (Marinol®) is synthetic THC. The two substances were administered orally in clinical trials. The recommended dosage of nabilone is 2-6 mg per day and 5-15 mg/m^2/dose, without exceeding 4-6 doses per day for dronabinol. Nabilone turned out to be

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significantly superior to prochlorperazine, domperidone and alizapride for treating nausea and vomiting associated with cancer chemotherapy whereas dronabinol exhibits an antiemetic effect equivalent to or significantly greater than chlorpromazine and equivalent to metoclopramide, thiethylperazine and haloperidol [21]. Levonantradol, a synthetic cannabinoid administered intramuscularly, has also proved its antiemetic efficacy in a controlled study.

Despite the existence of many clinical trials with cannabinoids against nausea and vomiting associated with cancer chemotherapy, none have compared their efficacy against newer generation agents such as the 5-HT3 receptor antagonists and the more recent neurokinin-1-receptor-antagonists [32].

Appetite stimulation

Anorexia (loss of appetite) and a progressive weight loss are observed in patients suffering from advanced stages of cancer or HIV infection. In the case of AIDS, cachexia (extreme weight loss) may be accompanied by chronic diarrhea and weakness [33]. Two controlled studies have demonstrated that oral THC stimulates appetite and helps retard chronic weight loss in adults suffering from various advanced cancers. THC tended to stabilize weight, while patients on placebo continued to lose weight. Health Canada has approved oral THC (Marinol®) as an appetite stimulant for the treatment of anorexia and weight loss associated with AIDS. This synthetic THC or dronabinol (Marinol®) is available in the form of 2.5, 5 and 10 mg THC capsules. The recommended dosage for this therapeutic indication is 2.5–20 mg per day [21].

Analgesic

Several cannabinoids proved to be effective analgesics in acute and chronic pain animal models [34-37]. Benzopyranoperidine (Figure 5), a synthetic nitrogen analog of THC, administered orally in the 4 mg dose, manifested an analgesic effect in a total of 45 patients suffering from cancerous pains [38]. Nonetheless, the beneficial effect of benzopyranoperidine was absent in a group of 35 subjects suffering from chronic pain [39]. The major undesirable effect of benzopyranoperidine was drowsiness.

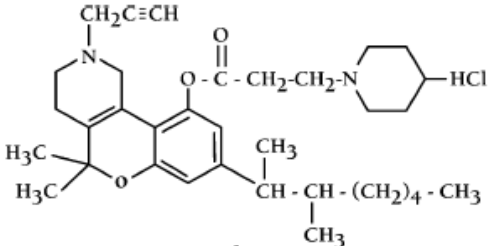

Figure 5: Benzopyranoperidine

Oral CT-3 (ajulemic acid), a synthetic analog of 11-hydroxy-THC, showed analgesic efficacy in a study of 21 patients suffering from chronic neuropathic pain, without exhibiting major adverse effects [40]. Levonantradol, a synthetic cannabinoid administered intramuscularly in 1.5, 2, 2.5 and 3 mg doses to 56 patients suffering from postoperative pain, manifested significant analgesic efficacy in the four dosages used. Analgesia persisted for more than 6 h with the 2.5 and 3 mg doses of levonantradol. Drowsiness was frequent but few other psychoactive effects were reported [41]. Blake published a study on the efficacy and the safety of a mixture of 2.7 mg THC and 2.5 mg CBD delivered via an oromucosal spray (Sativex®) and used against pain caused by rheumatoid arthritis [42].

Multiple sclerosis

Multiple sclerosis is a neurodegenerative disease which is accompanied by spasticity (muscle rigidity), painful muscle cramps, chronic pain in the extremities, tingling and prickling of the fingers of the hands and feet, as well as ataxia, tremors and vesical and intestinal dysfunctions [36, 43, 44]. Wade evaluated the effects of a cannabis extract containing almost equal quantities of THC (2.7 mg) and cannabidiol (2.5 mg) (Sativex®) administered in sublingual spray at 2.5-120 mg per day doses The improvements were objectively confined to patients taking THC alone, although patients reported beneficial effects with both THC alone (Marinol®) and the combination of THC and CBD (Cannador®) [45].

Spinal cord injuries

People suffering from spinal cord injuries often exhibit symptoms similar to those of multiple sclerosis, including spasticity, painful muscle spasms and urinary incontinence [46]. Oral THC or *Cannabis sativa* extracts containing THC, cannabidiol or a combination of the two, administered in sublingual spray, may, in some patients, lead to an improvement in spasticity, muscle spasms, pain, vesical dysfunction and sleep quality [47].

Gilles de la Tourette's syndrome

Gilles de la Tourette's syndrome is a neurobehavioral dysfunction characterized by motor and verbal tics, as well as a spectrum of behavioral and cognitive disorders. During their latest clinical trial, the researchers also reported that THC did not impair neuropsychological performances: treatment with up to 10 mg oral THC over a 6 w period and immediately as well as 5–6 w after withdrawal of THC use had no detrimental

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effects on learning, interference, recall and recognition of word lists, immediate visual memory and divided attention. To the contrary, the authors even found a trend towards a significant improvement during and after therapy while evaluating immediate verbal memory span. They concluded that treatment with oral THC in patients suffering from Tourette's syndrome did not impair their cognitive function and might even improve it [48, 49].

Epilepsy

Individuals who smoke marijuana to treat their epilepsy, stopping use of cannabis precipitates the reemergence of convulsive seizures, while resuming consumption of this psychotropic drug controls epilepsy (oral cannabidiol at 200–300 mg per day) [50]; these results are reproducible [51-54]. These results were not confirmed by other controlled clinical studies.

Glaucoma

Glaucoma is an eye affliction characterized by an increase in intraocular pressure. It can lead to blindness if it is not treated effectively. Several anecdotal reports observe that cannabis has the power to reduce the fluid pressure within the eye [53, 55, 56]. Even though these results are interesting; the use of cannabis against glaucoma is unsatisfactory.

Bronchial asthma

Acute administration of cannabis and THC exert a definite bronchodilator effect on the small airways of the lungs [57]. Tashkin studied 14 asthmatic volunteers and compared smoked cannabis (THC 2%), oral THC (15 mg) and a standard bronchodilator (isoprenaline 0.5%). They found that smoked cannabis and oral THC produced significant bronchodilation for at least 2 h [58]. However, smoking cannabis is not a therapeutic option because of the other smoke constituents.

Mood disorders, psychiatric conditions

Cannabis and cannabinoids have been advocated as antidepressants, anxiolytics, sedatives, hypnotics and as treatment for alcohol and opiate withdrawal syndromes. There is no convincing evidence that they are superior to existing drugs for these conditions. Animal work and some anecdotal reports suggest that THC and cannabinol can inhibit many of the signs of opioid withdrawal by a non-opioid mechanism [59]. This possibility may be worth pursuing in clinical studies to assist patients detoxifying from opiates.

Parkinson disease

The antiparkinsonian action of cannabinoids as well as their effect on levodopa induced dyskinesia has been evaluated. Oral nabilone had no antiparkinsonian action. However, nabilone significantly reduced total levodopa-induced dyskinesia [60]. Oral administration of a cannabis extract (2.5 mg of THC and 1.25 mg of cannabidiol per capsule) resulted in no objective or subjective improvement in parkinsonism or dyskinesias [61].

Dystonia

Oral nabilone did not showa significant reduction in total dystonia movement scale score compared to placebo. The authors stated that lack of effect of nabilone might have reflected the insufficient dose employed [62]. Further research will be necessary to determine the impact of cannabinoids in the management of different forms of dystonia.

Antidepressant-like effect

The antidepressant action of cannabis as well as the interaction between antidepressants and the endocannabinoid system has been reported. Cannabinoids were initially evaluated in the mouse tetrad assay to determine doses that do not induce hypothermia or catalepsy. The automated mouse forced swim (FST) and tail suspension (TST) tests were used to determine antidepressant action. At doses lacking hypothermic and cataleptic effects (1.25, 2.5, and 5 mg/kg, i.p.), both Δ^9-THC and Δ^8-THC showed a U-shaped dose response with only Δ^9-THC showing significant antidepressant-like effects at 2.5 mg/kg ($p<0.05$) in the FST. The cannabinoids cannabigerol (CBG) and cannabinol (CBN) did not produce antidepressant-like actions up to 80 mg/kg in the mouse FST, while cannabichromene (CBC) and cannabidiol (CBD) exhibited significant effect at 20 and 200 mg/kg, respectively ($p<0.01$). The antidepressant-like action of Δ^9-THC and CBC was further confirmed in the TST. Δ^9-THC exhibited the same U-shaped dose response with significant antidepressant-like action at 2.5 mg/kg ($p<0.05$) while CBC resulted in a significant dose-dependent decrease in immobility at 40 and 80 mg/kg doses ($p<0.01$). Results of this study show that Δ^9-THC and other cannabinoids exert antidepressant like actions and thus may contribute to the overall mood elevating properties of cannabis [63].

Antimicrobial activity

Study was focused on inhibitory activity of freshly extracted essential oils from three legal (THC<0.2% w/v) hemp varieties (Carmagnola, Fibranova and Futura) on microbial growth. The effect of different sowing times on oil composition and biological activity was also evaluated. Essential oils were distilled and then characterized through the gas chromatography and gas chromatography-mass spectrometry. Thereafter, the oils were compared to standard reagents on a broad range inhibition of microbial growth via minimum inhibitory concentration (MIC) assay. Microbial strains were divided into three groups: i) Gram (+) bacteria, which regard to food-borne pathogens or gastrointestinal bacteria, ii) Gram (−) bacteria and iii) yeasts, both being involved in plant interactions. The results showed that essential oils of industrial hemp can significantly inhibit the microbial growth, to an extent depending on variety and sowing time. It can be concluded that essential oils of industrial hemp, especially those of Futura, may have

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interesting applications to control spoilage and food-borne pathogens and phytopathogens microorganisms [64].

Anti-inflammatory activities

The anti-inflammatory activities of all classes of cannabinoids, including 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. A possible mechanism for these actions is suggested involving increased production of eicosanoids that promote the resolution of inflammation. This differentiates these cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process [65].

HIV/AIDS

THC shows to be useful in stimulating appetite and preventing weight loss in cancer and AIDS patients. Its use in these debilitating diseases raises reservations, because some authors report immunosuppressive properties of cannabinoids [66-69], while others do not [70, 71]. In this regard, work conducted with HIV- 1 infected patients has not proved that smoked marijuana or oral THC affects the viral load, the number of CD4+ and CD8+ lymphocytes or the progression of the disease [72-74]. For a definitive elucidation of the question of the safety of long-term use of cannabinoids in immunodepressed subjects, in-depth studies are still necessary.

Conclusion

Since most medicinal plants occur naturally in a large number of countries, a plant of potential importance in one country may well have been studied by scientists elsewhere. Pooled information is especially critical when it comes to drugs, as a value judgment on the safety or efficacy of a particular drug can rarely be based on the results of a single study. In contrast, a combination of information indicating that a specific plant has been used in a local health care system for centuries, together with efficacy and toxicity data published by several groups of scientists, can help in deciding whether it should be considered acceptable for medicinal use. The source of starting materials is normally abundant and readily available since in most developing countries the flora remains virtually unexploited, and we believe that over the next two decades many useful drugs will be isolated from plants. The relaxation of the regulatory norms for therapeutic cannabis and the accomplishment of a greater number of controlled clinical trials make it possible to affirm that cannabinoids exhibit an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, as well as in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma. In spite of its history of use, the many small clinical trials that have been published and anecdotal evidence that Cannabis can be used as a medicine, there is no good scientific evidence that Cannabis, Cannabis resin or the cannabinols and their derivatives have therapeutic benefit. Thus, the World Health Organization lists them under their Schedule 1 drugs, so that medical practitioners may not prescribe them. More clinical research is needed to investigate the potential therapeutic uses of cannabinoids in specific medical conditions. Scientifically designed trials will help to establish which of the cannabinoids produces the various beneficial effects described, or whether they result from a combination of cannabinoids. Research would also help to characterize the unwanted effects of individual cannabinoids more fully.

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Conflict of Interest: None declared,
Received: 12 March 2017, Revised: 29 March 2017, Accepted: 12 April 2017

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