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Pharmacological potential of phytochemicals from *Cannabis sativa*: A comprehensive review of therapeutic applications

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Abstract

Cannabis sativa is a controversial plant largely due to its association with marijuana, an illicit substance that is well known and often hotly debated. Despite this controversy surrounding the plant, *Cannabis sativa* L., also known as cannabis, has unique phytochemistry, considering the variety of cannabinoids that it encompasses. These cannabinoids have various pharmacological properties that have the potential for therapeutic use due to their capacity to interact with the human body's endocannabinoid system. The medical potential of *Cannabis sativa* is explored through an extensive review that investigates the phytochemical profile and pharmacological characteristics of *Cannabis sativa*, looking at the plant's chemical components, for example, cannabidiol (CBD), tetrahydrocannabinol (THC), and other cannabinoids and non-cannabinoid constituents. The analysis also scrutinizes the pharmacological actions of these phytochemical constituents, including their potential therapeutic activities, antiemetic, appetite-stimulating, analgesic activities and their potential for one of a number of disorders such as Tourette's, multiple sclerosis and spinal cord injuries. This review seeks to provide a comprehensive understanding of *Cannabis sativa*, its phytochemistry and pharmacological properties, as well as to highlight the potential therapeutic applications of *Cannabis sativa* as well as its phytochemical components. This type of understanding should facilitate the generation of potentially useful hypotheses for future work in the area of cannabinoid-based medicines.

Keywords: Cannabis plant, *Cannabis sativa* L., cannabinoids, phytochemical profile, pharmacological profile

Introduction

Cannabis, *Cannabis sativa* L. is a debated subject because of its link, to marijuana, which originates from this plant. It is known as one of the used illicit drugs worldwide with around 4% of the global adult population (about 160 million individuals) reported to have consumed cannabis in 2005 [1]. *Cannabis sativa* L. is a plant species that belongs to the Cannabaceae family and the only species within the Cannabis genus. Nevertheless, it is also important to recognize that other species of cannabis, for example *Cannabis indica* and *Cannabis ruderalis*, also exist. Among the three species of cannabis, *Cannabis sativa* is the most utilized and can exist in a variety of climates and regions, extending from tropical regions to temperate regions. Among the uses, cannabis can be used in many ways, among them marijuana and hashish, the two main preparations that can be obtained from the plant. The term marijuana comes from the Mexican original term for "cheap tobacco" and is now used to refer to the dried leaves and flowers of the cannabis plant. On the other hand, hashish is a product derived from the Arabic term for Indian hemp, which is the resin extracted from the plant. One of the most interesting aspects of the cannabis plant is its phytochemical profile that includes cannabinoids. Cannabinoids are chemicals that are derived from the cannabis plant, recognizing the crucial role of cannabinoids that interact with the human body's endocannabinoid system which will eventually exert diverse pharmacological effects. Understanding the phytochemical and pharmacological profile of the cannabis plant is critical in identifying both its therapeutic benefits and risks [2]. *Cannabis sativa*, is a versatile plant that can be grown in temperate to tropical areas. It can have a number of valuable components including seeds, flowering tops, leaves and stalks.

Also known as cannabinoids, these components can produce psychoactive effects when consumed, usually by smoke

inhalation or orally [3].



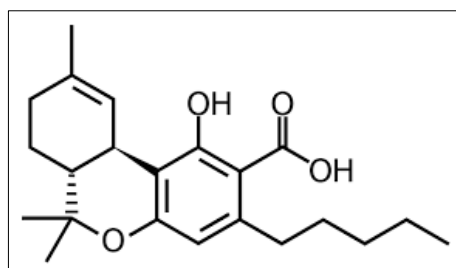
Fig 1: *Cannabis sativa*

Although the Western medical community has only recently recognized the benefits of *Cannabis sativa*, the plant has long been used medicinally by ancient Eastern physicians. Millennia of use have demonstrated the pharmacological potential of the phytochemicals found in *Cannabis sativa*, paving the way for a systematic investigation of its drug properties. In this context, the pharmacological potential of phytochemicals from *Cannabis sativa* offers great promise as an avenue for further exploration of medicinal treatments, with several therapeutic applications waiting discovery and adaptation to the benefit of human health [4]. The dried leaves, the flowering tops, resinous extracts of the flowering tops, and cannabis oil (hash oil) are all derived from the female plant of *Cannabis sativa* [5]. Throughout history, the recreational use of cannabis has spanned centuries and it is the third most popular recreational drug in the world, after tobacco and alcohol. One common way of consuming cannabis is through smoking in a “joint” or cigarette-like form. It is common to mix in tobacco to facilitate ignition. Another common feature of smoking cannabis is that in doing so, people copy heavy smokers of tobacco, inhaling deeply and holding their breath after inhalation to maximize the absorption through the lungs. Although cannabis and hashish can be consumed orally, the continued method of smoking is maintained, largely because it gives fast control over the levels of cannabinoids in the blood and it is easier to titrate blood levels [6]. Cannabis is well known for the acute effects it has on the person who uses it. When someone uses cannabis, they will get a high which creates a different reality for them where they feel happy and intoxicated. We call this experience a “high”. When a person is high they may experience some slight changes in

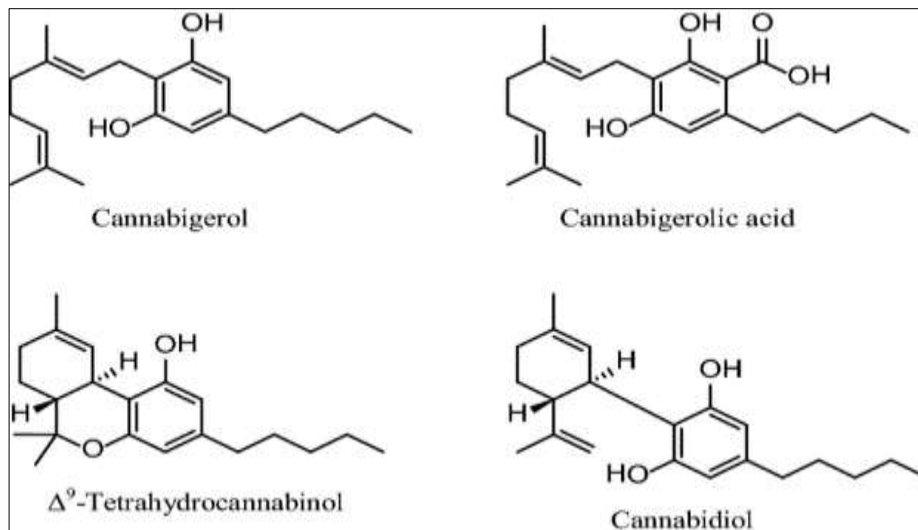
their mental and physical reactions. A majority of people have positive experiences from using cannabis, but there are some people who get a bad feeling from using it which can include anxiety, panic or a feeling that causes them to be nervous. Some people even experience acute psychosis, where they start to have a reality in a fantasy world and feel like there are visual or sound hallucinations present. CNS depression can lead to a syndrome of acute psychosis. With long-term frequent cannabis users, there is also a decrease in motivational syndrome. Marijuana affects physical changes in the body where people may experience an increase in the heart rate, a decrease in blood pressure and vasodilatation (causing red eyes), appetite stimulation and dry mouth, and dizziness [7].

Phytochemical profile

Cannabis extracts are known for their diversification of organic compounds. The term cannabinoids are used to describe the compounds found in *Cannabis sativa* and includes over 60 terpenophenolic compounds that contain numerous alkyl resorcinol, monoterpene and other phenolic groups. It is clear that *Cannabis sativa* produces very unique terpene and cannabinoid profiles, and the latter are of particular interest to health practitioners due to their potential medicinal properties. The plant produces many secondary metabolites that together form its characteristic phytochemical profile. *Cannabis sativa* provides a valuable source of various phytocannabinoids, including THC, which are often employed as therapeutic agents. Specifically, THC stimulates the CB1 receptor (inducing the psychoactive effects associated with marijuana) where the CB2 receptor induces an immunogenic response upon stimulation. [8].

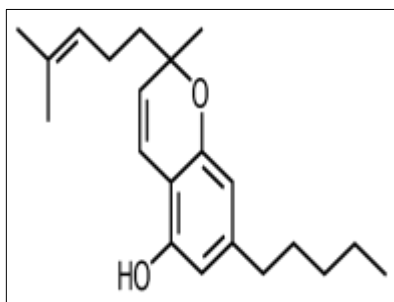


Tetrahydrocannabinolic acid

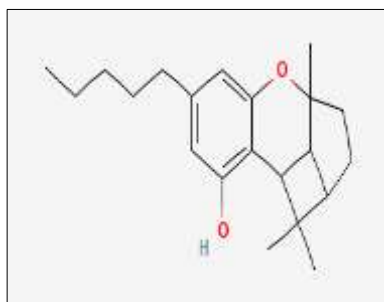


In the cannabinoid world, tetrahydrocannabinolic acid (THCA) is the main psychoactive compound. It is specifically produced as an acid in the glandular trichomes of inflorescence bracts, which are then transformed into the commonly known 9-tetrahydrocannabinol (THC) following the process of decarboxylation, either through heating or aging. THCA is a core ingredient in Cannabis extracts and has a significant impact on the psychoactive effect of Cannabis. Through extraction, THCA can be harnessed to produce any product of choice, accessible for a variety of needs and wants [9-10]. In cannabis, above and beyond the well-known psychoactive chemical THC, there are additional significant compounds. These include Cannabidiol (CBD) and Cannabigerol, which are believed to modify the effects of THC. These "cannabinoids" are crucial in controlling the overall effects of the plant. In recent years, CBD has received a lot of attention due to the beneficial effects it can provide. Known for its non-psychoactivity, there are numerous different forms in which it can be taken to treat a variety of ailments. At the same time, cannabigerol is yet another cannabinoid which is being researched to find

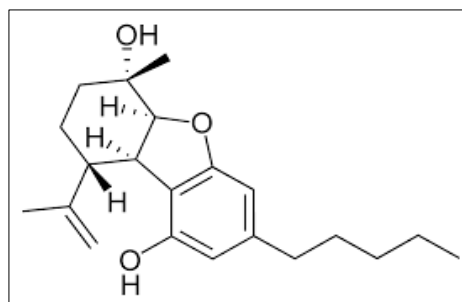
out how it could be medicinal. Even though THC is the main psychoactive component found in cannabis, CBD and cannabigerol are known to be non-intoxicating cannabinoids. These cannabinoids interact with the body's endocannabinoid system, which is responsible for many of the body's physiological functions [11]. The world of cannabinoids is full of phytocannabinoids, compounds that play a significant role in interactions with the human body, and has caused significant scientific interest. Cannabis, or marijuana, stores over 60 varieties of phytocannabinoids [12-14]. These cannabinoids are a class of nitrogenous compounds that includes various chemical classes. Identified cannabinoids include cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabicyclol (CBL), cannabielsoin (CBE), cannabinol (CBN), cannabinodiol (CBND), and cannabitrinol (CBT), along with various amino acids, proteins, enzymes, and lipids that are also unique to *Cannabis sativa*. Some phytocannabinoids influence the effects of tetrahydrocannabinol (THC), THC, for example, cannabidiol.



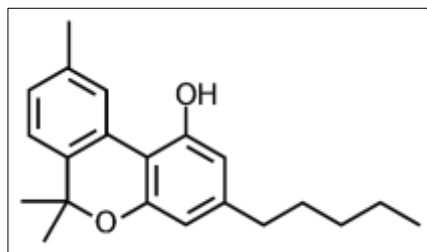
Cannabichromene



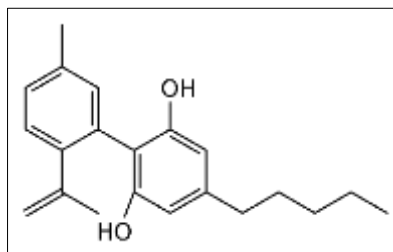
Cannabicyclol



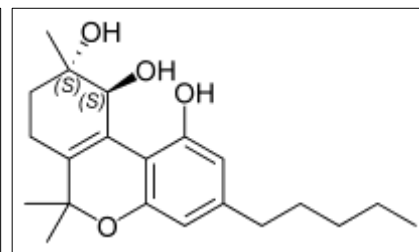
Cannabielsoin



Cannabinol



Cannabinodiol



Cannabitrinol

Analysis examples the sophisticated physiology of the cannabis plant and the subsequently possible therapeutic benefits. Non-THC phytocannabinoids, including phenols, terpenes, and flavonoids, can be found in cannabis. These phytochemicals further the overall chemical profile of the plant and comprise an important element framing the diverse effects of cannabis on the human body, including anti-inflammatory and pain relief effects. The universe of phytocannabinoids is a multitude of compounds that offer a limitless possibility of health benefits for medical and therapeutic utility. To allow signs of progress in cannabis-based medicine the study of the individual phytocannabinoids must be excluded, and the wide variety of opportunities and benefits these compounds have in the wellness and health of individuals [15-17]. The cannabis plant, scientifically referred to as *Cannabis sativa* contains a variety of compounds with Δ 9 tetrahydrocannabinol (THC) being the element. THC eventually breaks down into cannabimol while it's important to note that both THC and cannabidiol (CBD.) [12,13]. The psychoactive component was identified back in the 1960s [12]. THC; predominantly present, in the flowering head of cannabis plants THC levels have significantly increased over the 5 10 years due to selective breeding. From the era of "flower power" where THC content ranged from 1-3% levels have now reached beyond 6-13% in times. CBD; Isolated in 1940 [18] cannabidiols absolute configuration was determined through synthesizing (-) CBD as (-) trans (1R, 6R) [19]. The optical rotation of cannabidiol is reported as $[\alpha]$ D 139.5 (chloroform) [20]. It's worth noting that all known CBD type cannabinoids share the trans (1R 6R) configuration and likely exhibit an optical rotation. Nabilone has shown itself to be the most effective drug for dealing with nausea and vomiting as a result of cancer treatment, outperforming prochlorperazine, domperidone, and alizapride. Nabilone is preferred by patients based on their feedback due to its superior ability to alleviate symptoms. Given the favorable feedback, Health Canada has managed to acquire the medication's approval for sale. Sold under the trade name Cesamet®, nabilone entered the marketplace in 1982 and comes in 1 mg pulvules. The standard daily dosage of nabilone is 2 to 6 mg and is a dependable and helpful treatment option for patients to manage the debilitating symptoms associated with nausea and vomiting [21]. In the pursuit of distinguishing between the mind altering effects and pain relieving and anti inflammatory properties scientists have pinpointed Ajulemic Acid (AJA) as a substance. A notable variation is 1' 1' dimethylheptyl THC 11 oic acid, otherwise known as Ajulemic Acid. Structure and Function; Ajulemic Acid depicted in Figure 1 has attracted interest, for its effects with its production, chemistry and impacts extensively examined in scientific studies [22, 23]. A study conducted in rats with adjuvant arthritis showed promising outcomes with the oral administration of a low dose of Ajulemic acid (AJA) (0.1 mg/kg/day) in suppressing joint inflammation and tissue injury. The encouraging findings from the study have stimulated greater interest in understanding the mechanisms by which AJA provides these beneficial effects [24]. In further research, researchers found that the addition of AJA to human cells *in vitro* reduced IL-1 β production in the cells, but TNF α levels were not reduced. Furthermore, AJA inhibited matrix metalloproteinases, increased apoptosis of the human T lymphocytes, and several recent studies have

shown that AJA reduces IL-6 production by human monocyte-derived macrophages. Implications from these data suggest that AJA may be an effective treatment for adjuvant arthritis. Further research is necessary to fully understand the benefits and potential of Ajulemic Acid (CT3, IP751) who may have anti-inflammatory and tissue protective effects in arthritis in both animal models and in humans [25-26]. In the category of natural compounds, noncannabinoids have gained extensive attention. As a noncannabinoid, the geranylated flavone, cannflavin A, caught attention because of its inhibition abilities. It has been found that cannflavin A is a startling 30 times more effective than aspirin at inhibiting prostaglandin E2. Cannflavin A, a flavone compound with noncannabinoid properties, is becoming well-known for its significant impact on inflammatory pathways. Its efficacy as an inhibitor of prostaglandin E2 exceeds that of aspirin, a widely used anti-inflammatory drug. This remarkable compound, isolated from natural sources, may provide an alternative option for those seeking powerful pain relief and anti-inflammatory solutions. Research has elucidated the impressive potency of by a noncannabinoid flavone, cannflavin A. Cannflavin A is so effective at inhibiting prostaglandin E2 that it is 30 times more potent than aspirin, a common anti-inflammatory medication. This new finding highlights the potential of noncannabinoid compounds like cannflavin A in the realm of natural medicine [27, 28]. A recent groundbreaking finding reveals that scientists have identified six cannabinoid elements from a potent strain of *Cannabis sativa* L. These elements consist of 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 trihydroxyphenanthrenecannflavin C, b sitosteryl 3 O b D glucopyranoside 20 O palmitate and 4 hydroxy 2,3,6,7 tetramethoxy 9,10 dihydrophenanthrene. These fresh compounds supplement the known five substances; a cannabispiranol, chrysoeriol 6 prenylapigenin, cannflavin A and b acetyl cannabispiranol. The non-cannabinoid constituents derived from cannabis include an array of elements, like flavonoids, spiroindans, dihydrostilbenes, dihydrophenanthrenes, sterols and alkaloids among others. The unveiling of these newfound compounds paves the way for avenues in exploring the possibilities of *Cannabis sativa* L. It underscores the ranging chemical makeup of this plant beyond cannabinoids revealing the intricate interplay, among various bioactive components found in cannabis [28, 30].

Pharmacological profile

The medical characteristics of cannabinoids show promise; there are those who believe that cannabis may become the "aspirin of the century" [31]. When it comes to cannabinoids a lot of the support, for their effectiveness is based on stories than solid scientific evidence. The amount of research available is too vast to cover. However, there are accounts and some clinical trials exploring how cannabis and its derivatives could be used for therapeutic purposes. Cannabinoids are the substances, in cannabis plants. They interact with the body's system affecting bodily processes. The use of cannabinoids is often guided by experiences as people share their outcomes for a wide range of health issues. While these accounts hold value, they are not seen as proof of the advantages of cannabinoids.

Antiemetic effect

Chemotherapy, for cancer often leads to levels of nausea and vomiting which can be severe and lasting. Recent research has looked into how cannabinoids like nabilone and dronabinol can help with these symptoms showing that they are effective in providing relief. Nabilone, a man-made version of THC and dronabinol, THC have both shown results in carefully controlled studies. Nabilone is usually prescribed at a dose of 2.6 mg per day while dronabinol is given at 5.15 mg/m² per dose with no than 4.6 doses. Nabilone has proven to be more successful in managing nausea and vomiting caused by chemotherapy when compared to prochlorperazine, domperidone and alizapride. Meanwhile dronabinol displays a nausea effect similar to or even better, than chlorpromazine, metoclopramide, thiethylperazine and haloperidol [21]. Levonantradol, a man made substance, to cannabinoids given through a muscle injection has shown its effectiveness in controlling feelings of nausea and vomiting in a conducted study. While many research studies have looked into the use of cannabinoids for managing nausea and vomiting caused by chemotherapy comparing their effectiveness to medications like the 5-HT₃ receptor antagonists and the recent neurokinin 1 receptor antagonists has been explored. The study carried out on Levonantradol revealed promising properties in reducing feelings of sickness indicating its potential as an option for treating individuals dealing with side effects from chemotherapy. By comparing how well it works against used medications like the 5-HT₃ receptor antagonists valuable information can be gained on how effective Levonantradol's in handling chemotherapy induced nausea and vomiting. Through this comparison with medications such as the 5-HT₃ receptor antagonists's researchers can improve their understanding of how these treatments for reducing sickness measure up against each other. This insight can assist healthcare professionals in making choices when deciding on the suitable medication for alleviating chemotherapy related nausea and vomiting among cancer patients. Additionally investigating Levonantradol alongside sickness agents like the 5-HT₃ receptor antagonists could lead to better and individualized treatment approaches, for those undergoing chemotherapy. Comparing these findings could help enhance the effectiveness of nausea treatments and enhance the well-being of cancer patients dealing with treatment side effects [32].

Appetite stimulation

In patients with advanced stages of cancer or HIV infection, anorexia and progressive weight loss are common symptoms. Extreme weight loss in patients with AIDS, also known as cachexia, can be associated with chronic diarrhea and weakness [33]. Research has demonstrated that oral THC, the synthetic form of dronabinol (Marinol®), can not only stimulate appetite but can also slow progressive weight loss in adults with advanced cancer. Recent studies have demonstrated that oral THC may be able to stabilize weight in cancer patients while those on a placebo decreased in weight. Health Canada has approved the use of oral THC (Marinol®) as an appetite stimulant for the management of weight loss and anorexia in patients with AIDS. Oral Marinol® is available in a 2.5, 5, and 10 mg THC capsule. To stimulate appetite, it is recommended that the synthetic THC be used in doses of 2.5–20 mg per day [21].

Analgesic

In animal models of acute and chronic pain, several cannabinoids have shown efficacy as analgesics [34-37]. For example, Benzopyranoperidine, a synthetic THC nitrogen analog, demonstrated analgesic effects orally at a 4 mg dose in a study of 45 cancer-related pain patients [38]. However, its efficacy was not seen in a group of 35 chronic pain patients [39]. The main side effect of Benzopyranoperidine was sedation. In a study examining a product known as oral ct-3, a synthetic analog of 11-hydroxy-THC, 21 patients with chronic neuropathic pain were treated with the medication product and were found to have efficacy, but no significant adverse events were reported [40]. A single administration of the synthetic cannabinoid levonantradol in a range of intramuscular doses in in a study of 56 postoperative pain patients was found to have clinically significant analgesic efficacy for periods of over 6 hours, but did result in patients experiencing sedation and some additional psychoactive effects [41]. Blake examined the mechanism of action, efficacy, and safety of Sativex®, a combination of 2.7 mg THC and 2.5 mg CBD delivered as an oromucosal spray, in pain associated with rheumatoid arthritis in a study of patients in the UK [42].

Multiple sclerosis

Patients with multiple sclerosis often present with symptoms such as muscle rigidity, spasticity, painful muscle cramps, chronic pain in the extremities, tingling and prickling sensations in the hands and feet, in addition to ataxia, tremor, and vesical and intestinal dysfunctions [36, 43, 44]. The effects of a cannabis extract containing almost equal amounts of tetrahydrocannabinol (THC) (2.7 mg) and cannabidiol (2.5 mg) were investigated in a study, by Wade *et al.* The extract, under the trade name Sativex®, was administered as a sublingual spray at doses ranging from 2.5-120 mg per day. The improvements were found to almost exclusively occur with patients who received THC alone. This study indicates that patients experienced beneficial effects from dronabinol (Marinol®) and a combination of THC and dronabinol (Cannador®) [45].

Spinal cord injuries

People with spinal cord injuries present some similar symptoms to those seen in MS like spasticity, painful muscle spasms and urinary issues. [46]. Recent research suggests that THC (oral) or *Cannabis sativa* extracts THC and cannabidiol may help alleviate those symptoms for some patients. Through use of a sublingual spray, those treatments have been found to address spasticity, muscle spasms, pain management, vesical functions a sleep quality in people with a spinal cord injury [47]. This is a promising workaround for those with a spinal cord injury seeking natural relief from pain and spasticity.

Tourette's Disorder

TD, or Tourette's disorder, is characterized by motor and vocal tics and also associated with a variety of behavioral and cognitive abnormalities. A double-blind study investigated transmission of THC through word lists and immediate and delayed memory testing, as well as a visual memory and an array of attentional abilities. In the trial, researchers concluded that oral THC administration, up to 10 mg, for 6 weeks had no effect on word list learning, interference, recall or recognition, while using immediate

verbal memory sample, and the component divided attention scale. Actually, there was a trend toward enhancement of the immediate verbal memory scale upon or after the cessation of therapy^[48-49].

Conclusion

The pharmacological and phytochemical properties of *Cannabis sativa* L. Show promise, for applications and warrant further exploration in the field of medicine. Compounds like THC, CBD and other cannabinoids present in the plant interact with the system leading to a range of pharmacological effects. The review highlights the advantages of *Cannabis sativa* in various conditions such as alleviating chemotherapy induced nausea and vomiting boosting appetite in individuals with advanced cancer or HIV/AIDS and serving as a pain reliever for both acute and chronic pain. Phytochemicals derived from the plant could also help alleviate symptoms associated with Tourettes syndrome multiple sclerosis and spinal cord injuries. While more research is needed to understand the mechanisms of action and potential long term effects current data suggests that phytochemicals in *Cannabis sativa* possess pharmacological properties that could be beneficial for medical purposes. Exploring the composition of *Cannabis sativa* may pave the way for treatment approaches and potentially groundbreaking medical discoveries as our understanding of the endocannabinoid system and its interactions with cannabinoids progresses. However conducting studies and clinical trials is essential to ascertain the safety, effectiveness and appropriate dosing regimens, for these potential therapeutic uses. The phytochemical and pharmacological characteristics of *Cannabis sativa* L. Offer a pathway, for medicine showing promise in reducing pain and improving the well being of individuals, with various medical conditions.

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