

REVIEW ARTICLE

Potential Medical Benefits of *Cannabis sativa* and Its Controversies

Arisya Hanim Sharol Hisam¹, Nurfarhana Rasli¹, Nur Fatimah Abdul Razak¹, Ain Sofea Nabila Aidy Ajmer¹, Daniel Joe Dailin^{2,3}, Hesham Ali El Enshasy^{2,3,4}, Tan Wen Nee⁵, *Tong Woei Yenn¹

¹ Universiti Kuala Lumpur, Institute of Medical Science Technology (UniKL MESTECH), A1, 1, Jalan TKS 1, Taman Kajang Sentral, 43000 Kajang, Selangor, Malaysia.

² Institute of Bioproduct Development, Universiti Teknologi Malaysia, 81310, Skudai, Johor, Malaysia.

³ Department of Bioprocess and Polymer Engineering, Faculty of Chemical and Energy Engineering, Universiti Teknologi Malaysia, 81310, Skudai, Johor, Malaysia.

⁴ City of Scientific Research and Technology Applications (CSAT), New Burg Al Arab Alexandria, Egypt.

⁵ School of Distance Education, Universiti Sains Malaysia, 11800 Minden, Penang, Malaysia.

ABSTRACT

There are over 40 countries that have legalised the use of *Cannabis sativa* for medical purposes. The objective of this review is to discuss the benefits of *C. sativa* usage for medical purposes and the conflicts that may arise from its usage. In terms of neurological disorders, medical *C. sativa* is effective in reducing the symptoms of neuropathic and peripheral pain, Tic disorder, Parkinson's Disease, and Alzheimer's Disease. Besides, *C. sativa* has been proven to reduce the symptoms of post-traumatic stress disorder, insomnia, anxiety, and schizophrenia. With the legalization of *C. sativa* for medical purposes, there are conflicts that arise, including public attitudes and social acceptability. In conclusion, medical *C. sativa* showed significant medical benefits in managing neurological, mental, and other pain-related illnesses. However, *C. sativa* can also cause conflicts in the legalization process due to adverse effects shown to users after consuming it for a period of time.

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Corresponding Author:

Tong Woei Yenn, PhD

Email: wytong@unikl.edu.my

Tel: +6016-4822046

INTRODUCTION

Back in 2900 B.C., the usage of *Cannabis sativa*, which is usually known as Marijuana was widely used for medical purposes. In present, *C. sativa* is more commonly used for recreational purposes and crimes than for medical purposes (1). *C. sativa* is more common in high-income countries such as Europe, than in low- and middle-income countries (2). Back in 1957, Malaysia was one of the countries that legalized the use of medical *C. sativa*, but due to its misuse, Malaysian government declared *C. sativa* as a national emergency (3). According to the Dangerous Drug Act 1952, *C. sativa* was listed as one of the most dangerous drugs along with morphine and cocaine (3). Any *C. sativa*-related offences with more than 200g may face a mandatory death sentence (3). Aside from Malaysia, *C. sativa* was also previously listed under Schedule IV of the 1961 Single Convention on Narcotic Drugs by the United Nations Commission

on Narcotic Drugs, which was categorised as deadly and addictive before being delisted in December 2020 (1).

The United Nations Office on Drugs and Crime (UNODC) predicted that the misuse of *C. sativa* would increase as more countries start to legalize it (3). There is also an increase in the number of people who are beginning to abuse and become addicted to this substance. Therefore, this study is to review the effectiveness of *C. sativa* for medical purposes and indicate a few controversies that may arise by legalising medical *C. sativa*.

CHEMICAL COMPOUNDS IN C. SATIVA

C. sativa is an important plant that has been used as a source of fibre, food, oil and for medicinal purposes for centuries (1). Cannabinoids are a class of terpene-phenolic compounds present in *C. sativa*, accumulated mainly in the trichome cavity of female flowers (2, 4). *C. sativa* has become the focus of attention in the world scientific community, where it is one of the most studied plants. A total of 538 natural compounds have been identified from *C. sativa*. Of those, more than 100 are known as

phytocannabinoids because of their chemical structure. Tetrahydrocannabinol, cannabinol, and cannabidiol are the 3 main chemicals that have effects on humans and are of medical importance (4). The term “pyhtocannabinoid” has been proposed for natural plant components and “endocannabinoid” for components synthesized in animals and humans (2). Cannabinoids are substances that have a carbolic structure with 21 carbons and are usually formed by 3 rings, namely cyclohexene, tetrahydropyran and benzene (5). *C. sativa* contains a complex chemical composition because it contains 400 chemical products including mono- and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous complexes, amino acids, and a total of 66 cannabinoids, with 9-tetrahydrocannabinol as a psychostimulant present in a high proportion (6).

EFFECTS OF C. SATIVA ON NEUROLOGICAL DISEASES

Table I shows the effects of *C. sativa* on neurological diseases. In neurological pain, Parkinson’s Disease (PD) was the most tested with medical *C. sativa*. With the number of reported PD cases continually increasing, there is a need for new treatment options. *C. sativa* has shown to treat both motor and non-motor symptoms experienced by PD patients, as medical *C. sativa* is one of the alternatives suggested by a few researchers (7,8,9). Cannabidiol is the most common

chemical intervention used in various studies, and the compound has the ability to improve the patient’s symptoms (7,8). In one of the randomised, double-blinded, crossover clinical trials conducted on 24 volunteers with idiopathic PD, they were asked to consume either cannabidiol or a placebo (9). It was stated that the ability of cannabidiol to have a direct effect on the amplitude of the tremors or reduction in anxiety levels could not be proven, as there were no major differences found in the drug–phase interaction (9). However, this statement conflicts with another study where the group that consumed cannabidiol showed major improvement compared to the placebo group (10).

Tetrahydrocannabinol is a chemical compound of *C. sativa* that can be used to treat neuropathic pain. Medium-dose (3.53% tetrahydrocannabinol), low-dose (1.29% tetrahydrocannabinol), and placebo *C. sativa* were given to 38 participants that were experiencing neuropathic pain (11). The participants were asked to indicate the intensity of their current pain after consuming Tetrahydrocannabinol. In this study, 10 participants exposed to a placebo had a 30% reduction in pain intensity compared to 21 participants exposed to the low dose and 22 participants who received the medium dose of *C. sativa*. Hence, there is a significant improvement in pain relief between tetrahydrocannabinol and placebo (11).

Table I : The effects of medical *C. sativa* on neurological disorders

No	Refer-ence	Year Published	Illness Condition(s)	Chemical Compound(s)	Outcome(s)	Notes
1	(12)	2014	Chemotherapy-induced neuropathic pain	Cannabinoids	Fatigue, dizziness, nausea, increased appetite	There is no significant difference in term of statistic between the treatment group and placebo group.
2	(13)	2013	Neuropathic and peripheral pain	Cannabinoids	Pain relief	There is significant difference in pain relief between smoked group and placebo group.
3	(14)	2012	Tic disorder	Tetrahydrocannabinol	Tiredness, dry mouth, dizziness	There is low positive effect shown from tetrahydrocannabinol.
4	(7)	2020	PD , Alzheimer’s Disease	Tetrahydrocannabinol, Cannabidiol	Cannabidiol was effective in preventing seizing and repairing neurodegeneration for PD treatment.	Hyperkinesia in PD was treated by the activation of cannabinoid receptor antagonists.
5	(8)	2019	PD , Alzheimer’s Disease	Tetrahydrocannabinol, Cannabidiol	Improved motor and non-motor symptoms. Improved levodopa-induced Dyslexia	46% out of 85 individuals relieved PD symptoms after consuming Cannabinoid after 1.7 months. 14% out of 85 individuals reported to improved levodopa-induced Dyskenia by usage of Cannabinoid.
6	(15)	2016	PD	Tetrahydrocannabinol and Cannabidiol	The motor symptoms of PD patients improved	Out of 339 PD patients, 46% improved general PD symptoms, 31% improved resting tremor and 38% relieved muscle rigidity.
7	(9)	2020	PD	Cannabidiol	Tremor symptoms reduced	Cannabidiol administrative decreased tremor symptoms shown anxiety for PD patients along with anxiety.

EFFECTS OF *C. SATIVA* ON MENTAL DISORDERS

Table II shows the effects of medical *C. sativa* on mental disorders. The effectiveness of *C. sativa* on Post Traumatic Syndrome Disease (PTSD) was reported in 5 studies (16-20). Out of these 5 studies, 4 of them had recorded that there is decreased in the symptoms of PTSD after consuming *C. sativa*. The studies used either tetrahydrocannabinol or cannabidiol, while only one study recorded no significance benefits to treat PTSD (20). In other studies, the usage of *C. sativa* reduced the symptoms of PTSD especially in improving sleep (16, 17). In terms of anxiety, medical *C. sativa* significantly reduced the patients' anxiety scores toward decreasing anxiety level (19). Study on insomnia conducted with cannabidiol has shown that the patients showed improvement in their sleeping problem (18). In a study conducted on 103 adult patients of a psychiatric clinic who complained about inability to sleep, 72 of the patients had completed the assessment after the first month, while the remaining 41 patients continued the assessment until the second month after starting (19). The study had used self-report measure, the Pittsburg Sleep Quality Index for the assessment. After one month, the results showed that 48 over 72 patients (66.7%) had improved their sleeping problem before taking cannabidiol. In the second month, 23 out of 41 or 56.1% patients reported improvement with their sleeping condition after taking cannabidiol (19).

Medical *C. sativa* also showed significant effects on various mental disorders. A case study was done on a ten year old girl who had been diagnosed with PTSD (18). At the same time, she also suffered with insomnia and anxiety. After the second month of the assessment, the girl has started to be assessed with Sleep Disturbance Scale for Children and Screen Anxiety Related Disorders (SCARED) for 7 months (18). Cannabidiol was also given to the girl daily before bedtime. Upon ingestion of cannabidiol, the girl's insomnia and anxiety condition has gradually getting better with no side effects. The girl's sleep scale score at first month was 59 and at the seventh month, her sleep score decreased to 38. Sleep scores higher than 50 are considered as having sleep disorder or insomnia (18). The SCARED score of the girl at the first month was 34 then decreased to 18 at the seventh month. Score with higher than 25 for SCARED indicated the high chances of childhood anxiety disorder. By this study, it has proven that cannabidiol can reduce the condition of insomnia and anxiety (18). For Schizophrenia and hyperactivity or ADHD, the usage of tetrahydrocannabinol showed improvement. Besides, tetrahydrocannabinol can enhance anandamide, the neurotransmitter that binds with cannabinoid receptors in both brain and body (21). Thus, it improves the patient in terms of decreased psychotic symptoms. However, some side effects upon taking tetrahydrocannabinol to the patients include motor disturbances, weight gain, and sexual

Table II : The effects of medical *C. sativa* on mental disorders

No	Author	Year Published	Illness Condition(s)	Chemical compound(s)	Outcome(s)	Notes
1	(16)	2014	PTSD	Cannabinoids	Reduced PTSD symptoms	Patients reported 75% decreased in PTSD symptoms when cannabis were used.
2	(17)	2019	PTSD	Cannabidiol	Reduced PTSD symptoms	Patients reported reduced 28% of PTSD symptoms.
3	(18)	2016	Anxiety, insomnia and PTSD	Cannabidiol	Increase in sleep quantity and quality	The patient's SDSC and scared score decreasing indicates better sleep quality.
4	(19)	2019	Insomnia and anxiety	Cannabidiol	Anxiety and sleep improved	Anxiety scores decreased by 79% in the first month and remained decrease. Insomnia score improved by 67%.
5	(20)	2013	PTSD	Cannabinoids	Improved sleep quality	-
6	(21)	2012	Schizophrenia	Tetrahydrocannabinol	Decreased in psychotic symptoms	There is improvement in clinical symptoms for Schizophrenia but it shown high side effects.
7	(22)	2017	ADHD/Hyperactivity	Tetrahydrocannabinol, Cannabidiol	Improvement in paying attention	-
8	(23)	2014	Anxiety	Cannabinoids	Able to reduce the symptoms of anxiety	There is small positive relationship between anxiety disorder and medical cannabis use but not suitable as a treatment.
9	(24)	2015	PTSD	Cannabinoids	The symptoms of Anxiety and Insomnia improved	Reduction of 75% in all areas of PTSD while consuming medical cannabis.

dysfunction (21).

EFFECTS OF C. SATIVA TO OTHER DISORDERS

C. sativa also showed significant effect on other disorders (Table III). Multiple Sclerosis (MS) is a disabling non-traumatic disease that usually affects adults and it is also one of the autoimmune diseases (25). A study was conducted randomly by administering Tetrahydrocannabinol and placebo to 277 MS patients (25). After 12 weeks, the MS symptoms were significantly reduced, with a high rate of muscle spasm relief and a reduction in sleep disturbances when using tetrahydrocannabinol compared to placebo (25). An anonymous survey conducted on MS patients showed that medical *C. sativa* could relieve their pain

symptoms in a medium or higher scale (26). Both studies showed that medical *C. sativa* can reduce the symptoms of muscle spasms and relieve pain in MS patients (25,26).

It was found that the consumption of *C. sativa* can increase the inability to feel pain (27). A study was conducted in a double-blinded and randomized controlled trial for cancer patients. In the same study, they administered tetrahydrocannabinol, cannabidiol and placebo to cancer patients during a 3-week treatment period (28). After 3 weeks, the percentage of average pain from patients using tetrahydrocannabinol and cannabidiol was 10.7% higher than placebo (4.5%) (28). A positive treatment effect was reported for the cannabidiol-tested group (28). In a cross-sectional

Table III :The effects of C. sativa in the treatment of disorders

No	Refer-ence	Year Published	Illness Condition(s)	Chemical compound(s)	Outcome(s)	Notes
1	(25)	2012	MS	Tetrahydrocannabinol, Cannabidiol	Muscle stiffness relief and improvement of sleep disturbance	The Cannabidiol tested group showed effectiveness of 29.4% compared to placebo group.
2	(28)	2018	Cancer	Tetrahydrocannabinol, Cannabidiol	Reduced pain	There is possibility positive treatment effect from Cannabidiol tested group in cancer but it was not a positive treatment as compared to placebo group.
3	(26)	2017	MS	Cannabinoid	Reduced pain	Patient with MS reported prescription of placebo is reduced since they consumed Plant-derived Cannabinoid. Thus, leading to greater perceive effectiveness.
4	(40)	2013	HIV/AIDS	Cannabinoid	Reduced HIV/AIDS symptoms	72% from survey reported Cannabinoid was always helpful while another 24% reported as often helpful.
5	(31)	2018	Fibromyalgia	Cannabinoid	Improvement in Fibromyalgia treatment	100% participant agrees that medical cannabis treatment brought positive improvement. 50% of participants has stop taking other type of medication to treat the disease. Only 30% shown minor side effect.
6	(35)	2017	Headaches	Tetrahydrocannabinol	Reduced in pain	Tetrahydrocannabinol tested group shows relieved in pain while placebo shows no improvement in terms of Spasticity, motor function and daily routine.
7	(41)	2019	Pain and back problem	Tetrahydrocannabinol, Cannabidiol	28.2% individuals reduced their pain while 13.8% reported reduced back problems	Medical cannabis was more trusted compared to mainstream drugs according to the survey done
8	(42)	2013	Pain	Tetrahydrocannabinol, Cannabidiol	Participants reported relieved in chronic pain by 15.4%	-
			Muscle spasms		Participants reported reduced in muscle spasm by 25.6%	
			Nausea		Participants reported relieved nausea by 25.5%	

study of 628 self-selected AIDS patients, medical *C. sativa* was used to reduce symptoms due to AIDS. According to Lucas et al., AIDS patients experienced a 15-30% reduction in symptoms such as nausea, pain and mood-related symptoms after taking medical *C. sativa* in treatment (29). Therefore, 72% of those surveyed reported cannabinoids are always helpful, while another 24% reported regularly helping to reduce symptoms for AIDS patients (29).

Fibromyalgia is one of the most common chronic pain syndromes. It is characterized by pervasive musculoskeletal pain, extreme fatigue and mood and sleep disturbances. (30). A study was conducted by obtaining data from hospital registration where patients diagnosed with fibromyalgia were treated with medical *C. sativa* (31). Medical *C. sativa* was used to improve the treatment of fibromyalgia compared to placebo (31). Among 30 identified patients, 19 female patients (73%) reported a significant improvement in the treatment of fibromyalgia due to the use of medical *C. sativa*, while 13 patients (50%) had stopped taking any other medication for fibromyalgia which indirectly almost 100% of the participants agreed that medical *C. sativa* treatment brings an improvement in treating fibromyalgia (32). Medical *C. sativa* users showed a significant reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence (32).

Tetrahydrocannabinol and cannabidiol can relieve pain and headaches (33). The use of tetrahydrocannabinol and cannabidiol has the potential to reduce alertness and cause cognitive effects (33). Besides, tetrahydrocannabinol also stimulates beta-endorphin production, inhibiting opioid tolerance and decreasing headache frequency. (34). A small, randomized trial with 12 patients showed a decrease in pain compared to placebo but no improvement in spasticity, motor function, and activities of daily living (35).

CONTROVERSY OF MEDICAL *C. SATIVA*

While the legalization of *C. sativa* for medical purposes may benefit to the healthcare industry, some conflicts arise from the action, including public attitudes and the social acceptability of using *C. sativa*. Changes in the public's perception of *C. sativa* risk are aligned with states' policies on legalizing the drug (36). Concerns have been expressed that legalization of *C. sativa* will change perceptions of the potential risks of *C. sativa* use, increase usage and increase the possibilities of negative health effects since more states are considering legalizing it (37). However, in the same study, it was stated that the availability of information on the health risks of *C. sativa* may be improved, and thus the awareness of *C. sativa* use disorders will be increased once the drug is legalized.

Participants in a focus group study with older persons who use *C. sativa* for medical and recreational purposes stated that despite it being legal, there is still a stigma associated with *C. sativa* usage (38). However, this statement contradicts another research on the attitudes of older generations about *C. sativa* where 60% of them strongly believed that the use of medical *C. sativa* was relevant (39). A policy of consumer oppression has also been implemented because of the increase in the sale of *C. sativa* on the black market, where it is sold for extremely high prices (36). Legal approval in buying and selling *C. sativa* is not approved in many countries (35). Many governments have established a new alternative to approve the use of *C. sativa* in the community but subject to the only permitted dose limit of 10g or less (35,43). It can prevent *C. sativa* users from buying illegally and indirectly engaging in criminal activities. With the approval of the law from the government, the illegal sale of *C. sativa* can be curbed except for medicinal purposes (43). In addition, the sale price of *C. sativa* will also be considered according to the law. The control method for the abuse of *C. sativa* is to allow *C. sativa* to be used in coffee shops with an age limit set only (43).

The usage of *C. sativa* has been widely used in medication. However, there is no standardized prescription of dosage given to the patients. Therefore, the side effects of taking *C. sativa* are not predictable (44). There is various type of disease that have been using *C. sativa* as a remedy to lessen the symptoms. Furthermore, there is limited research and studies on *C. sativa* effect on PTSD to achieve a proper and standardized dosage for patients (44). Another study also suggested that *C. sativa* could cause physical harm, but more evidence is needed (45). Besides, patients that took *C. sativa* have a higher risk of cancer, especially in the head, neck and pharyngeal areas (45). The group that smoked *C. sativa* for 20 years has a higher risk of having head and neck cancer.

CONCLUSION

In conclusion, medical *C. sativa* showed significant medical benefits in managing neurological, mental and other pain-related illnesses. *C. sativa* functions as a pain reliever to reduce the symptoms of other related pain, mental illness such as PTSD, anxiety, insomnia and even manage to reduce symptoms of neurological illness. To ensure the practical and safe application of medical *C. sativa*, the pharmacy and biomedical research communities must innovate new parameters to overcome the obstacles. Additional scientific research is urgently required to understand the mechanisms of action of medical *C. sativa*, to develop more effective drug therapies with fewer side effects.

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