Review Article

Cannabis in Thai conventional medicine: Friend or Foe?

Sukpapohn Phummisutthigoon[1], PhD, Tanawan Kummalue[2*], MD, PhD

[1] *Division of Physiology, Department of Preclinical Sciences, Faculty of Medicine, BangkokThonburi University, Bangkok, Thailand 10170*

[2] *Department of Medicine, Faculty of Medicine, BangkokThonburi University, Bangkok, Thailand 10170*

Cannabis has been prescribed as medicine for over a hundred years, especially in the field of traditional medicine. Cannabis has various therapeutic properties, such as analgesic and sedative properties, to relax patients' minds and relieve pain symptoms. Under the restriction for over decades, recently cannabis has been taken out of regulations with the permission of the Thai government. Nowadays, there are two fields of cannabis usage in Thailand, i.e., conventional medicine, which uses cannabis oil as complementary and alternative medicine, and traditional medicine, which uses cannabis in the form of cannabis oil and crude extract of leaves, including stems and roots in the mixture. This article will briefly review the benefits and adverse events (AEs) of cannabis use in conventional medicine, including the endocannabinoid system and cannabinoid receptors.

Keywords: Cannabis; Conventional medicine; Therapeutic use

Received: 1 Apr 2022 | **Revised:** 15 Apr 2022 | **Accepted:** 1 May 2022

J Med Glob 2022 May; 1(1)

Website: https://he01.tci-thaijo.org/index.php/JMedGlob/

*** Correspondence to**:
Tanawan Kummalue
Department of Medicine, Faculty of Medicine, BangkokThonburi University, Thawi Watthana, Bangkok, Thailand 10170
E-mail: tanawan.kum@bkkthon.ac.th
Tel: (+66)838805615
ORCID: 0000-0002-8666-892X

INTRODUCTION

Cannabis has been prescribed as medicine for over a hundred years, especially in the field of traditional medicine. The earliest evidence of cannabis use was found in China. In Chinese history, cannabis was recorded for treating more than 100 ailments, including gouty arthritis, rheumatic diseases, analgesic, and malaria, which was used in the form of cannabis mixture [1]. Cannabis has spread quickly throughout India, Arab, Africa, South America, and Western Europe. In Europe, it was prescribed with analgesic and sedative properties to relax patients' minds and relieve pain symptoms. Cannabis use in medicine increased in the late eighteenth to the early nineteenth century. Then in the 1930s, cannabis was pushed for restrictive legislation, and later, it was non-existent in medicine. In Thailand, cannabis has ever been traditionally used in the form of herbal recipes for treating insomnia, increasing appetite, and alleviating pain from all kinds of organs before under legislation for over decades. Until recently, cannabis has been taken out of the regulations under the permission of the Thai government. Nowadays, there are two fields of cannabis usage in Thailand, i.e., conventional medicine, which uses cannabis oil as complementary and alternative medicine, and traditional medicine, which uses cannabis in the form of cannabis oil and crude extract of leaves, including stems and roots in the mixture. This article will briefly review the benefits and adverse events (AEs) of cannabis use in conventional medicine, including the endocannabinoid system and cannabinoid receptors.

Endocannabinoid system (ECS) and cannabinoid receptors

How to cite this article: Phummisutthigoon S, Kummalue T. Cannabis in Thai conventional medicine: Friend or Foe? J Med Glob 2022;1(1):54-58.

In the human body, endogenous cannabinoids and the endocannabinoid system have emerged over the last twenty-five years. The Endocannabinoid system is composed of endogenous cannabinoids, cannabinoid receptors, and enzymes involved in synthesis and degradation. Endogenous cannabinoids, such as anandamide and 2-AG, are synthesized and degraded by different enzymes. 2-AG is biosynthesized by the sequential hydrolysis of an archidonoyl-containing PIP2 and diacylglycerol lipase (DAGL), as the primary pathway. The secondary pathway is occurred by cleavage of the phosphatidyl inositol precursor by a phospholipase A. 2-AG degradation is caused by three hydrolytic enzymes, i.e., monoacylglycerol lipase (MGL), and alpha/beta domain hydrolases 6 and 12 (ABHD-6 and 12). Interestingly, 2-AG is an important metabolic intermediate in lipid synthesis, especially as a major source of arachidonic acid in prostaglandin synthesis [2-4]. For anandamide, most are produced from N-arachidonoyl phosphatidyl ethanol (NAPE) with multiple pathways, for example, the pathway synthesized by the hydrolysis of NAPE with a NAPE-specific phospholipase D [5]. The anandamide degradation in the CNS is usually by the enzyme fatty acid amino hydrolase (FAAH) from anandamide to arachidonic acid and ethanolamine. The second and minor pathway for degradation of anandamide is oxidation with cyclooxygenase-2 (COX-2), to create prostamides [2]. These compounds have therapeutic effects for treating intraocular hypertension.

Endocannabinoids are mostly involved in the suppression of synaptic transmission in the nervous system. Upon the neuronal activation at presynaptic sites, the specific neurotransmitters are liberated and acted on the postsynaptic sites. Then the endocannabinoids are released from postsynaptic neurons and targeted CB receptors located on presynaptic neuronal terminals. This process represents the retrograde endocannabinoid signaling as negative feedback in the nervous system. The functions of endocannabinoids are mediated through cannabinoid receptors, CB1 and CB2. CB1 receptor (CB1R) is encoded by the gene CNR1 located at chromosome 6q14-15, whereas CB2 receptor (CB2R) is encoded by the gene CNR2 located at chromosome 1p36 [6]. CB1R has more amino acids than CB2R, containing 472 amino acids as compared to 360 amino acids, respectively [7]. Considering of the endocannabinoid agonistic activation, 2-AG is a full agonist toward CB1R and CB2R, while anandamide is a weakly and partial agonist to both receptors [8].

CB1R is classified in the group of G protein-coupled receptors (GPCR), which are primarily localized in the cell membrane. In functional studies, the CB1Rs are expressed both in glutamate and GABA neurons at similar levels. Other neuronal types, such as noradrenergic and dopaminergic neurons, contain low to moderate levels of CB1R [9]. The highest level of CB1R expression is found in the brain, especially in the cerebral cortex, septum, amygdala, hypothalamus, and parts of the brainstem and dorsal horn of the spinal cord. Region such as the thalamus and ventral horn of the spinal cord shows low CB1R expression [10]. The activation of CB1R results in two major downstream effects of ion channels and intracellular kinases regulation, such as inhibition of adenylyl cyclase. Previous studies demonstrated that the CB1R modulation of neurotransmitters function could be through the inhibition of calcium channels independently of cAMP. Intracellular signaling cascades of CB1R signaling, including MAP kinases, mTOR pathway, and RAK pathway, were demonstrated [11]. The levels of CB1R expression remarkably fluctuate in various pathologies and diseases.

CB2R is in the group of G protein-coupled receptors (GPCR), which suppresses the adenylyl cyclase and the formation of cAMP upon receptor activation. In contrast, the distribution of CB2R was predominantly identified in peripheral organs with immune cells, such as the spleen, tonsils, thymus, and leukocytes, with the moderate expression of CB2R in other tissues, including the cardiovascular system, GI tract and liver, and reproductive system [12]. CB2R has much lower expression in the brain when compared to other organs. However, it still plays important roles in neurological activities, such as nociception, drug addiction, and neuroinflammation [13]. Notably, upregulation of CB2R is found in response to immune activation and inflammation.

Naturally occurring cannabis and cannabinoid

The naturally occurring cannabis family has three major species, i.e., Cannabis sativa, Cannabis indica, and Cannabis ruderalis. In Thailand, the common species found in Cannabis sativa, named in Thai "Hang-Kra-Rok" which grows spread throughout the Northeastern part of Thailand, such as Sakonnakorn province. The cannabis plant usually contains more than 100 cannabinoids which can be classified into 11 chemical classes, such as terpenes, carbohydrates, fatty acids, amides, amines, phytosterols, phenolic compounds, and cannabinoids [14]. The important psychoactive substance in cannabis is delta-9-tetrahydrocannabinol (▪9-THC) which can induce "high", and the non-psychoactive compound

named cannabidiol (CBD). Both ▪9-THC and CBD have the same molecular weight as C21H30O2, but with different structures and heating points [15]. Cannabinoids in the plant are first predominantly found in the acid forms. ▪9-tetrahydrocannabinolic acid (▪9-THCA) is derived from the enzymatic process of cannabigerolic acid with THCA synthase. Following this, decarboxylation of ▪9-THCA will get ▪9-THC. The oxidative degradation of ▪9-THCA and ▪9-THC produces cannabinolic acid (CBNA) and cannabinol (CBN), respectively. These processes usually happen in aged cannabis. Most ▪9-THC are mediated by CB1R, while CBD has a low affinity to both CB1R and CB2R [14]. In contrast, cannabidiolic acid (CBDA) is derived from the substrate cannabigerolic acid and CBDA synthase. After decarboxylation of CBDA, cannabidiol (CBD) will be produced. Notably, both enzymatic processes of ▪9-THC and CBD have the same original substrate, "cannabigerolic acid", but with different enzymes in the processes [14]. The metabolism of cannabinoids is by a phase I hepatic cytochrome P450 enzyme, primarily by CYP3A4, CYP2C9, CYP2C19, and the UGT enzymes, such as UGT1A9, and UGT2B7 [15]. CBD is metabolized primarily by the enzymes CYP2C19 and CYP3A4 [16]. Because of these, the increase or decrease of blood cannabinoid levels after consuming cannabis together with other drugs might have resulted in drug-drug interaction and serious adverse events.

Guidelines of cannabis therapy in conventional medicine

Cannabis therapy in conventional medicine is limited to the use only cannabis oil, which is usually extracted from cannabis flowers by high technology, such as the supercritical CO2 extraction technique (liquid CO2 under very high pressure) [17]. Usually, cannabis oil is composed of cannabinoids and terpenoids in the concentrated extract. The government pharmaceutical organization (GPO) has produced three different kinds of therapeutic cannabis oil, as follows:

1. THC is high in the concentration of 0.5 mg per drop of cannabis oil.
2. CBD is high in the concentration of 4 mg per drop of cannabis oil.
3. THC: CBD equally mixed to a 1:1 ratio in the concentration of 1 mg per drop of cannabis oil.

THC has a therapeutic effect on nociceptive pain and anti-convulsant properties, while CBD shows anxiolytic, anti-stress, and neuroprotective, including antioxidant, anti-inflammatory, and anti-convulsant properties [14,18]. All these kinds of cannabis products are recommended for treating many diseases but with strict inhibition in pregnant women [19]. According to the Thai government guidelines, these cannabis oils can be definitely used to treat diseases as follows [19]:

1. Chemotherapy-induced nausea and vomiting

This indication involves malignant patients treated with chemotherapy that highly induces nausea and vomiting, not in the case of treatment for cure. However, the use of cannabis in this condition is limited to those who do not respond to standard conventional therapy for relieving chemotherapy-induced nausea and vomiting. The basic physiology of this indication is due to the activation of CB1R resulting in the inhibition of gastric acid secretion, lower esophageal sphincter relaxation, alteration of the intestinal motility, and delaying the gastric emptying time.

2. Intractable epilepsy

Cannabis is recommended to use in various neurological diseases both in young age groups and in adults, such as Dravet and Lennox-Gastaut syndrome. Those with intractable epilepsy and patients with their ages under 2 years must be regularly followed up and evaluated for the response after cannabis treatment. The basic physiology of this property is because of the cannabis retrograde inhibition of neurotransmitters in the brain.

3. Spasticity in multiple sclerosis

Multiple sclerosis is one of the most common demyelinating diseases with chronic and disabling disorders of the central nervous system. Muscle weakness, muscle spasms, fatigue, and tremor, are common symptoms found in this disease. In cannabis therapeutic use, multiple sclerosis with spasticity is highly indicated. The antispastic property of cannabis or cannabinoid in multiple sclerosis has long been investigated and yet confirmed [20]. Moreover, in my experience, other spasticity resulting from any other neurological disease, such as brainstem atrophy, can also be useful.

4. Neuropathic pain

In this case, resistance to neurological pain is an indication of using cannabis therapy. However, in previous reports, chronic non-cancer pain is not recommended [21].

In some special diseases, such as advanced stages of cancer, cannabis may be beneficial, as mentioned in the Thai guideline. According to this government guideline,

cannabis oil use in cancer patients is just for palliative care only, not for cure. The utility of cannabis in the treatment of cancer has still been on research with great interest. Compared with other countries, the indication of cannabis therapy is quite similar to Thai guidelines. In Australia, the clinical application of medical cannabis has been trialed such as multiple sclerosis, HIV-associated weight loss, appetite stimulation in cancer, and epilepsy [21,22]. To a previous meta-analysis study, the medical use of cannabis included nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS infection, chronic pain, spasticity due to multiple sclerosis or paraplegia, and sleep disorder [23]. Recently, cannabidiol (CBD) has shown promising results as an anti-cancer drug [24].

Adverse effects of medical cannabis

The adverse events of medical cannabis after the interaction with its receptor are obvious. These adverse events can affect various systems, such as neurological, cardiovascular, respiratory, and GI systems [25].

1. Neurological and mental effects

The effects include depression, anxiety, and personality disturbances [26]. Cannabis can impair memory and also learning perception, leading to many problems together with a decrease in the quality of life. These symptoms are usually reported in the cases with long-term or chronic administration of cannabis. Psychosis can be developed and occur after using cannabis for at least a year. Babies born to women who use cannabis can have an abnormal visual response, tremulousness, and a high-pitched cry.

2. Cardiovascular effects

Cannabis can also have systemic effects, such as decreasing or increasing blood pressure and heart rates and lowering the oxygen-carrying capacity of the blood. The risk of myocardial infarction may also increase.

3. Respiratory effects

Smoking cannabis frequently leads to respiratory problems, such as infections, daily cough, and sputum production. Obstructive airways can also occur from excessive sputum production. Smoking cannabis may develop oral leukoplakia and later may develop oral cancer.

4. Gastrointestinal effects

Those who have long-term daily use of cannabis, especially marijuana, can lead to one important syndrome called cannabinoid hyperemesis syndrome (CHS). This syndrome was first described in the Year 2004 by Allen and colleagues. The symptoms are found in chronic cannabis use and manifested with the cyclic episode of nausea and vomiting. CHS can be divided into 3 phases: pre-emetic or prodromal phase, hyperemetic phase, and recovery phase. Differential diagnoses of cyclic vomiting syndrome (CVS) should be recognized. Though both conditions have similar symptoms, there are several significant differences, i.e., psychological comorbidity in CVS, such as depression and anxiety, and a high prevalence of migraine in CVS group. History of chronic marijuana use may help distinguish CVS and CHS [27].

Cannabis use in the younger age group will have more adverse long-term outcomes than in the adult group, especially in brain development. In addition, long-term use of cannabis can lead to addiction. Cannabis withdrawal syndrome, such as irritability, sleeping difficulties, dysphoria, craving, and anxiety, can make the cessation more difficult and easy to relapse. Regarding safety issues of CBD, a previous study showed that the side effects between CBD and the placebo group did not differ. However, another study demonstrated that the CBD group had fewer extrapyramidal symptoms, less weight gain, and prolactin release. The most common side effects of CBD reported are tiredness, diarrhea, and changes in appetite and weight, with fewer side effects when used in the cases of epilepsy and psychotic disorders [28].

CONCLUSION

Cannabis has many properties for treating various diseases, as discussed. However, not only the therapeutic effects that are considered but also the side effects of cannabis must be recognized. Thus, doctors, who plan to use cannabis, must always think and weigh thoroughly between the therapeutic and side effects, including drug dependence, before prescribing cannabis to their own patients.

Conflicts of Interest: All Authors declare no conflict of interest

Acknowledgments: I would like to thank Dr. Sirisak Titidilokrat, the deputy director of the Department of Mental Health, Ministry of Public Health, for his kindness in giving me the opportunity to take care of patients with cannabis use which I can gain more experience. I also would like to thank

Prof. Dr. Saranatra Waikakul for his kind encouragement and support in my writing of this manuscript.

REFERENCES

1. Hand A, Blake A, Kerrigan P, Samuel P, Friedberg J. History of medical cannabis. J Pain Manage. 2016;9(4):387-94.
2. Lu H, Mackie K. An introduction to the endogenous cannabinoid system. Biol Psychiatry. 2016;79(7):516-25.
3. Nomura DK, Morrison BE, Blankman JL, Long JZ, Kinsey SG, Marcondes MC, et al. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science. 2011;334:809-13.
4. Murataeva N, Straiker A, Mackie K, Parsing the players: 2-arachidonoylglycerol synthesis and degradation in the CNS. Br J Pharmacol. 2014;171:1379-91.
5. Di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz JC, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature. 1994;372:686-91.
6. Howlett A, Abood M. CB1 and CB2 receptor pharmacology. Adv Pharmacol. 2017;80:169-206.
7. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. Int J Molec Sc. 2018;19:833-56.
8. Bile B, Wu J, Foss J, Naguib M. An overview of the cannabinoid type 2 (CB2) receptor system and its therapeutic potential. Curr Opin Anaesthesiol. 2018;31(4):407-14.
9. Busquets-Garcia A, Bains J, Marsicano G. CB1 receptor signaling in the brain: Extracting specificity from ubiquity. Neuropsychopharmacol. 2018;43:4-20.
10. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. 2005;299-325.
11. Nogueras-Oritz C, Ydowski GA. The multiple waves of cannabinoid 1 receptor signaling. Mol Pharmacol. 2016;90:620-6.
12. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. Classification of cannabinoid receptors. Pharmacol Rev. 2002;54:161-202.
13. Dhopeshwarkar A, Mackie K. CB2 cannabinoid receptor as a therapeutic target-what does the future hold? Mol Pharmacol. 2014;86:430-7.
14. Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L. Cannabis sative L. and nonpsychoactive cannabinoids: Their chemistry and role against oxidative stress, inflammation, and cancer. BioMed Res Int. 2018. https://doi.org/10.1155/2018/1691428.
15. Kocis P, Vrana K. Delta-9-tetrahydrocanabinol and cannabidiol drug-drug interaction. Med Cannabis Cannabinoids. 2020;3:61-73.
16. Zendulka O, Dovetelova G, Noskova K, Turjap M, Sulcova A, Hanus L, et al. Cannabinoids and cytochrome P450 interactions. Curr Drug Met. 2016;17(3):1-21.
17. Grof C. Cannabis, from plant to pill. British J Pharmacol. 2018;84:2463-7.
18. Lee J, Bertoglio L, Guimaraes F, Stevenson C. Cannabidiol regulation of emotion and emotional memory processing: relevance for treating anxiety-related and substance abuse disorders. British J Pharmacol. 2017;174:3242-556.
19. Guidance on cannabis for medical use. Department of Medical Services, Ministry of Public Health. 2nd revision, 2019.
20. Malfitano A, Proto M, Bifulco M. Cannabinoids in the management of spasticity associated with multiple sclerosis. Neuropsychiatric Dis Treat. 2008;4(5):847-53.
21. Murnion B. Medicinal cannabis. Aust Prescr. 2015;38:212-5.
22. Ablin J, Ste-Marie PA, Schafer M, Hauser W, Fitzharles MA. Medical use of cannabis products. Schmerz. 2016;30:3-13.
23. Whiting P, Wolff R, Deshpande S, Nisio M, Duffy S, Hernandez A, et al. Cannabinoids for medical use: A systemic review and meta-analysis. JAMA. 2015;313(24):2456-73.
24. Seltzer E, Watters A, MacKenzie D, Granat L, Zhang D. Cannabidiol (CBD) as a promising anti-cancer drug. Cancer. 2020;12:3003.
25. Scully C. Cannabis; adverse effects from an oromucosal spray. British Dental J. 2007. Doi:10.1038/bdj.2007.749.
26. Volkow N, Baler R, Compton W, Weiss S. Adverse Health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.
27. Galli J, Sawaya R, Friedenberg F. Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev. 2011;4(4):241-9.
28. Larsen C, Shahinas J. Dosage, efficacy and safety of cannabidiol administration in adults: A systematic review of human trials. J Clin Med Res. 2020;12(3):129-41.