IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

CANNABIS SATIVA AND ITS ROLE IN NEUROTRANSMITTERS - A CRITICAL REVIEW

Dr. Ankita Singh[*1], Dr. Ramesh Chandra Tiwari[2], Dr. Manisha Dikshit[3], Dr. Ved Bhushan Sharma[4]
Dr. Bhawana Mittal[5], Dr. Naveen Kumar[6]
[1]Post Graduate Scholar, [2]Prof. and H.O.D, [3]Associate Professor, [4]Assistant Professor, [5]Assistant Professor,
P.G. Department of Agad Tantra Evum Vidhi Vaidayak, Uttarakhand Ayurved University, Rishikul Campus, Haridwar,
[6]Associate Professor KLDAV PG College Roorkee, Uttarakhand, India.

ABSTRACT

Bhanga is one of the plant described in ayurvedic literature. *Bhanga* (Indian hemp, pot, dope) is a Neurotoxic cerebral deliriant poison, obtained from *Cannabis sativa*. It is the oldest plant to be cultivated in the past 10,000 years for both agricultural and industrial use. It is used for both social and legal purposes for recreational and therapeutic purposes. Its cultivation is restricted by law due to its excessive use for Addiction as it owes psychoactive compounds. The *Cannabis sativa* plant contains more than 400 chemical compounds, including over 100 Phytocannabinoids, which can cause drug-like effects in humans. The most well-known are delta-9-tetrahydrocannabinol (THC), which produces a mental "high," and cannabidiol (CBD) cannabis can be smoked, inhaled, taken by mouth, rubbed into the skin, or mixed into food and beverages. With a recent increase in the rates of cannabis use disorder (CUD) and a decrease in the perceived risk of cannabis use, it is crucial to assess the addictive potential of cannabis. It is enclosed Under Narcotic drugs and psychotropic substances (NDPS) Act 1985. The common preparation of the plant are *Majoon, Ganja, Hashish/charas*. The derivative of *bhanga* is resin and the active principle constituents of resin are cannabinol, cannabidiol. The main chemical, which is responsible for its pleasurable effects, is called delta-9-tetrahydrocannabinol or THC. In *Agad Tantra, bhanga* is described as CNS stimulant. In *ayurveda* it is described as *pramastisk-prabhavak* (CNS stimulant), *Pralapaka* (blabbering), and *vibhramjanak* (delusion) *visha*. It has been used for various therapeutic purposes as it acts as a sedative and have numerous pharmacological effects on both human and animal trial. Its management and effects have been mentioned very well in *ayurvedic* literature and modern science. In this article, we will review about the *ayurvedic* literature of *bhanga*, its mechanism and effects on the brain.

Keywords*: Bhanga*; *Ayurveda*; *Cannabis sativa;* Ethanocannaboid system.

INTRODUCTION

Ayurveda has delineated a group of semi-poisonous plants classified as "*Upvisha Varga*". *Bhanga* (*Cannabis*) is one amongst them in this category hudepicting its narcotic nature from *Sanskrit* synonyms. Cannabis grows wild in the Himalayas, in India from Kashmir in the east to beyond Assam in the west, and all throughout Central and West Asia. *Cannabis* is nowadays cultivated mostly in the tropical and subtropical parts, Unrestricted use of powerful Narcotic

products of this plant, not only spoil the health of the people but gave room for criminal and nefarious activities. So, Government of India has made its cultivation and trade its Monopoly and any individual possession of even one plant is punishable.[1] The *Atharva Veda* mentions cannabis as one of the five most sacred plants on Earth and says that a guardian angel resides in its leaves. It also refers to it as a "source of happiness," a "joy-giver" and a "liberator" [2]. Ayurveda considers the cannabis plant to be of medicinal value and in the *Sushruta Samhita* (6 BCE) it is used to aid digestion and appetite. In *Sushruta Samhita bhanga* is described in *moolaj visha* under *sthavar visha* named as *Vijaya* [3].

***BHANGA* SYNONYMS** are *bhanga, bhangi, madiani, matika, matuli, tandrakarini, bahuvadini*.[4]

भङ्गिका पित्तला तिक्ता तीक्ष्णोष्णा ग्राहिणी लघुः । कर्षणी दीपनी रुच्या मदकृत् कफवातजित् ॥१६३७॥

कै. नि.[5]

भङ्गा कफहरी तिक्ता ग्राहिणी पाचनी लघुः । तीक्ष्णोष्णा पित्तला मोहमदवाग्वह्निवर्धिनी ॥ २०५ ॥

भा. प्र. नि.[6]

Kaphahari: Promotes loosening, separation and the elimination of phlegm.
Grahini: Promotes retention and binds the bowels.
Pachani: Promotes digestion.
Ushna: Promotes heat.
Pitala: Excites the flow of bile.
Mada-vardhani: Promotes talkativeness or releases the volitional restraint of speech.
Moda-vardhani: Promotes happiness.
Vag-vardhani: Stimulates the digestive fire.
Dipani: Stimulates appetite.
Ruchya: Promotes taste.
Nidraprada: Hypnotic.[7]

MEDICINAL PROPERTIES

Rasa(taste)- ***tikta (***bitter)

Guna(qualities)- ***laghu***(light), ***teekshna***(strong), ***vyavayi***(spreads to all body parts swiftly)

Vipaka - ***katu*** (undergoes pungent taste conversion after digestion)

Virya - ***ushna*** (hot potency).

Effect on ***tridosha*** - Balances ***Vata*** and ***Kapha dosha.***

TAXONOMICAL CLASSISFICATION

Kingdom-Plantae

Sub-kingdom-Tracheobionta

Division –Spermatophyta

Sub-division –Magnoliophyta

Class-Magnoliopsida

Sub-class-Hamamelididae

Order-Utricales

Family –Cannabaceae

Genus –Cannabis

Species-Sativa

Bhanga has mainly three principle form in which it is used -

Ganja –the flowering head branches or shoots of the female plant semipressed into compact, masses, brown or green in colour, characteristic colour is mainly used for smoking like tobacco either in a pipe (*chillam*) or *hukka*.

Bhanga -dried leaves and female flower heads semicolin this is grounded up mixed with water or milk added with sugar and consume as a drink (*sharbat*/syrup).

Charas -it is the resin of the leaves of the plant obtained either by kneeding the leaves with hands or clothed with leather trousers walk through the plants violently causing bruises on the plant from which the resin oozes out and adheres to the trousers. It is then scrapped and rolled into pills. It is green or dark brown has a strong odour,no taste and chiefly used for smoking.

In small doses, all the preparations of the plant are antispasmodic, analgesic, stomachic, sedative produce a mild narcotic effect.

In moderate dose, it is exhilerant and powerful aphrodisiac in the beginning and after a while, a good sedative.

In large doses, produces mental exaltation, intoxication, double consciousness, delusion, depression, loss of memory emaciation and impotence.[8]

- Particularly important classes of neurons that express high levels of CB_1 receptors are GABAergic interneurons in hippocampus, amygdala and cerebral cortex, which also contain the neuropeptides cholecystokinin. Activation of CB_1 receptors leads to inhibition of the release of amino acid and monoamine neurotransmitters.[9]

METABOLISM

An amount of 2 to 22 mg of THC dose in smoking is required in humans to produce pharmacological effects. It is soluble in lipids and gets quickly absorbed after inhalation. It is extremely protein bound and spreads easily from blood to other tissues after its absorption. About 2/3 of the drug is defaecated and the remaining 1/3 is thrown out through the kidney in the form of urine. Majority of the metabolites of THC are formed in liver. From these compounds, in routine toxicology analyses 11-noncarboxyTHC which is having maximum concentration in urine, is usually screened. It can be detected in the urine for 2-3 days after casual use along with some other cannabinoids. In case of addicts or heavy users, this can be detected ever up to 4 weeks. Only 3-6% THC is absorbed through orally ingested *marijuana* which is much less than the smoked. (Even though most of these compounds are not having psychoactive properties, they can produce potential physiologic effects [10].

ETHANOCANNABOID SYSTEM AND THEIR RECEPTORS

The ECS comprises a vast network of chemical signals and cellular receptors that are densely packed throughout our brains and bodies. The "cannabinoid" receptors in the brain are — the Cannabinoid Receptor Type 1(CB1) and Cannabinoid Receptor Type 2 (CB2) — outnumber many of the other receptor types on the brain. They act like traffic cops to control the levels and activity of most of the other neurotransmitters. To stimulate these receptors, our bodies produce molecules called endocannabinoids, which have a structural similarity to molecules in the *cannabis* plant. The first endocannabinoid that was discovered was named anandamide after the Sanskrit word *"Ananda"* for bliss. The ECS regulates and controls many of our most critical bodily function, such as learning and memory, emotional processing, sleep, temperature control, pain control, inflammatory and immune responses, and eating. [11]

CB1 receptors are seven transmembrane G-protein-coupled receptors which modulate neurotransmitter release. These receptors are found throughout the body with the most density of CB1 receptors in the brain and spinal cord. CB1 controls Glutaminergic and GABAergic activity. This means it is in charge of energizing and calming down the central nervous system. It plays a critical role in striking a balance between glutamate (Energizing) and GABA (Calming).

Glutamate – a neurotransmitter which is the major mediator of excitatory signals.
GABA – an inhibitory neurotransmitter that calms the central nervous system. THC binds to CB1 receptors in the ventral tegmental area. This disinhibits dopaminergic signaling and results in a reward response. The feeling of being high.

CB2 Receptors-

CB2 receptors are seven transmembrane G-protein-coupled receptors, much like CB1. These receptors inhibit adenylyl cyclase and modulate Cyclic Adenosine Monophosphate (cAMP) levels.

CB2 receptors are responsible for cytokine release in the immune system. It acts as a moderator of immune responses like inflammation, and cell proliferation/survival. This gives researchers reason to believe therapies which target the CB2 receptors a possibility for treating various neurodegenerative diseases.[12]

CANNABIS AND ENDOCANNABINOIDS

Anandamide and 2-arachidonoyl-glycerol are endogenous bioactive lipids that activate 2 G-protein–coupled receptors designated as cannabinoid receptor type 1 (CB1) and 2 (CB2). These lipids, called endocannabinoids, are not stored in vesicles but are synthesized on demand. The system formed by the cannabinoid receptors CB1 and CB2, endogenous ligands, and enzymes involved in their production and degradation is known as the endocannabinoid system (ECS).[13] To understand the nature and potency of *cannabis*,first it is necessary to knowledgeably aware of the two main chemicals components with *Cannabis*: tetrahydrocannabinol (THC) and Cannabidiol (CBD). Tetrahydrocannabinol (THC), is the chemical constituent responsible for the psychoactive response within the mind and body. It attaches to Cannabinoid receptor sites within the brain which are responsible for pleasure, relaxation, memory and time perception. As THC attaches to these sites and activates them, it creates a cascade affect of relaxation and nervine sedation[14]. THC is also responsible for creating a dopamine response in brain cells, giving the consumer a sense of euphoria and ease, though in a higher dosage, one may experience symptoms of anxiety, panic and hallucinate.[15] Synthetic THC, such as nabilone and dronabinol, are FDA approved for chemotherapy-induced nausea and vomiting. Dronabinol is also FDA approved for HIV/AIDS anorexia for appetite stimulation.[16] THC binds to cannabinoid receptors CB1 and CB2, which are part of the endogenous cannabinoid system. THC binds primarily to CB1 receptors though there is a weak binding of CB2 receptors.The expression and pathway of these receptors are still the focus of research; however, it is known that CB1 receptors predominantly express in the central nervous system(CNS), while CB2 receptors are expressed in the peripheral nervous system(PNS) immune cells and organs.[17][18]

ADVERSE EFFECT

The most commonly reported side effects of THC that require its discontinuation are dysphoria, hallucinations, and paranoia. Other common side effects include sedation, confusion, headache, dry mouth, dysphoria, euphoria, and hypotension. Seizures and seizure-like activity have been known to occur in patients using THC.[19][20] THC is a psychoactive alkaloid that signals through CB1 and CB2 receptors. Cannabinoid receptor type 1 is expressed abundantly in peripheral and central neural cells. In the periphery, CB1 localizes to sympathetic nerve terminals and sensory neurons. In the central nervous system, it is expressed mainly in presynaptic membranes of excitatory and inhibitory neurons, where it regulates the vesicular release of dopamine, GABA, and glutamate. In comparison, CB2 is expressed mainly in immune cells, including microglia.[21]CBD blocks the THC chemical's ability to bind the cannabinoid receptor sites in the brain, somewhat mitigating the psychotropic effects of THC, lessening possible

feelings of anxiety, overwhelm and panic often associated with consuming *Marijuana*. CBD does however have an effect on the consciousness of the consumer, though not in a psychotropic way. Due to it's highly sedative nature, CBD is often used in a medicinal setting when treating conditions such as anxiety, post traumatic disorder(PTSD), epilepsy and as an anti-psychotic.[22]

Toxic effect – The eyes become red after consuming *cannabis* and *ganja* in excess. The face becomes puffy, the legs stumble and the destruction of intelligence and memory, fire, insomnia, debility, delirium and headache sometimes death occurs due to heart attack.[23]

DISCUSSION

Several studies have demonstrated the therapeutic effects of cannabinoids for nausea and vomiting in the advanced stages of illnesses such as cancer and AIDS. Other therapeutic uses of cannabinoids are being demonstrated by controlled studies, including treatment of asthma and glaucoma, as an antidepressant, appetite stimulant, anticonvulsant and anti-spasmodic, research in this area should continue. For example, more basic research on the central and peripheral mechanisms of the effects of cannabinoids on gastrointestinal function may improve the ability to alleviate nausea and emesis. More research is needed on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents can be found. There is evidence that demonstrates both the harms and health benefits of cannabis. Yet despite the emergence over the past couple of years of very comprehensive, up-to-date reviews of the scientific studies evaluating the benefits and harms of the drug, it's clear that more research is needed to fully determine the public health implications of rising cannabis use.

CONCLUSION

According to a review of the literature, cannabis formulations are utilized for their aphrodisiac, appetizer, analgesic, and retentive qualities. Various claims of traditional medicine, such as anti-asthmatic, hypnotic, analgesic, anti-inflammatory, and anticonvulsant effects, have been proven by scientific studies on plant and its bioactive constituents. The initial discovery and subsequent intensive research of the endocannabinoid system in the last three decades have revealed probably the most well-known retrograde neurotransmission system. As the main mediator of psychoactive effect of THC, CB1R has gained tremendous interest over these years. Its widespread expression and versatile functions not only support its promising potential as a drug target for various diseases, but also make the undesired side effects almost inevitable.

REFERENCES

1. Bhavaprakasha of Bhavamisra Vol.I translated by:Prof. K.R.Shrikantha Murthy Chowkhamba Krishnadas Academy. haritkyadi varga- page no. 197 and shloka no. 233 and 234)
2. Lbid
3. Susruta Samhita Vol. II Translator Prof.K.R Srikantha Murthy;Chaukhamba Orientalia Edition:Second 2005.
4. rastarangani.Edited by Kashinath Shastrinaa: Motilal Banarsidas:Pg.No.718.
5. kaidev Nighantu:pathaapthya-vibhodhakah-Edited and translated by Prof. Priyavrata Sharma and Dr. Guru Prasada Sharma; Chaukhambha Orientalia; Re-edited edition 2019.
6. Bhavaprakasha nighantu: Vol.I translated by:Prof. K.R.Shrikantha Murthy Chowkhamba Krishnadas Academy haritkyadi varga- page no. 137 and shloka no. 233 and 234
7. www.unodc.org
8. Bhavaprakasha of bhavamisra: Vol.I translated by:Prof. K.R.Shrikantha Murthy Chowkhamba Krishnadas Academy haritkyadi varga- page no. 137 and shloka no. 233 and 234)
9. Cannabis and the brain Leslie Iversen*Brain*, Volume 126, Issue 6, June 2003, Pages 1252–1270, https://doi.org/10.1093/brain/awg143 **Published:**01 June 2003}

10. Krishan VIJ. "Textbook of Forensic Medicine and Toxicology Principles and Practice". Sixth edition, Reed Elsevier India Private Limited, (2014): 479
11. **www.health.harvard.edu**
12. The Endocannabinoid System (CB1 and CB2 Receptors Explained)

    By CannEvolv
13. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system.Int J Mol Sci. 2018; 19:833. doi: 10.3390/ijms19030833Google Scholar
14. Bradford, Alina. What is THC? http://www.livescience.com/24553-what-is-thc.html
15. Lbid
16. Chow R,Valdez C,Chow N,Zhang D,Im J,Sodhi E,Lock M, Oral cannabinoid for the prophylaxis of chemotherapy-induced nausea and vomiting-a systematic review and meta-analysis. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 2020 May [PubMed PMID: 31916006]
17. Wilson RI, Nicoll RA, Endocannabinoid signalling in the brain. Science (New York, N.Y.). 2002 Apr 26 [PubMed PMID: 11976437]
18. Alexander A, Smith PF, Rosengren RJ, Cannabinoids in the treatment of cancer. Cancer letters. 2009 Nov 18 [PubMed PMID: 19442435]
19. Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ, Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ (Clinical research ed.). 2001 Jul 7 [PubMed PMID: 11440936]
20. Kleine-Brueggeney M, Greif R,Brenneisen R,Urwyler N,Stueber F,Theiler LG, Intravenous Delta-9-Tetrahydrocannabinol to Prevent Postoperative Nausea and Vomiting: A Randomized Controlled Trial. Anaesthesia and analgesia. 2015 Nov [PubMed PMID: 26426861]
21. Cristino L, Bisogno T, Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. Nat Rev Neurol. 2020; 16:9–29. doi: 10.1038/s41582-019-0284-zGoogle Scholar
22. US LIbrary of Medicine. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481531/, Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Felipe Villela Gomes, Francisco Silveira Guimarães. Philos Trans R Soc Lond B Biol Sci. 2012 Dec 5; 367(1607): 3364–3378. PMCID: PMC3481531
    doi: 10.1098/rstb.2011.0389

23. Bhavaprakasha nighantu commentary by Dr.K.C Chunekar;Edited by Dr.G.S Pandey.Chaukhambha Bharti Academy Reprint year 2006.