

Cannabinoids in anesthesia and chronic pain: Where do we stand?

ABSTRACT

Cannabis derivatives have been conventionally employed globally for their curative and restorative properties for various ailments. However, its recreational use and consequent legal restrictions have substantially cramped its scientific research. An emerging interest regarding the profound therapeutic potential of cannabinoids has been observed among clinicians. Despite a rich cultural background, high-quality research on cannabinoids is lacking in the Indian scenario. This review readdresses the challenges on this front and brings an insight into the current status of cannabinoids and their utility in scientific exploration. Cannabinoids have a significant medicinal value in various clinical disorders. Its use so far has been based on scarce resources and corroborations, as evidence-based substantiation is limited. Through this review article, we emphasize the remarkable role enacted by cannabinoids in the treatment of various clinical disorders and an utterly significant need to formulate stringent research methodologies to promote its systematic investigation.

Keywords: Cannabinoids, chronic pain, current status, Indian hemp, medical cannabis

Introduction


Cannabis is an archaic drug, existing in natural to synthetic formulations, having versatile medicinal value as well as psychoactive properties. Various studies on cannabinoids have brought about an emerging interest regarding the profound therapeutic potential of cannabinoids among clinicians. Regardless of their notable role in medicine, the practical utilization of cannabinoids in the clinical field is still not up to the mark, due to inadequate knowledge and scientific research in this particular sphere of influence. Through this review article, we wish to emphasize the remarkable role enacted by cannabinoids in the treatment

of various clinical disorders and an utterly significant need of the hour to formulate stringent research methodologies to promote scientific exploration.

Definition and Classification

Cannabinoids are referred to as a group of compounds with active ingredients derived from cannabis sativa, that is, the Indian Hemp plant, in natural or synthetic form. Classical division segregates them into two broad categories, that is, Endocannabinoids and phytocannabinoids.^[1] The clinical application of cannabinoid is rooted down to the existence of endogenous cannabinoid receptors in the human neuronal

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system, known as CB1 and CB2; where inherently produced cannabinoids known as endocannabinoids are functional to sustain several physiological functions of the body such as mood, appetite, sleep, pain regulation, emotional balance, and many others.^[2]

The other category of cannabinoids known as phytocannabinoids are naturally derived from cannabis, as one of the several cannabinoid constituents out of which, tetrahydrocannabinol (THC) (further in majority constituted by Δ^8 -THC and Δ^9 -THC), cannabidiol (CBD), and cannabigerol (CBG) are most explored ones.^[3]

Mechanism of Action

Cannabinoids are known to have agonistic activity at CB1 and CB2 receptors, which primarily belong to a family of G-protein coupled receptors (GPCRs). The binding of cannabinoid-based medicines (CBMs) leads to the activation of voltage-gated channels and signal transduction, resulting in the conduction of nerve impulses through descending pain pathways.^[3,4]

The existence of CB1 at a variety of central nervous system (CNS) locations such as basal ganglia, limbic system, the dorsal horn of the spinal cord, and dorsal root ganglia manifests with the maintenance of physiological functions of the body such as pain modulation and transmission, management of anxiety or stress response, etc. Other potential sites of activity for cannabinoids include Peroxisome Proliferator-Activated Receptor (PPAR), Transient Receptor Protein Vanilloid (TRPV1), and other different classes of GPCRs.^[5]

The classic features of CB1 receptor stimulation such as suppressed behavioral or locomotor activity, a cataleptic state, altered memory, reduced body temperature, and antinociception have been well demonstrated in animal models involving rodents.

Other significant properties associated with cannabinoids, as demonstrated by strong opioids include drug tolerance to pharmacological doses, physical dependence, and drug reinforcement. One of the plausible causes for such clinical manifestation could be an expression of these receptors in the limbic system of the central nervous system.

Physiological functions of the endocannabinoid system

The physiological functions of the human body are maintained through the coordination of several organ systems and neuronal feedback, including the endocannabinoid system (ECS), which is responsible for the regulation of gastrointestinal (appetite, feeding, nausea/vomiting),

central neuronal pathways (cognitive responses, sleep, anxiety, memory, emotions, regulation of pain, neuronal development, neuroprotection), temperature regulation, cellular physiology, and numerous other homeostatic functions.^[6] Enhanced learning about ECS over the years has suggested the potential role of cannabinoids in the management of several pathophysiological states. Chronic inflammatory states, cancer, metastasis, autoimmune diseases, multiple sclerosis, chronic pain, rheumatoid arthritis, etc., are a few to enumerate.^[6,7]

Tolerance is defined as diminished clinical response to a given therapeutic dose of the drug, rendering a potential drug abuse, possibly attributed to altered drug response at the cellular level associated with receptor desensitization.^[8]

Physical dependence typically manifests with withdrawal symptoms after the administration of antagonists. The severity of physical dependence is proportional to drug dose in experimental studies with mice.^[9]

Besides their beneficial pharmacological effects, these adverse effects can alter the utility in clinical practice; hence drawing an important proposition towards further research in the exploration of human volunteers.

Potential role of cannabinoids in anesthesia

The pharmacological effects of cannabinoids can be extrapolated to a wide variety of clinical applications in anesthesia such as chronic pain management, opioid-sparing effects, and anti-tumor activity. However, their practical utility in the aforementioned areas stands partially explored to date. Though certain animal models have shown a promising effect, studies utilizing human volunteers are yet an area of future research.

Cannabinoids for pain management

Several animal studies have deciphered the value of cannabinoids in various etiologies of pain such as noxious stimuli, visceral pain, post-operative pain, and chronic cancer pain management. It appears that cannabinoids are a feasible substitute/adjuvant to prevalent analgesics such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs) due to lesser adverse effects on organ systems and low addiction potential as compared to opioids.^[4,10] Furthermore, a greater therapeutic index of cannabinoids further enhances their clinical efficacy with reduced adverse effects.^[5,11] The promising role of cannabinoids in chronic pain management has been well postulated. Recently, an extensive meta-analysis by Vuckovic *et al.*^[12] decrypted the role of cannabinoids in cancer pain, chronic neuropathic pain, and refractory pain conditions such as fibromyalgia. The authors reviewed several scientific publications from 1975 to 2018 and hypothesized

various probable mechanisms for the analgesic potency of cannabinoids such as modulation of pain pathways, control/suppression of inflammatory mediators and neurotransmitters, stimulation of inhibitory neurons, and attenuation of neuronal activities. These mechanisms have been found to play a significant role in the pathophysiology of chronic pain.^[12]

Opioid sparing effect of cannabinoids

Opioids have been regarded as the cornerstone of chronic pain and cancer pain management. However, the potential adverse effects such as physical dependence, abuse potential, tolerance, and side effects over various organ systems have inspired the exploration of adjuvant analgesics to opioids. Cannabinoids with their beneficial pharmacological properties can be implemented in anesthesia and chronic pain management, as a suitable adjuvant to opioids. Furthermore, recent studies have demonstrated the probable anti-tumor and anti-metastatic properties, providing a significant role in cancer therapeutics.^[13]

A close resemblance in pharmacokinetic properties, receptor function, and action over the GPCR system suggests a possible synergistic activity of cannabinoids about opioids. Furthermore, the prevalence of cannabinoid receptors over the central (spinal and supraspinal) as well as peripheral nervous systems can potentiate the analgesic effects of opioids with cannabinoids.^[3,14]

This phenomenon of the opioid-sparing effect of cannabinoids has been supported by Shah *et al.*, in 2019,^[9] where the authors demonstrated that the overall opioid consumption was reduced in countries where medical prescription of cannabinoids was legalized. Similar findings were noted in an observational by Bulbul *et al.* in 2018,^[15] where the authors reported a 41% reduction in overall opioid consumption with the use of cannabinoids.

Anti-tumor and anti-metastatic effects of cannabinoids

Cannabinoids have a proven role in cancer biology, including their favorable therapeutic effects to combat cellular multiplication and cell cycle progression through the promotion of cell-cycle arrest, inhibition of neovascularization, cell adhesion/invasion, and anti-metastatic effect, address adverse effects of chemotherapy such as loss of appetite, nausea/vomiting, and combatting cancer pain.^[16,17] One of the proposed mechanisms for anti-neoplastic activity is through impairment of cell signaling pathways promoted by cannabinoids in cancer cells.^[18] Additionally, several experimental evaluations have deciphered the expression and upregulation of cannabinoid receptors in oncological tissues.^[19] The role of cannabinoids in cancer pain

management^[20] and palliative care^[21] is a renowned entity. Furthermore, the implementation of cannabinoids for cancer therapeutics serves as a very important clinical domain for opioid-sparing strategy.^[22]

Historical aspects and current status of cannabis-related research in India

Since time immemorial, India has had a rich culture concerning the production and consumption of cannabis, contributing to a significant global proportion. Cultivation and export of cannabis products from several states of India have been widely practiced on legal as well as illegal grounds. Commonly cultivated formulations in India include marijuana or *ganja* that is the dried fruit (flower bud) of the plant, hashish or *charas* is a potent resin extract from the plant and *bhanga* that is the powdered form of plant leaves.^[23] All these compounds are a rich source of cannabinoids, known to produce psychoactive effects with substance abuse.^[24] Many countries including India are striving hard to legalize the medicinal and scientific/research-based use of cannabinoids. The United States of America (USA) government has had an antecedent role in the approval of commercial and recreational use of cannabinoids.^[25] As a possible consequence, there has been a huge surge in reports regarding substance abuse and illicit drug use from Western countries.^[25] These issues need to be taken into serious consideration before the amendment of laws about the production and use of cannabinoids.

Regardless of ongoing efforts, the Indian federal government has yet to legitimize commercial and scientific use of cannabinoids.^[26] With a proposal submitted to the Indian parliament in 2016, Madhya Pradesh and Uttarakhand state governments have permitted the rearing of cannabis for therapeutic utility in 2019. Nevertheless, the Ministry of Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) has been recently authorized by the central government to explore the therapeutic potential of cannabinoids in various clinical disorders.

In the face of a well-off bequest of cannabis, that is, the Indian hemp plant in India, there's a profound paucity of quality research from Indian scenarios in the existing literature regarding cannabinoids. Several prohibitions imposed by the government as a measure to prevent criminal use of cannabinoids among the local communities have negatively affected the scientific research and academic growth of the country in the concerned specialty.

Nevertheless, it is noteworthy that the Indian federal government, in 2023, has recently initiated a cannabis

research project in the state of Jammu with the Council of Scientific and Industrial Research-Indian Institute of Integrative Medicine (CSIR-IIIM), under the partnership of a private Canadian firm, to promote research and produce export quality drugs derived from cannabis for the treatment of various neuropathies, malignancies, and other clinical disorders.^[27] A major stride like this will also enlighten the local community regarding manifold medicinal uses of cannabinoids and may prove helpful to channelize substance use disorder in the best interest of mankind.^[27]

Challenges with cannabis-related research in India

Aside from legitimate and executive limitations in India, there exist further prospective challenges with research and experimental trials utilizing cannabis. The use of cannabis formulations has been associated with psychosis, dependence, abuse potential, behavioral disorders, and adverse effects on physical and mental health.^[28] It has also been designated as a substance use disorder under the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Cannabis use disorder has been attributed to increased hospitalization and overall healthcare-associated expenditure.^[29] Nevertheless, there's limited information available about the efficacy of treatment and management of cannabis-related disorders.^[30] In the Indian scenario, the consumption of cannabis is also influenced by several innate cultural beliefs, perceptions, and consumption during festive celebrations, despite the legal consequences of such an act. The Indian government needs to come up with ingenious processes to encourage research and analysis on cannabis consumption. This could be implemented by controlled liberalization for the utility of cannabinoids for research purposes and experimental studies.

Future direction

Cannabinoids have gained enormous interest lately, due to their encouraging pharmacological and clinical effects on humans.^[31] It appears through the current knowledge and clinical status of cannabinoid use, that there is an immense scope for learning and research in this field. Several clinical trials involving animal models have generated significant hypotheses regarding their safety and clinical efficacy in several diseases.^[32] An ample amount of probable contribution to this area of interest could be expected from the federal government, research scientists, clinicians, and academicians in the concerned matter. In Figure 1, an overview of the role of cannabinoids in anesthesia and chronic pain is presented. This visual representation helps illustrate the key mechanisms and potential applications of cannabinoids in clinical settings.

CONCLUSION

Cannabis has been formulated abundantly in various drug preparations commercially and implemented to treat numerous diseases. The emerging role of cannabinoids in the management of a wide variety of malignancies and palliative ailments is worthy of attention. Meticulous investigation and research are indispensable to explore it to the highest prospects. Extensive research over a broad range of populations must be encouraged by the federal government to assess and avail of its comprehensive medicinal value.

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Conflicts of interest

There are no conflicts of interest.

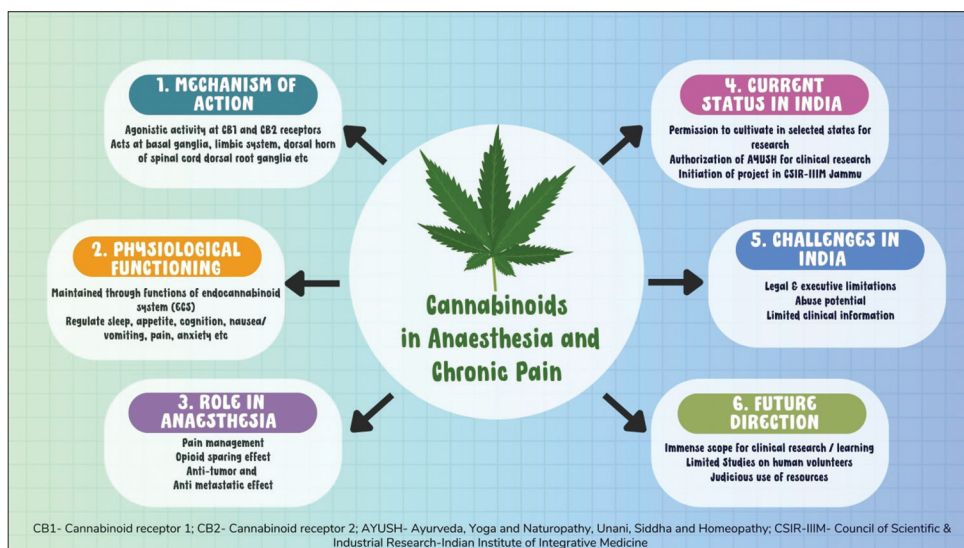


Figure 1: Overview of cannabinoids in anesthesia and chronic pain

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