How do specific cannabinoids exhibit anti-cancer properties, and what strategies can be employed to optimize their efficacy for targeted cancer therapies?

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Abstract

Cannabis, derived from the Cannabis sativa plant, has historically been utilized for its medicinal properties, notably for pain management and symptom relief in various health conditions. Recent research has expanded its potential therapeutic applications, particularly in cancer treatment and chronic pain management. This paper explores the role of two primary cannabinoids, Delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD), in addressing cancer-related symptoms and chronic pain. THC and CBD have demonstrated significant anti-tumor and anti-inflammatory activities, which are mediated through interactions with the endocannabinoid system (ECS). THC primarily targets CB1 receptors to modulate pain and neuroinflammation, while CBD exerts effects through a more complex mechanism involving various receptors, including CB2, TRPV1, and 5-HT1A. The paper reviews clinical and preclinical studies to elucidate the efficacy of these cannabinoids in alleviating symptoms such as pain, anxiety, and nausea in cancer patients and their role in enhancing traditional cancer treatments. Additionally, it addresses the potential risks and side effects associated with cannabinoid use, including cognitive and psychological effects linked to THC. The paper emphasizes the need for standardized dosing and formulation in cannabinoid therapies and calls for further research to optimize treatment protocols, assess long-term safety, and explore new therapeutic targets. The findings underscore the promising role of cannabinoids in improving the quality of life for cancer patients and managing chronic pain, highlighting their potential as adjunctive therapies in modern medicine.

Introduction

Cannabis, more commonly known as marijuana, originated in Central Asia and was extracted from the cannabis plant. It was found effective in the treatment of the nervous system (depression, arthritis, asthma, etc.) and the immune system (reduces body temperature, anti-inflammatory, etc.). Although the negative stigma around cannabinoid use is well-known in society, they can also serve healthy benefits in the human body as their cancer treatment and chronic pain management properties have been uncovered in recent years.

Recent studies found cannabis to be an effective treatment for managing symptoms such as pain, anxiety, sleep, depression, nausea, and appetite in cancer patients. The American Society of Clinical Oncology published a list of guidelines regarding the use of cannabis to treat chronic pain in cancer patients in 2016. In 2017, both the National Academy of Sciences and the Oncology Nursing Society proposed that cannabinoids found in cannabis have effective control of chronic cancer pain (Byars et al., 2019). The use of cannabis in cancer treatment has successfully begun to be established, and scientific research on these cannabinoids, which are responsible for treating chronic pain, has also arisen. Out of more than a hundred cannabinoids isolated from Cannabis sativa (cannabis plant) during laboratory research, Delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) were found responsible for better anticancer activity than other cannabinoids (Tomko et al., 2020).

This paper focuses on the effects of THC and CBD, such as its anti-tumor and anti-inflammatory activities, on specific cancer cells as their intercellular mechanisms will be uncovered by past clinical research as early as 2014. The potential risks and side effects, both short and long-term, will be identified as it is crucial for patient safety. The mechanism of THC

and CBD in specific cancer treatment will be used to compare and examine for potential cures in other related diseases.

Methodology

Our research paper was a collaborative effort that commenced with the formation of our team and effective communication channels. Beginning with a thorough review of background literature and existing findings, we honed our research question. Our journey commenced with an exploration of cannabis's impact on youth, which organically led us to delve deeper into its potential therapeutic effects on cancer. We meticulously refined our research question by gathering recent clinical and scientific studies on the utilization of cannabinoids in the human body and summarizing them to answer our research question, to indicate the potential use of cannabis in treating neuro pain and diseases. As we continued this process, our focus shifted to drafting our paper, crafting tertiary proposals, and refining successive drafts. Culminating in the creation of this poster and our final manuscript, our process epitomizes our commitment to rigorous inquiry and scholarly advancement.

Cannabis and Cancer Treatment

Cannabis has a long-standing historical use medicinally. The use of cannabis medicinally cantraced back thousands of years, with there being evidence of its use across several ancient civilizations such as China and Egypt. The late 19th century is referred to as the “first Golden Age of medical cannabis,” and became widely incorporated into medical practices in the Western World with its primary use being to treat pain and insomnia. However, the use of medicinal

cannabis took a sharp decline nearing the 20th century due to harsher restrictions as well as a lack of standardization in the formulation for medicinal cannabis. Despite its decline in the West, medicinal cannabis remains in use traditionally in other parts of the world. In recent times, there has been a resurgence in the use of medicinal cannabis because of growing evidence/research pointing to its therapeutic benefits as well as updates being made on the legality of cannabis as a whole. In more recent research, medicinal cannabis has been shown to aid in symptom relief of chronic illnesses, leading to its resurgence in its use in medicine. The mechanics behind the use of cannabinoids in cancer treatment revolve around the cannabinoids' ability to hinder the growth/spread of cancerous cells- more specifically, works by focusing on targeting the endocannabinoid system (ECS). Cannabinoids (THC & CBD) are able to bind to cannabinoid receptors within the endocannabinoid system which leads to therapeutic-like effects on cancer cells. Some results that come from cannabinoid binding within the ECS include induced apoptosis (programmed cell death) and inhibited cell proliferation (slows down their ability to reproduce quickly). The cannabinoids also cut off the blood supply around cancerous/tumor cells- cutting off blood supply decreases the ability for a tumor to grow or cancer cells to replicate. By affecting the necessary processes for cancer and tumor cells to reproduce, cannabinoids are showing great potential and are being integrated into cancer treatments.

Recent preclinical research has shown that cannabinoids exhibit anti-cancer properties; as well as cypress metastasis (the spread of cancer cells to the rest of the body), and the use of cannabinoids works well coinciding with traditional cancer treatments/therapies- enhancing the overall effectiveness of the traditional treatments, while in some cases also reducing their side effects. In specific criteria, research has shown "...it seems more likely that cannabinoid compounds will be used as a combination and add-on option with currently employed

cytostatics, assuming successful clinical trials. THC and CBD, which are currently being tested in some studies as combination, have been pre clinically shown to enhance the effect of various cytostatics, such as for vinca alkaloids, cytarabine, doxorubicin, mitoxantrone, carmustine, temozolomide, bortezomib, carfilzomib and cisplatin Thereby, combined administration of CBD and temozolomide in patient-derived neurosphere cultures and orthotopic mouse models was demonstrated to exert a significant synergistic effect in both reducing tumor size and prolonging survival." Cannabinoids are displaying positive results, especially in coinciding with many determined cancer treatments. In more concrete clinical trials, results are consistent with those of pre-clinical research. For instance, "findings from a recent randomized clinical trial (RCT) with 18 healthy adults, in which the effects of oral 20 mg THC plus oral 640 mg CBD were compared to 20 mg THC alone and placebo, suggest that high doses of CBD can inhibit the metabolism of THC, resulting in stronger drug effects (greater impairment of cognitive and psychomotor activity, greater increase in heart rate)" (Woerdenbag et al., 2023). In the article where this clinical data is found, there are several more, very similar trials all pointing towards the same conclusion; the use of cannabinoids alongside traditional treatments of cancer displays better outcomes with patients as far as symptom relief and recovery.

Cannabinoids for Chronic Pain Management

Chronic Pain and Its Impact on Patients

Studies from scientific research indicate that cannabinoids are clinically used to treat chronic pain, yet it is essential to understand what exactly chronic pain is, why it occurs, and its impact on patients. A pain response begins with a nerve cell's receptor which sends a signal along a nerve pathway to the central nervous system's spinal cord, then carries it to the brain.

Pain is considered chronic when it lasts for more than 3 months, which is quite irritable for a patient. These nerve receptors are signaled throughout a longer period, often after a major injury or illness, which can be “on” and “off” or continuous (Hopkins et al., 2024). To prevent this discomfort, patients are often prescribed medications, some of which may be cannabis.

Pharmacology of Cannabinoids and Interaction with the Endocannabinoid System

The pharmacology of cannabinoids and their interaction with the endocannabinoid system present a complex interplay between exogenous and endogenous compounds within the body. Phytocannabinoids such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are primary constituents of cannabis and have been extensively studied for their medicinal properties as they both show promise in alleviating chronic pain through interaction with the endocannabinoid system. THC, in particular, mediates its effects primarily through the activation of CB1 receptors, which are highly expressed in the nervous system, modulating neurotransmitter release, including the inhibition of pain signals. On the other hand, CBD exhibits a more nuanced pharmacological profile, exerting its effects through various mechanisms, including allosteric modulation of cannabinoid receptors. Its reach to various pathways includes the desensitizing of TRPV1 receptors which reduce pain signals, inhibiting inflammatory mediators, modulation of serotonin thus influencing pain perception, and enhancing endocannabinoid signaling by inhibiting the breakdown of enzymatic activity. The discovery of the endocannabinoid system, consisting of CB1 and CB2 receptors along the endogenous ligands, opened doors to understanding physiological processes modulated by cannabinoids. Pharmacological research on cannabinoids led to the approval of THC by the FDA for chemotherapy-induced nausea amongst other chronic pains. In the context of cancer

treatment, cannabinoids have demonstrated potential in managing chemotherapy-induced symptoms like nausea and stimulating appetite, thereby improving the quality of life for cancer patients. Furthermore, cannabinoids have shown anti-tumor properties in preclinical studies, suggesting their potential as adjunctive therapy in cancer treatment.

Mechanistic Insights into Cannabinoids' Effects in the Endocannabinoid System

The endocannabinoid system is a neuromodulatory system that was first discovered in the mid-1990s along with the effects of cannabinoids on human health. The endocannabinoid system is composed of two distinct parts: CB1 and CB2 receptors. The CB1 receptors play a major role in controlling one's central nervous system (CNS) such as emotions, appetite, etc., while the CB2 receptors focus more on the immune system of the human body. Cannabinoids binding to these receptors were found to have different contributions to the effects on the human body.

Cannabinoids in CB1 of the Endocannabinoid System

CBD in the endocannabinoid system does not directly bind to either CB1 or CB2 receptors. Rather, it activates CB1 and CB2 through allosteric regulation by binding to the sites of other effective receptors in the human body to trigger CB1 and CB2 activities. The most known receptors that contribute to CBD's antipsychotic properties are the fatty acid amide hydrolase (FAAH), TRPV1, and 5-HT1A receptors (Peng et al., 2022).

As CBD enters the endocannabinoid system of the CNS, it inhibits the FAAH receptor, leading to an increase in anandamide (ANA) level that triggers the response of the CB1 receptor to couple with the GPCRs to decrease cAMP levels by inhibiting adenylate cyclase activity. Upon the activation of CB1 receptors and its coupling with GPCRs, the calcium channels will

also be inhibited and the potassium channels will be activated to allow the excretion of potassium ions while blocking calcium intake, which inhibits presynaptic neurotransmission release and was believed to be one of the pathogenesis of epilepsy (Kendall et al., 2017). THC, different from CBD, can bind to CB1 receptors directly and activate it to modulate neurotransmitter release and inhibit pain signals, giving cannabinoids its anti-neuropathic activity. A similar mechanism was found when CBD binds to the 5-HT1A receptor, where CBD acts as an agonist directly to 5-HT1A.

On the other hand, CBD binding to TRPV1 channels was found to have antitumor effects by regulating the calcium levels in the cytoplasm and endoplasmic reticulum in the neuron. As CBD activates TRPV1, it opens the channel to allow calcium entry to the cytoplasm and reduce the stress of the endoplasmic reticulum (Haustrate et al., 2020), which decreases the risk factors for Alzheimer's, Parkinson's, and other neuro disorders.

Cannabinoids in CB2 of the Endocannabinoid System

Unlike CB1, which is expressed primarily in the human brain, CB2 works more toward the circulation of the human immune system, spleen, and macrophage-derived cells. As CBD activates the CB2 receptors, the neuroinflammatory signaling pathway gets inhibited, which changes the pro-inflammatory to anti-inflammatory phase, giving CBD its anti-inflammatory activity in the central nervous system.

CB2 in the microglial cell is responsible for its neuropathic pain treatment. As CBD activates the CB2 receptors on the microglial cell membrane, it inhibits the microglial cell from promoting consolidation and progression of neuropathic pain, which decreases the manifestation of the pain (Bie et al., 2019).

Potential Risks Associated with Cannabinoid Use

One reason that cannabinoids, especially THC, have not yet been widely used as a prescription for neuro-disorders is due to their instability in human health. Clinical studies have shown that the psychoactive effects of cannabinoids on the human nervous system were primarily the result of the use of THC rather than CBD. The most common psychoactive effects of long-term exposure to THC were found to have altered sensory perception, changes in mood, impaired body movement and memory, hallucinations, delusions, and psychosis. However, the direct potential risks associated with taking CBD have not been discovered yet.

Future Directions and Implications

Yet, cannabis use and cannabinoids in cancer treatments in the current stage lack the understanding of standardized dosing and formulation, as different strains and preparations of cannabis can have varying levels of cannabinoids. The inconsistency makes it difficult to determine an optimal therapeutic dosage, as legal restrictions can hinder research and access to cannabis-based treatments for patients. Although there are sounds of cannabis research rising in recent years, not enough high-quality clinical trials can be used to determine the efficient and accurate use of cannabis for cancer treatment, presenting a challenge to using cannabis as a course of treatment. Further research and clinical trials are required to indicate the use of cannabis to show a promising future in cancer treatment.

One potential future research involves the study of the refinement of treatment protocols. More clinical trial research is needed to optimize dosing and administration methods for cannabinoids to maximize therapeutic benefits while minimizing potential side effects of cannabinoid use. In addition, clinical scientists should conduct longitudinal studies to assess the

long-term safety and efficacy of cannabinoid-based therapies, which will provide valuable insights into the sustained benefits and potential risks of cannabinoids over an extended treatment period. Such a method would also be able to investigate the synergistic effects of cannabinoids with existing pain management therapies could enhance overall efficacy and broaden treatment options for patients with chronic pain. As more study trials are conducted, the exploration of the endocannabinoid system and other potential molecular targets of cannabinoids may uncover new avenues for therapeutic intervention in chronic pain and related conditions.

Conclusion

Cannabis helps with cancer treatment and chronic pain management. In cancer treatment, cannabinoids help reduce the side effects and stop metastasis, or the spread of cancer, from happening throughout the body. In chronic pain management, it releases inflammatory mediators to help reduce pain and other symptoms of cancer, such as nausea. Overall, the use of cannabis in healthcare can help cancer patients by preventing the metastasization of tumor cells and decreasing chronic pain. This improves the quality of life for cancer patients and can potentially save their lives.

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Acknowledgement:

1) Undergraduate Lab at Berkeley (ULAB) - Public Health Division provided their unique opportunity and methodology for constructing a research

2) University of California, Berkeley for providing the opportunity and access to past research articles