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Review Article

Analyzing the medical use of cannabis for cancer patients: a critical perspective

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ABSTRACT

The utilization of cannabis in oncology presents a multifaceted approach to addressing the complex challenges associated with cancer treatment. With roots tracing back to ancient medicinal practices, cannabis contains numerous compounds, including cannabinoids like tetrahydrocannabinol (THC) and cannabidiol (CBD), that interact with the body's endocannabinoid system. These interactions offer potential therapeutic benefits, ranging from antiemetic and analgesic effects to the inhibition of cancer growth processes. While clinical evidence supports the efficacy of cannabinoids in managing symptoms and enhancing the quality of life for cancer patients, caution is warranted due to potential interactions with conventional medications. Understanding the mechanisms of action, optimal administration routes, and potential side effects is crucial for integrating cannabis into personalized cancer care plans. By navigating these considerations thoughtfully, medical practitioners can harness the therapeutic potential of cannabis to complement traditional cancer treatments and improve patient outcomes in the field of oncology.

Keywords: Cannabis, Cannabinoids, Cancer treatment, THC, CBD, Symptom management, Pharmacological interactions, Administration routes, Oncology

INTRODUCTION

Cannabis can be medically applied in the treatment of various medical conditions-tracing back to the historical background of the cannabis plant's therapeutic potential. With around 540 distinct compounds, the cannabis plant possesses over a hundred cannabinoids sharing a similar structure capable of actively interacting with the human body's endocannabinoid system and the nervous system.[1] THC and CBD are the two most abundant psychoactive and non-psychoactive cannabinoids of the cannabis plant, respectively.[1] These cannabinoids induce their therapeutic effects by acting as either partial agonists or antagonists as they interact with the cannabinoid receptors, i.e., CB1 and CB2.

CBD and THC can potentially act as antiemetic, anti-inflammatory, analgesic, and sleep-inducing agents-ultimately contributing to cancer treatment.[2] This diligent perusal assesses and reviews several well-controlled clinical trials and research papers to reveal the clarity of efficacy of the cannabinoids of the cannabis plant for cancer treatment.[2]

It is critical to evaluate the safety parameters including the side effects of cannabis use, especially THC, for cancer patients. THC is the psychoactive compound of

the cannabis plant, and the application of cannabis for therapeutic outcomes must be assessed in consideration of the legalization aspects and accessibility.

CANNABIS-TRACING BACK TO ANCIENT MEDICAL APPLICATIONS

Cannabis sativa L. (*C. sativa*) boasts a substantial medicinal legacy as a therapeutic agent spanning ages, with roots deeply embedded in the traditions of Eastern societies. Numerous scholars have meticulously delved into the extensive history of cannabis, acknowledging its profound healing properties. Ancient oriental healers conducted numerous experiments on local patients to alleviate various medical conditions.[3] The therapeutic utilization of *cannabis sativa* dates back approximately 10,000 years, with its applications evolving over time, transitioning from informal use to a more structured incorporation into medical treatments in ancient Eastern Medicine during the 1st and 2nd millennium B.C. These practices have continuously evolved, influencing and merging with Western medical approaches.[4]

INTERACTIVE MECHANISMS OF CANNABIS IN THE HUMAN BODY

CBD and THC, as the most prevalent phytocannabinoids, demonstrate robust binding interactions with the body's G-protein coupled cannabinoid receptors. CB1 receptors are widely distributed throughout various regions of the nervous system, including the basal ganglia, hippocampus, frontal cortex, and the peripheral nervous system, while CB2 receptors are predominantly present within the immune system, glial cells, and hematopoietic cells.[5] In instances of medical conditions such as cancer, CB2 receptors are notably expressed in unhealthy states within the brain.

The structural makeup of cannabinoids facilitates their binding interactions with GPR55, GPR12, GPR18, GPR6, GPR3, and other receptors. Similar interactive patterns have been observed between cannabinoids and transient receptor potential channels, including TRP ankyrin (TRPA1), TRP vanilloids (TRPV1 to TRPV4), and TRP M member (TRPM8).[5] Additionally, these interactions can modulate peroxisome proliferator-activated receptors and monoamine transporters, thereby influencing the regulatory functions of dopamine, norepinephrine, and serotonin.[6] A thorough examination of the interactive effects of CBD and THC reveals their potential impact on adenosine equilibrative nucleoside transporters as well.

CANNABIS AND CANCER TREATMENT

Research indicates that cannabinoids effectively demonstrate a robust anticancer potential and exert influence on cancerous growth within the body. However, while anecdotal evidence supports this notion, formal clinical reports provide limited backing. Conversely, 40% of patients have reported significant positive effects, often expressing considerable relief from debilitating symptoms.[7]

Clinical trials involving various cancer types, such as breast cancer, CNS cancer, leukemia cancer, prostate cancer, lung cancer, and pancreatic cancer, have underscored the efficacy of cannabis cannabinoids in symptom management, achieving a success rate of approximately 52%. Among approximately 77 cancer cases studied, cannabis extracts showed positive effects, with 14% experiencing major benefits and 5% reporting moderate benefits, while the remaining 81% exhibited weaker benefits.[8]

Moreover, approximately 10% of pediatric patients confirmed the relative safety of cannabis treatment for pediatric cancer, with doses ranging from 10mg to 800mg. While acknowledging the positive contributions of cannabinoids to cancer patient wellness, the study highlights the inability of cannabinoids to fully replace traditional cancer medications and treatments due to the lack of formal clinical research.[9]

A PERUSAL OF THE POTENTIAL BENEFITS OF CANNABIS FOR CANCER PATIENTS

Cannabis presents a promising medical avenue, as its cannabinoids mimic the physiological effects of endogenous cannabinoids found in the body, interacting with cannabinoid receptors. Among these cannabinoids, CBD and THC stand out as the most dominant, showcasing remarkable capabilities in addressing chemotherapy-induced symptoms, primary cancer symptoms, and tumor progression. When used synergistically along with the other conventional medications, cannabis can augment their effectiveness manifold, even in cases where patients have become unresponsive to these medications.

Antiemetic potential of cannabis

Vomiting and nausea represent prevalent symptoms among patients in oncology departments, often caused by chemotherapy. Despite available treatments for nausea, many patients do not find them sufficiently effective, highlighting the importance of exploring alternative antiemetic remedies.[10]

The utilization of CBD (a non-psychoactive compound) and THC (a psychoactive compound) found in cannabis extracts has shown significant efficacy in managing intense nausea and vomiting. Interestingly, the acidic precursors of CBD, such as cannabidiolic acid (CBDA) and methyl ester of cannabidiolic acid (CBDA-ME), exhibit greater effectiveness compared to CBD alone.

The physiological mechanisms underlying cannabis's ability to alleviate chemotherapy-induced nausea are meticulously examined, attributing its effectiveness to the interactive dynamics of the endocannabinoid system in

regulating gut function. Specifically, the CB1 receptors present in the central nervous system play a crucial role in mitigating the neurotransmitter-induced reverse-peristaltic movements responsible for vomiting.[10]

CBD, on the other hand, employs a distinct set of interactive abilities to aid cancer patients in managing nausea and associated symptoms like appetite loss and vomiting. It interacts specifically with the 5-HT1A receptors, which are integral in this context.[11] Additionally, by modulating serotonin production in the nervous system, CBD can effectively reduce nausea.

Pain relief for cancer patients

Cancer patients endure debilitating pain conditions that often go inadequately managed, significantly compromising their quality of life. While some patients develop resistance to opioid painkillers, others experience severe side effects and limited pain relief. The exploration of cannabis's pain-relieving effects for cancer patients traces back to small clinical trials in 1975, evolving into more sophisticated and controlled studies conducted in 2014 and beyond.[12] These trials consistently indicate the potential efficacy of cannabinoid-based analgesic treatments, whether administered independently or in conjunction with conventional cancer medications. Among available products, cannabis capsules and oromucosal sprays are highly recommended, offering easier dose administration and faster relief.[12]

However, patients treated with high THC doses reported side effects such as mental fog and drowsiness. CBD's ability to modulate pain perception stems from its interactions with various G-coupled receptors in the body, including δ-opioid receptors, dopamine receptor D2, and μ-opioid receptors. Scientific studies evaluate pain modulation by targeting interactions between TRPV1 channels, cannabinoids, and cannabinoid receptors. Upon cannabis administration, cannabinoids, being lipophilic, accumulate in the body's adipose tissues.[12] Both CBD and THC demonstrate potent abilities to influence pain perception and alleviate neuropathic pain caused by cancer. Moreover, CBD can enhance the analgesic effects of opioids through synergistic interactions.

Anticancer effects

Cannabis contains compounds that demonstrate effectiveness in impeding molecular processes such as inflammation, proliferation, and oxidative stress, closely associated with cancer initiation and growth. With its potent antioxidant and anti-inflammatory properties, cannabis emerges as a potential inhibitor of cancer. Examination of tumor tissues reveals abundant endogenous ligands and cannabinoid receptors, suggesting potential interactions with cannabinoids derived from the cannabis plant. Additionally, the onset of cancer often involves an increase in the production of enzymes by the endocannabinoid system, contributing to the aggressiveness of cancer. CBD, THC, and other cannabinoids from cannabis can address various aspects of cancer growth, including tumor cell proliferation, growth and invasion, apoptosis, and angiogenesis. These interactions effectively impede cancer's progressive growth and inhibit tumors' metastatic potential.[13]

The molecular mechanisms underlying cannabis's ability to impede cancer growth involve the stimulation of targets actively involved in tumor progression. CBD and other cannabinoids interact with glycine receptors, transient receptor potential channels, peroxisome proliferator-activated receptors, and G-protein-coupled receptors to halt cancerous growth.[14] A case study focusing on two cancer patients treated solely with cannabis, without any other cancer medications or treatments, revealed complete regression of tumors within three years. Thus, clinical evidence supports the notion that cannabis can contribute to tumor regression, and further studies are needed.[15]

Effects on cachexia and chemotherapy-induced anorexia

The mechanisms underlying appetite enhancement by cannabinoids are elucidated through a comprehensive examination of research and clinical trials. By interacting with the endocannabinoid system (ECS) and the nervous system, cannabinoids effectively address the diminished appetite experienced by cancer patients. Ghrelin, known as an appetite stimulant, plays a pivotal role in hunger induction.[16] Studies indicate that THC interacts with the brain, stimulating ghrelin production to promote appetite in cancer patients. This physiological interaction underscores a significant association between appetite regulation and cannabis.[17]

Furthermore, the dynamic regulation of brain signaling by the leptin hormone significantly influences appetite in cancer patients, leading to prolonged periods of starvation. Cannabinoids derived from the cannabis plant can actively engage with neuropeptide Y signals, ghrelin, and leptin hormone, thereby regulating appetite.[18]

Cachexia due to cancer and chemotherapy-induced anorexia is effectively controlled by cannabis, thereby reducing the likelihood of cachexia in oncology patients.

The hypothalamus, a crucial regulator of appetite in humans, can be influenced by cannabis cannabinoids, notably CBD and THC. These interactions between the hypothalamus and THC can stimulate appetite, triggering various neurotransmitters that alter appetite perception. Additionally, severe nausea, which can diminish appetite, is mitigated by THC's well-studied antiemetic effects, contributing to improved appetite in patients. Treatment-induced anorexia, a prevalent cause of appetite loss in cancer patients, particularly those undergoing chemotherapy, is effectively managed by cannabis. This

prevents malnutrition and loss of body mass in cancer patients.[19]

PHARMACOLOGICAL INTERACTIONS OF CANNABIS WITH CONVENTIONAL ANTI-CANCER TREATMENTS

Cancer patients often rely on a variety of medical treatments and anti-cancer drugs to manage their condition. These medications encompass drugs designed to counteract the effects of chemotherapy, provide pain relief, address anorexia, and aid sleep, among other functions.

Studies evaluating the pharmacokinetics of anti-inflammatories and analgesics reveal certain insights into their interaction with cannabinoids. NSAIDs, opioids, and paracetamols are among the most commonly used painkillers by cancer patients to alleviate symptomatic pain. These painkillers impact patients through cytochrome P450 enzyme metabolism.[20] Cannabis has been found to enhance the effectiveness of these drugs, potentially reducing the required dosage while maintaining their pain-relieving effects.

In cancer treatment, corticosteroids like triamcinolone, dexamethasone, and prednisolone are utilized for nausea management. However, THC and CBD can inhibit them at higher doses. Additionally, other medications such as NK-1 receptor antagonists and dopamine receptor antagonists may interact with cannabinoids.[21] Therefore, studies suggest the importance of ensuring proper dosing of these drugs when used alongside cannabis supplements, taking into account their potential interactions. Haloperidol, another antiemetic drug, relies on conversion by the enzyme CYP3A4. Research indicates that cannabinoids can significantly impact the efficacy of these drugs for cancer patients.[22] These studies suggest that while interactions may enhance the efficacy of some drugs, they may reduce effectiveness in others. Thus, the effects may vary depending on the doses and modes of administration of cannabis.

CANCER TREATMENT-POSSIBLE SIDE EFFECTS OF CANNABIS

Critically analyzing the potential side effects of cannabis, several studies focus on the long-term and short-term consequences. The practical application of cannabis in the field of oncology requires achieving a balance between the potential therapeutic effects and side effects for cancer patients. The prevalence of cannabis usage disorders has been rising, with 15% of substance abuse cases in California, USA, linked to cannabis. This underscores the importance of studying the integrated application of cannabis in medical treatments.[23]

Experts have expressed concerns regarding the interactions between anti-cancer drugs and cannabinoids derived from the cannabis plant. A study investigating the drug-drug interaction between cannabis extracts and cancer medications found that cannabis use reduced the efficacy of nivolumab immunotherapy, resulting in a decreased response rate for patients. The recorded reduction was 16% from 38%, indicating a significant decrease in effectiveness.[23]

Cannabis can adversely affect the efficacy of cytochrome P450 metabolism and membrane transporters, necessitating caution when administering these in parallel. Elderly patients are particularly vulnerable to adverse effects, as cannabinoids strongly interact with cytochrome P450 3A4 substrates, including drugs like bosutinib and tamoxifen.[24] The study suggests that cannabis treatment can modulate these chemotherapeutic drugs, potentially exacerbating negative effects in patients undergoing this class of medications.

Medications metabolized through phase 2 hepatic metabolism, such as glucuronidation, can be inhibited by active interactions with cannabinoids derived from the cannabis plant.[25] Consequently, the metabolizing processes for methotrexate, regorafenib, sorafenib, and imatinib are impaired, leading to ineffective excretion of these chemotherapeutics from the body. This poses a significant challenge in combining cannabinoids with anti-cancer medications. Furthermore, the cannabinoid metabolite 7-COOH-CBD (7-Carboxy-Cannabidiol) can inhibit resistance proteins and bile salt export pumps in breast cancer patients, hindering the excretion pathways utilized by chemotherapeutic drugs like paclitaxel.[26]

Experts aim to effectively co-administer various chemotherapeutics and cannabinoids derived from the cannabis plant without adversely affecting the health of cancer patients. When administering cannabis alongside these chemotherapeutics, medical practitioners must carefully assess side effects and adjust doses as necessary. Overdosing on cannabis can lead to overlapping effects such as nausea, headaches, and sleep disturbances.

ADMINISTRATION OF CANNABIS FOR CANCER PATIENTS

A comprehensive evaluation of the administration routes of cannabis for cancer patients reveals several considerations for optimizing cannabis treatment in oncology. Various products are utilized, each featuring distinct routes of administration. Oral solutions, transdermal products, oromucosal sprays, and capsules are among the most frequently employed methods for effectively administering cannabis to cancer patients with diverse conditions.[27]

Studies indicate that inhalation solutions constitute 50% of cases involving cannabis treatment, with their efficacy relatively higher compared to other forms.[27] However, oral administration results in lower bioavailability of cannabis cannabinoids compared to other routes, attributed to the involvement of first-pass metabolism. It

takes up to 90 minutes to reach maximal concentrations in plasma, with effects lasting up to 8 hours, depending on absorption rates through the epithelium.[28]

In inhalation administration, bioavailability depends on factors such as inhalation depth, lung capacity, breath holding, exhalation fraction, and heating temperatures. Plasma concentration peaks within a short period of 10 minutes in this method. Sublingual administration of oromucosal oil offers another impactful approach for cannabis administration, providing rapid relief within 30 minutes.[28]

However, oral administration yields longer-lasting effects, and the flavor of oils can be unpleasant for cancer patients, particularly those experiencing chemotherapy-induced nausea, posing challenges for patient acceptance. Inhalation devices can be expensive and inaccessible to some patients. Transdermal and rectal routes of administration are under further research to investigate their efficacy and limitations. Smoking cannabis is strictly prohibited due to potential lung damage caused by pyrolysis products, leading to inflammation and irritation in the throat, lungs, and nose.[29]

CONCLUSION

The legalization of medicinal *Cannabis sativa* should signify a significant stride toward enhancing its accessibility for cancer patients within the field of oncology. With an expanded array of pharmaceutical cannabis options and clear professional guidelines, the utilization of cannabis for oncological treatment can be effectively tailored to meet the needs of patients, thereby alleviating potential side effects and legal concerns. Many cancer patients grappling with various forms of the disease turn to the therapeutic benefits of medical cannabis as a means of self-managing numerous debilitating symptoms, including nausea and pain. To enhance patient well-being, safety, and the overall quality of oncological care, it is imperative to explore aspects such as drug interactions, routes of medical cannabis administration, potential side effects, and the unique conditions of individual patients. Through comprehensive understanding and effective implementation of these factors, the utilization of medical cannabis in oncology can be optimized to better serve patients.

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