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Cannabinoids: Do they alleviate pain in cancer patients?

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Abstract

More than half of cancer patients experience chronic pain, especially those who have the disease in an advanced stage. Cancer is a complex illness that causes substantial morbidity and mortality. The mainstay of traditional pain care is opioids, which, although useful for some people, usually lead to insufficient pain relief and a host of negative side effects, such as opioid-refractory pain and reliance. A growing number of people are interested in alternative treatment choices, including cannabinoids made from the cannabis plant, as a result of these difficulties. This review centers on the endocannabinoid system (ECS), a sophisticated network of cell signals that is essential for controlling a number of physiological and pathological functions, including the feeling of pain. Major cannabinoids including Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are being investigated for their potential to lessen the negative effects of chemotherapy as well as their analgesic and anti-inflammatory qualities. The promising role of cannabis in cancer pain management is highlighted in this review, which also discusses the need for more study to determine their safety, effectiveness, and incorporation into clinical practice.

Methods

A review of the literature was conducted using the WHO and PubMed databases. Keywords: oncology, chronic pain, pain, endocannabinoid system and cannaboids. A total of 33 papers or websites were included in the review.

Keywords

oncology, chronic pain, pain, endocannabinoid system cannaboids

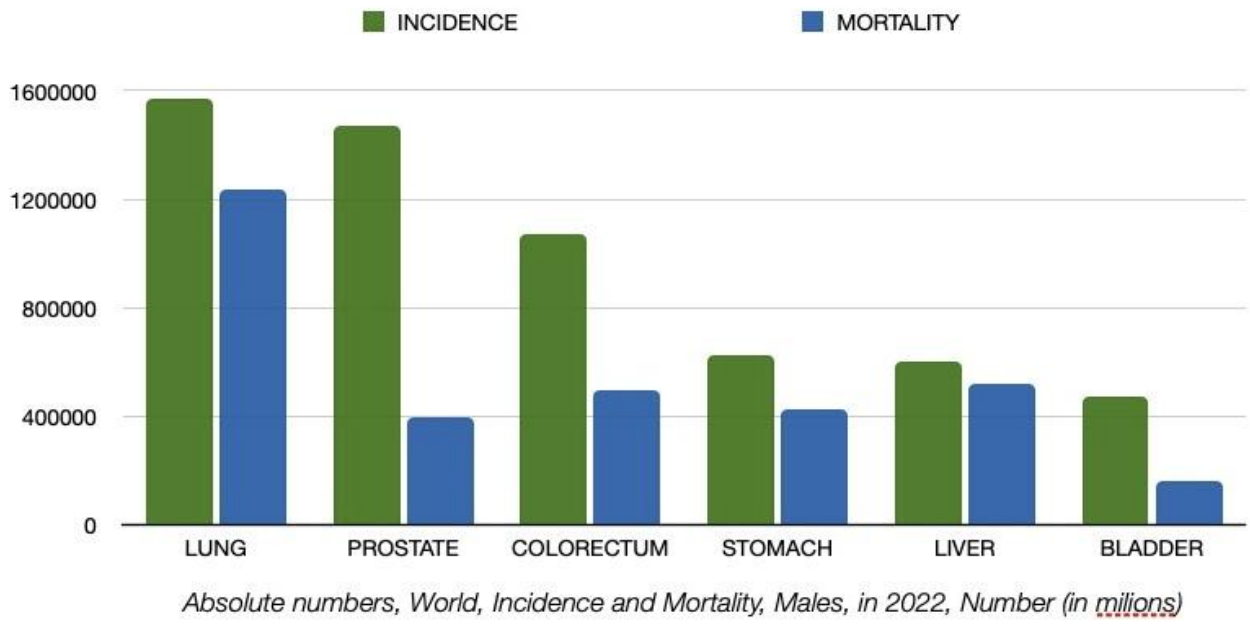
I. Introduction

Cancer is a broad category of disorders that can begin in practically any organ or tissue of the body when normal cells turn into tumor cells. Following that, aberrant cells proliferate out of control, cross normal borders, and infiltrate nearby bodily components and/or organs. A multi-stage process that often leads from a precancerous lesion to a malignant tumor. [1][3] More than 100 varieties of cancer appear. Medical professionals classify them based on the tissue type they impact and where they originate in your body. Cancer symptoms differ from individual to person. They are contingent upon the type and stage of your cancer. [9]

Figure 1. [9]

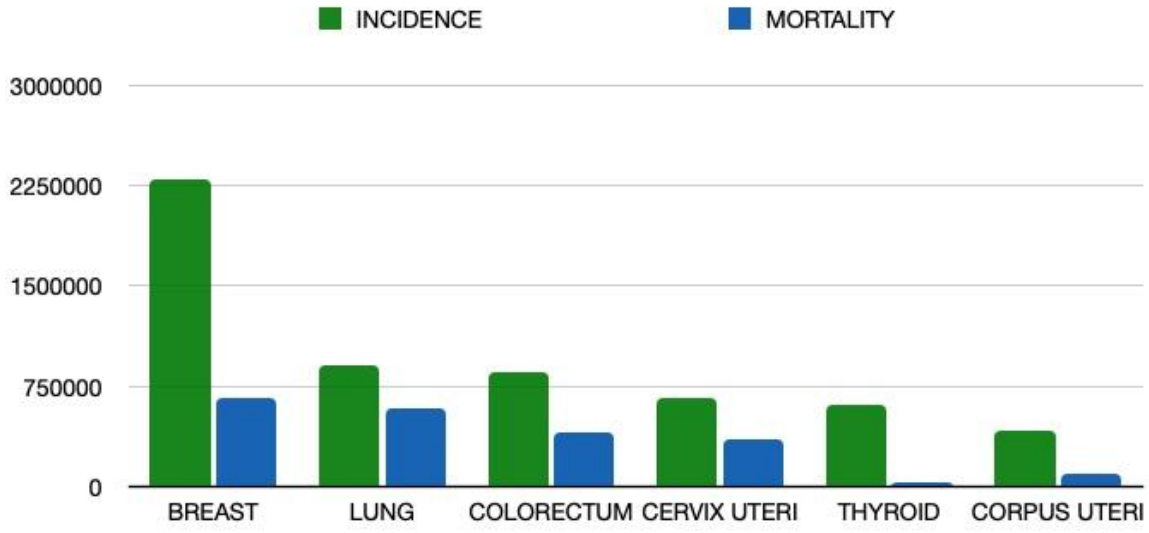
Since each type of cancer demands a different treatment plan, a proper diagnosis is necessary for suitable and successful treatment and after that establishing the treatment's objectives is a crucial initial step. [3] Treatments for cancer may have a number of adverse consequences. Depending on the treatment you receive and how well your body handles it, these side effects can change. [9] Surgery, radiation, and/or systemic therapy (chemotherapy, hormonal treatments, targeted biological therapies) are typically used as forms of treatment. When choosing a treatment plan, it is important to take into account the malignancy as well as the patient. To obtain the anticipated therapeutic outcome, the treatment procedure must be finished within the allotted time. Usually, the main objective is to either cure cancer or significantly extend life. Enhancing the patient's quality of life is another crucial objective. Support for the patient's physical, mental, and spiritual health as well as palliative care throughout the last stages of cancer might help achieve this. [3]

2. Rate of Cancer Incidence and Death Females and Males.



Absolute numbers, World, Incidence and Mortality, Males, in 2022, Number (in milions)

[14]



Absolute numbers, World, Incidence and Mortality, Females, in 2022, Number (in milions)

[17]

3. Pain- definition, ascpect of oncology patient

Pain is defined as an unpleasant emotional and sensory experience that is connected to or described in terms of tissue damage, even when it is not there. Despite their close relationship, this definition emphasizes that the concepts of pain and nociception are not interchangeable. The term "nociception" describes the process by which potentially hazardous stimuli are picked up by particular receptors (which differ according on the kind of environmental stimulus) and sent to the central nervous system. [4] There are many persons with various cancers who have commented on their excruciating chronic and neuropathic pain. A nociceptive component is released as a result of an inflammatory response at the site of injury, which is the primary cause of chronic pain in cancer patients. The nociceptive neurotransmission, which is projected from the spinal cord to different parts of the brain such the thalamus and parabrachial nucleus, is caused by the interaction of the nociceptive component with nociceptors located at the periphery of primary nerve fibers. This results in pain arousal. [11] Chronic pain (CP), including cancer-related pain, affects around 2 billion people globally. [28] Described as pain that is frequent or continuous for at least three months

[18], severely reducing quality of life and causing financial hardships. [28][8]Treatment for chronic pain is frequently challenging and can be quite incapacitating. [15] About 54.6% of people with cancer have pain, particularly those who are in advanced, metastatic, or fatal stages. In addition to lowering quality of life, unresolved pain in cancer patients disrupts comfort, capability, motivation, and relationships with friends and family. This leads to the development of anxiety, sadness, greater rates of depression [19][32], life dissatisfaction, sexual issues, and trouble performing daily chores. Patients are much more likely to consider suicide if their pain is not adequately treated. [32] Cancer pain may be caused by the cancer itself, its consequences, or therapeutic side effects (e.g., peripheral neuropathy caused by chemotherapy and post-operative pain). As cancer survivorship improves, it's critical to recognize the potential for persistent pain. [33] Reducing pain to a level that permits a satisfactory quality of life is the aim of cancer pain management. [2] A percentage of people with chronic pain issues stop receiving treatment because they don't always get enough relief from traditional pain management methods or because they have unpleasant side effects. This is where the interest in cannabis therapy as a supplemental or alternative therapeutic option for patients with chronic pain that is not responding to treatment began. [18]

II. Overview of Cannabinoids

1. An intricate cell-signaling system, the endocannabinoid system (ECS) controls a number of physiological and pathological functions in the human body, such as sleep, temperature, pain perception, immunological and inflammatory reactions, learning and memory, processing emotions, eliciting hunger and the urge to eat, and encouraging energy storage, which is why the majority of drug development research focuses on it. [31][25][6] It includes the accompanying endogenous ligands, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), at least two G protein-coupled receptors (GPCR), and the synthesis and degradation-related enzymes. Cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) are the two main GPCRs. [31] CB1 is widely expressed in the hippocampus, prefrontal cortex, and basal ganglia of the central nervous system. CB2 immune cells are more common in peripheral areas and less so in central ones. [26][31] After being stimulated by endogenous cannabinoids like N-arachidonylethanolamine (AEA) and 2-arachidonylglycerol (2AG) or exogenous cannabinoids like those in cannabis, CB1R and CB2R regulate the release of neurotransmitters, including dopamine. Through the activation of peripheral and central

CB1R and CB2R, the endocannabinoid system contributes to pain perception and regulation. [26] GPCRs CB1 and CB2 can mediate the effects of endogenous cannabinoids (such as the primary endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2-AG)), synthetic cannabinoid agonists and antagonists, and the more than 100 phytocannabinoids present in the cannabis plant, Cannabis sativa L. (e.g., Δ9-tetrahydrocannabinol (Δ9-THC), Δ8-THC, cannabinol (CBN), CBD, cannabigerol (CBG), etc.). [4] Finding and describing the cannabinoid receptors was the initial step in the discovery of endocannabinoids. The psychotropic component of cannabis, Δ9-tetrahydrocannabinol (THC), is one of the chemicals that researchers found bind to and function through the cannabinoid CB1 and CB2 receptors. These receptors' activation increases potassium influx and blocks voltage-gated calcium channels, which in turn prevents the release of neurotransmitters. [23] The majority of cannabinoids' actions on neural and non-neuronal tissues depend on the CB1 receptor being activated. [22] The ECS has consequently drawn sustained interest in clinical practice and pharmacology. The challenge of putting this knowledge into clinical practice is highly contentious, but research in animal models offer strong evidence that external regulation of the ECS has tremendous promise for the creation of analgesic medicines. Therefore, more research in the area is required to evaluate treatments, enhance clinical translation, and comprehend molecular causes. [4]

2. Cannabinoids' primary classifications

Endogenous cannabinoids, such as anandamide, are substances produced by our bodies that activate cannabinoid receptors. The two most studied endogenous cannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG). In essence, phytocannabinoids are cannabinoids found naturally in cannabis plants. C. sativa is the most widely used, fruitful, and thoroughly researched source of phytocannabinoids. Human-made mind-altering substances called synthetic cannabinoids, sometimes referred to as herbal or liquid incense, are sold as liquids or poured on dried, shredded plant material for smoking. [5] The two main phytocannabinoids found in cannabis, Δ9-tetrahydrocannabinol (THC, which has the potential to be intoxicating) and cannabidiol (CBD, which is not), can be used to categorize the chemotypes of the plant. [21] To produce therapeutic effects, patients can receive cannabis sativa and its derivatives in a variety of ways. [27][29] Cannabis-based product administration methods include sublingual application of cannabis-infused sprays, inhaling smoke from burning cannabis, and inhaling aerosolized cannabis. [29]

3. Scientific reports on the effects/ side effects of cannabis and how it differs from opioids.

A non-psychoactive cannabinoid found in the cannabis plant Cannabis sativa, cannabidiol (CBD) has been linked to analgesic, anti-inflammatory, antioxidant, anticonvulsive, and ansiolitic properties. This suggests that CBD may find use in clinical settings, including cancer. The cannabis plant contains a cannabinoid called cannabidiol (CBD), which has garnered attention since it is not intoxicating and shows promise in treating pain. [4][24] In order to prevent vomiting, cannabinoids interact with centrally placed CB1 and 5-HT3 receptors as well as those in the dorsal vagal complex (DVC), which is where vomiting is triggered. [13] Since they have analgesic and antiemetic effects, cannabinoids and cannabinoid-based formulations have primarily been used in palliative care, reducing the side effects of chemotherapy [7] [10] and stimulate appetite. [13] The most often used medications to treat pain related to cancer are opioids. As a result, in addition to the negative effects of opioids, almost one-third of patients on opioids experience opioid-refractory cancer pain. This emphasizes the need to develop novel medications that can be taken either on their own or in conjunction with opioids. [20] Opioids are prescribed to one in three individuals with chronic pain; nevertheless, growing awareness of the negative effects of long-term opioid usage and a greater appreciation for their, at best, limited benefits have sparked interest in alternatives, such as medicinal cannabis. [16] In particular, gastrointestinal, neurological, and psychological side effects seem to be modest to moderate when using cannabis medication to treat chronic pain. Although it is believed that major side effects are uncommon, there is insufficient data to draw firm conclusions in this regard because of often uneven reporting. [18] Frequent adverse effects of products containing tetrahydrocannabinol (THC) include weariness, dry mouth, dizziness, and moderate disorientation; more severe side effects include tachycardia, orthostatic hypotension, severe confusion, and paranoia. In order to reduce the negative effects of THC-based products, especially in older persons and those who are unfamiliar with cannabis and/or cannabinoids, these products should be begun at a low dose and adjusted gradually. [30] The use of cannabis plants and their constituents, known as cannabinoids, as adjuvant analgesics to treat chronic pain has long been controversial. [15] The neuropsychiatric effects of opioids may be worsened by cannabis. Adult cancer patients who consume large quantities of cannabis and/or other cannabinoids do not have the same risk of respiratory depression that comes with opiate overdoses. [30] In vitro and in vivo, cannabinoids have been shown to activate cannabinoid receptors, which in turn cause apoptosis and decrease tumor cell proliferation, angiogenesis, and invasion. To support the

Function	Cannabioids	Opioids
Main action	Varies according on the particular cannabinoid- e.g. CBD use suggests analgesic, anti-inflammatory, antioxidant, anticonvulsant, and anxiolytic effects [4]	Reduction of pain [4]
Mechanism	Connects to the body's and brain's cannabinoid (CB) receptors [4][10]	Attaches itself to opioid receptors in the body and central nervous system [4][8]
Risk	Can be psychoactive (THC, CBD isn't) [4][7]	Addiction, excessive dosage, death [4]
Additional adventages	Management of pain, inflammation, anxiety, antioxidant, anticonvulsive [4][24], reducing side effect of chemotherapy and stimulate appetite [13]	Pain control [4]
Side effects	Weariness and sleepiness, diarrhea, dry mouth, nausea, and decreased appetite [4]	nausea, constipation, and sleepiness [4], respiratory depression [13]

introduction of cannabis as anticancer medicines, more research is required. [13] Relieving chronic pain is one therapeutic area where medical marijuana may offer the most promise. [12]

Conclusion

In conclusion, despite the use of traditional treatments, a significant percentage of patients get insufficient pain relief from cancer-related chronic pain, making its management a crucial issue in oncology. Since the endocannabinoid system (ECS) controls pain perception and is impacted by cannabinoids like CBD and THC, it is an appealing target for therapeutic intervention. These substances have been demonstrated to have analgesic, anti-inflammatory, and antiemetic qualities, providing a comprehensive strategy for reducing cancer pain and enhancing patients' quality of life. Because of their distinct pharmacological properties, cannabinoids may work in concert with opioids to reduce the risk of side effects and reliance by enabling lower dosages of opioids. Further highlighting their potential utility in palliative care, cannabinoids have also been shown to be able to reduce common chemotherapy-related symptoms like nausea and appetite loss. Notwithstanding the encouraging results, there are still difficulties with using marijuana in therapeutic settings. Caution in their use is required due to the possibility for negative effects, the complexity of dose, and the heterogeneity in individual reactions to cannabinoid therapy. THC side effects like lightheadedness, dry mouth,

and cognitive decline emphasize the importance of cautious titration, especially for elderly patients or those who are not experienced with cannabis products. Additionally, there are significant differences in the legal and regulatory frameworks now in place for medical cannabis, which affect patient education and accessibility. Thorough clinical trials are necessary to fully grasp the promise of cannabis in the treatment of cancer pain. Clarifying the ideal dosage schedules, long-term safety profiles, and particular patient groups who might profit most from cannabis therapy should be the main goals of these investigations. In order to develop targeted cannabinoid-based therapeutics, research should also attempt to elucidate the processes by which cannabinoids produce their analgesic benefits. In conclusion, the incorporation of cannabis into pain treatment techniques is a viable way to improve patient care as the field of oncology develops further. Cannabinoids have the potential to greatly enhance the quality of life for cancer patients navigating the intricacies of their illness and treatment by resolving the drawbacks of conventional pain management techniques and broadening the therapeutic toolkit accessible to physicians.

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