Analyzing The Risks, Benefits, and Therapeutic Potential of Cannabis And Cannabinoids in Tumor Therapy – A Review

Poorti Sharma [1], Lukeshwari Sahu [1]

Abstract

Cancer patients dealing with metastatic tumors often turn to Cannabis and cannabinoids to alleviate symptoms and enhance their quality of life. Cannabis is used to address issues like pain, nausea, appetite loss, stress, sleep difficulties, and emotional distress for individuals facing cancer. While cannabinoids, such as CBD, may lead to side effects like fatigue, disorientation, psychological effects, and a dry throat, their usage has surpassed scientific research on both positive and negative effects. This study focuses on developing and validating a Nanotechnology-based methodology (NT-CBD) to measure active components in different Cannabis specimens, including both recreational and drug-type varieties. Fiber-type plant varieties are also examined for non-psychoactive chemicals with potential medicinal and dietary supplement applications. This review paper aims to understand the potential negative impacts of Cannabis and cannabinoids on normal human function, discussing both therapeutic uses for specific medical conditions and potential short-term and long-term adverse effects. Recognizing these effects is crucial, and training healthcare providers to guide cancer patients in the proper use of Cannabis can enhance safety and effectiveness, ensuring optimal symptom relief.

Keywords: Cannabis, Cannabinoids, Nanotechnology, Tumor therapy.

Significance | Study explores Cannabis use by metastatic tumor patients, analyzing active components, addressing gaps in research, and promoting informed medical guidance.

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1. Introduction

Cannabis, also known as marijuana, is a biennial anemophilous plant belonging to the Cannabaceae family. It encompasses all species of marijuana and contains over 100 active chemical components called cannabinoids (Cherkasova, V., 2022). Among these cannabinoids, Delta-9-tetrahydrocannabinol (THC) stands out as the most psychotropic, possessing energy euphoric, pain-relieving, and anti-emetic properties, making it a potential medicine (Baroi, S., 2020).

Utilized in textiles and food, cannabis is rich in CBD or similar compounds and low in delta-9-THC. Drug-type cannabis plants commonly contain THCA and THC, while fiber-type plants include cannabinoid acids like CBGA and CBDA, along with their reduced forms such as CBG and CBD (Sheriff, T., 2020) (Zenone, M., 2020). Cannabis has shown promise in alleviating cyclic symptoms of discomfort, anxiety, motion sickness, and depression after tumor detection and treatment, addressing concerns about pain, sleep disturbances, and overall quality of life (Gonçalves, E. C., 2020).

Research indicates that the cannabinoid CB1 acts as a catalyst for activating monocyte-activated protein kinase (MAPK) and inhibiting adenylate cyclase. Both cannabinoid receptors, CB1 and CB2, are G proteins linked positively to potassium channels and negatively to N-type and P/Q-type calcium channels (Turgeman, I., 2019) (Xiong, X., 2022). CB1, spread across the nervous systems

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of the body, is linked to the psychotropic effects of THC. Activation of CB1 receptors at direct afferent regional termini reduces irritability and pathogenic cytokine production (Johal, H., 2020).

In immunological tissues, CB2 receptors are found on peripheral monocytes, B, T, and mast cells. Agonism at CB2 reduces inflammation-related discharge, lymphocyte bleeding, and afferent endpoint desensitization (Ritter, S., 2020). Peripheral CB1 and CB2 receptor agonism in pain management reduces heightened terminal excitability caused by local damage and inflammation. Cannabis, through the pharmacologic processes of THC and CBD, may help manage cancer symptoms and adverse effects by activating cannabinoid receptors (Yekhtin, Z., 2022) (Sadhu, P. K., 2020). Ongoing exploration of cannabis for symptom relief in cancer patients emphasizes the need for further research on safety and effectiveness in both recipients and survivors (Uziel, A., 2020) (Mahmoudinoodezh, H., 2022).

Nanotechnology has revolutionized the targeted treatment of tumor cells and tissues, enabling the safe administration of chemotherapy, radiation, and contemporary immuno- and genetic therapies to tumors (Hasan, N., 2022) (Fraguas-Sánchez, A. I., 2020) (Lipnik-Štangelj, M., 2020). In addition to its impact on conventional cancer treatments, nanotechnology plays a crucial role in enhancing the bioavailability and thermodynamic longevity of cannabis. This interdisciplinary field brings together experts from various disciplines, including physicists, chemists, engineers, IT professionals, computer scientists, mathematicians, material scientists, and biologists (Reddy, T. S., 2023).

Nanotechnology finds applications in diverse fields such as electronic devices, magnetics, optical science, IT, material creation, and medicine, with nanotechnology-based materials and gadgets driving numerous innovative medical applications (Afrin, F., 2020).

This review focus is twofold: firstly, advocating for evidence-based therapy and steering discussions by examining the risks and benefits of cannabis, encompassing THC and CBD; secondly, research reveals that cannabinoids in both natural and synthetic cannabis formulations can enhance specific medical conditions, while adopting suggested systems in cannabis formulations offers advantages such as increased efficacy, improved bioavailability, reduced toxicity, and controlled and targeted distribution.

2. Literature Review

A compilation of diverse research studies sheds light on various aspects of cannabis and its potential applications. Hardy's study (2020) focused on a comprehensive trial, utilizing a randomized, double-blind, placebo-controlled approach to assess the impact of increasing dosages of an oral 1:1 THC/CBD cannabis mixture on advanced cancer symptoms. The findings aim to equip doctors with valuable data to guide patients considering cannabis treatment.

Rabgay's research (2020) investigated randomized controlled trials, specifically examining the analgesic benefits of cannabis or cannabinoids. Employing a random-effects model to combine treatment effects, the study suggests that manufacturers could leverage these results to develop products maximizing the pain-relieving effects of cannabis.

Krüger's study (2022) explored the phytocannabinoid and nutritional profiles of low-THC Cannabis sativa, emphasizing the need for clear packaging and labeling of culinary cannabis goods to distinguish them from non-cannabis alternatives. This, along with tamper-evident wrapping, is proposed to reduce the appeal of such products to minors.

Riboulet-Zemouli's research (2020) takes a philosophical approach, combining insights from various sources to benefit fields such as investigation, packaging, customer safety, drug surveillance, healthcare guidelines, and harm reduction measures. The study's interdisciplinary nature offers a holistic perspective on cannabis-related considerations.

Heblinski's study (2020) delves into the efficacy of terpenoids, phytocannabinoids, and endocannabinoids using inducible HEK Flp-In T-Rex cells. The results indicate no activation of specific channels, providing insights into the interactions between these compounds.

Khodadadi's research (2020) utilized Poly(I: C) to simulate severe viral infections, showcasing CBD's potential to safeguard respiratory tissues, reduce cytokine storms, and restore immunological regulation during Acute Respiratory Distress Syndrome (ARDS). These findings suggest a potential avenue for treating conditions like COVID-19.

3. The Potential of Cannabinoids in Cancer Treatment

Currently, there is limited evidence supporting the effectiveness of cannabis-based medicines in treating malignancies or tumors. In pre-clinical laboratory trials, the cannabis compounds THC and CBD have demonstrated promise for inhibiting the growth of glioblastoma (GBM) cells, leading to the eventual death of tumor cells and disrupting blood circulation to the tumor (Robinson et al,2016). Additionally, cannabinoid-containing pharmaceuticals may offer potential benefits in treating certain rare seizures, chemotherapy-induced symptoms, vomiting, and wasting. In adults, cannabis poisoning primarily manifests as anxiety, mental health issues, and cognitive impairments affecting decision-making, awareness, and motor control. It's important to note that synthetic cannabinoids, often mistaken for cannabis, differ significantly (Bifulco et al ,2015). While hundreds of cannabinoids have been identified, tetrahydrocannabinol (THC) and

cannabidiol (CBD) are the most widely recognized, largely due to THC's psychoactive properties (ko et al,2016). Cannabinoids play various roles in the brain, including modulating movement and reward networks in the cerebral cortex, influencing memories and learning, and regulating hunger in the pituitary gland. Despite ongoing research, the full scope of cannabis-based medicines and their potential therapeutic applications for tumors remains an area of exploration (Birdsall et al,2016).

The historical use of cannabis for both recreational and therapeutic purposes has a brief yet intriguing narrative. Ongoing investigations, spanning the past and present, have unveiled the biological mechanisms underlying Cannabis and its unique chemical constituents, known as cannabinoids, which disrupt the body's normal processes (Davis et al,2016). Cannabinoids, a class of 21-carbon compounds exclusive to the Cannabis plant, exhibit diverse effects. Smoked cannabis contains up to 61 individual cannabinoids, with cannabidiol (or "delta-9 THC") emerging as the primary psychoactive compound responsible for the drug's addictive and psychoactive qualities (Müller et al,2017). Unlike specific interactions with membrane-associated receptors on cell membranes, cannabinoids induce physiological and behavioral changes through nonspecific conversations. Central to these interactions are the two main cannabinoid receptors, CB1 and CB2 (Javid et al,2016).. The CB1 receptor is particularly associated with a broad spectrum of effects induced by cannabinoids. This interplay between cannabinoids and receptors sheds light on the intricate mechanisms that contribute to the pleasurable and therapeutic aspects of cannabis use, forming a captivating chapter in its history (Skosnik et al,2016).

Cannabinoids exert various crucial effects, demonstrating potential in selectively eliminating tumor cells while exhibiting a lower likelihood of harming surrounding non-transformed cell types. Notably, cannabinoids have been observed to shield normal astroglial and oligodendroglial cells from apoptosis while instigating cell death in glioma cells through CB1 receptors. Animal studies further underscore cannabis's protective role against various tumor types (Console-Bram et al,2012).

Two pivotal mechanisms for controlling aberrant cell growth, autophagy, and apoptosis, are influenced by cannabinoid interactions. Both CB1 and CB2 receptors play a role in the autophagic action of cannabis, documented across numerous significant malignancies (Latorre et al,2015). Disruption of the autophagic function is noted in CB1-deficient mice, while the CB1 receptor's palmitoylethanolamide enhances phagocytosis in human microglial cells. CB2 receptors have demonstrated a reduction in cell survival for hepatic carcinoma transplanted cells, highlighting their potential anti-cancer impact, attributed to macro-autophagy induction and eventual apoptosis through the endoplasmic reticulum stress response (Perez-Gomez et al,2015).

Research suggests that CB1 and CB2 receptors emerge as promising targets for inducing apoptosis in small-cell cancer cells. In the case of CBD, it has shown the potential to trigger apoptosis in estrogen-dependent cancer cells during pre-clinical stages of the disease, with minimal impact on normal ductal cells. Intriguingly, this effect does not depend on cannabinoid receptors CB1 or CB2, nor the vanilloid system. These findings contribute to the evolving understanding of cannabinoids' intricate role in cancer treatment (Vercelli et al,2014).

Synthetic cannabis agonists exhibit the ability to stimulate ceramide production and activate tumor necrosis factor receptors, ultimately promoting apoptosis. Additionally, studies have demonstrated that the activation of CB1 receptors can suppress critical tumor survival pathways, such as RAS/MAPK, ERK1, and PI3K/AKT, in various colorectal cancer (CRC) cells. Furthermore, CBD, functioning as an inhibitor of GPR55 and an imperfect agonist of CB1/CB2 receptors, may hinder mTOR/AKT transmission and induce proapoptotic NOXA in CRC cells. CBD also inhibits the synthesis of apoptosis-inhibiting proteins in colorectal tumor cells by downregulating survival and c-FLIP (Velasco et al,2016).

Promising research is underway regarding the medicinal use of synthetic cannabinoids, mimicking the effects of their natural counterparts. Marijuana has been employed for therapeutic purposes, addressing issues such as nausea, vomiting, immune system activation in infections, and alleviating symptoms associated with blindness and neurological diseases (Orellana-Serradell et al,2015). Patents and scientific investigations highlight the cannabinoid system as a potential therapeutic target for neurological conditions. The activation of CB1 and CB2 receptors with non-psychoactive doses of natural or synthetic antagonists shows promise in clinical trials, mitigating the detrimental actions of beta-amyloid peptides, reducing tau degradation, and fostering inherent repair processes in the nervous system (Pecze et al,2016).

In experiments involving cultured neurons from fetal rats, WIN55,212-2 demonstrated an increase in the production of reactive Cu/Zn SOD and a reduction in inflammation induced by amyloid 1-42 (Petrocellis et al,2013). Synthetic marijuana chemicals like WIN55,212-2 may play a preventive role in dopaminergic neuronal death caused by nervousness, oxygen depletion, and activated microglial cells, particularly in the context of schizophrenia. These findings contribute to the evolving understanding of the therapeutic potential of cannabinoids, both natural and synthetic, in addressing neurological and psychiatric conditions (Pineiro et al,2011).

Cannabinoids have demonstrated a spectrum of effects in pre-clinical research at various stages of cancer development. These

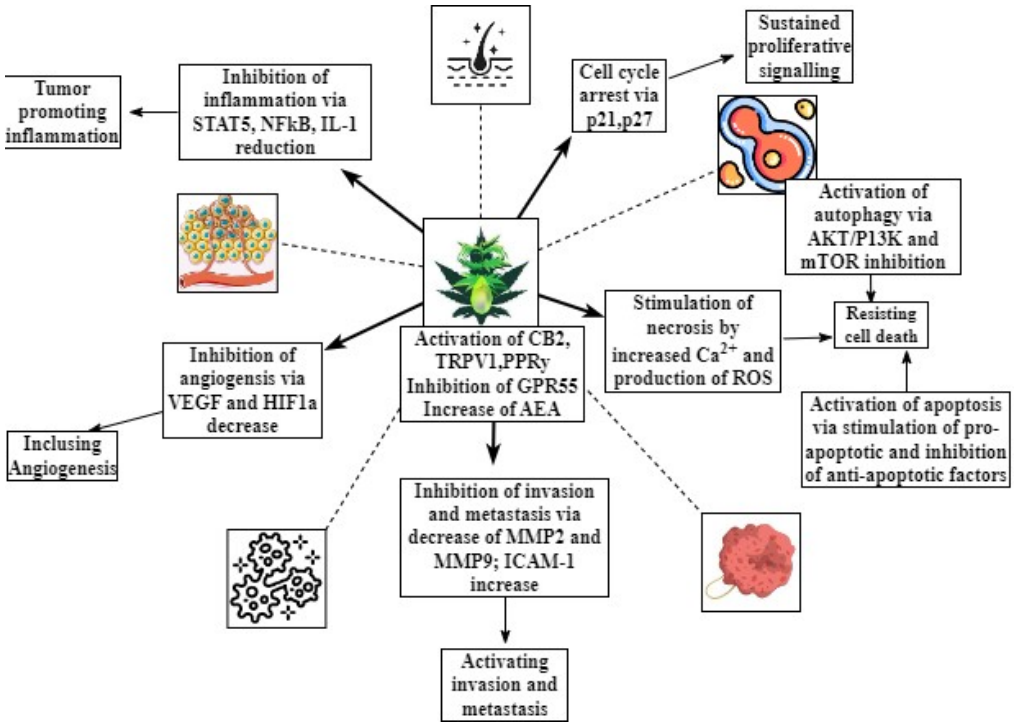

Figure 1. Effects of Cannabis and Cannabinoids in Tumor Therapy

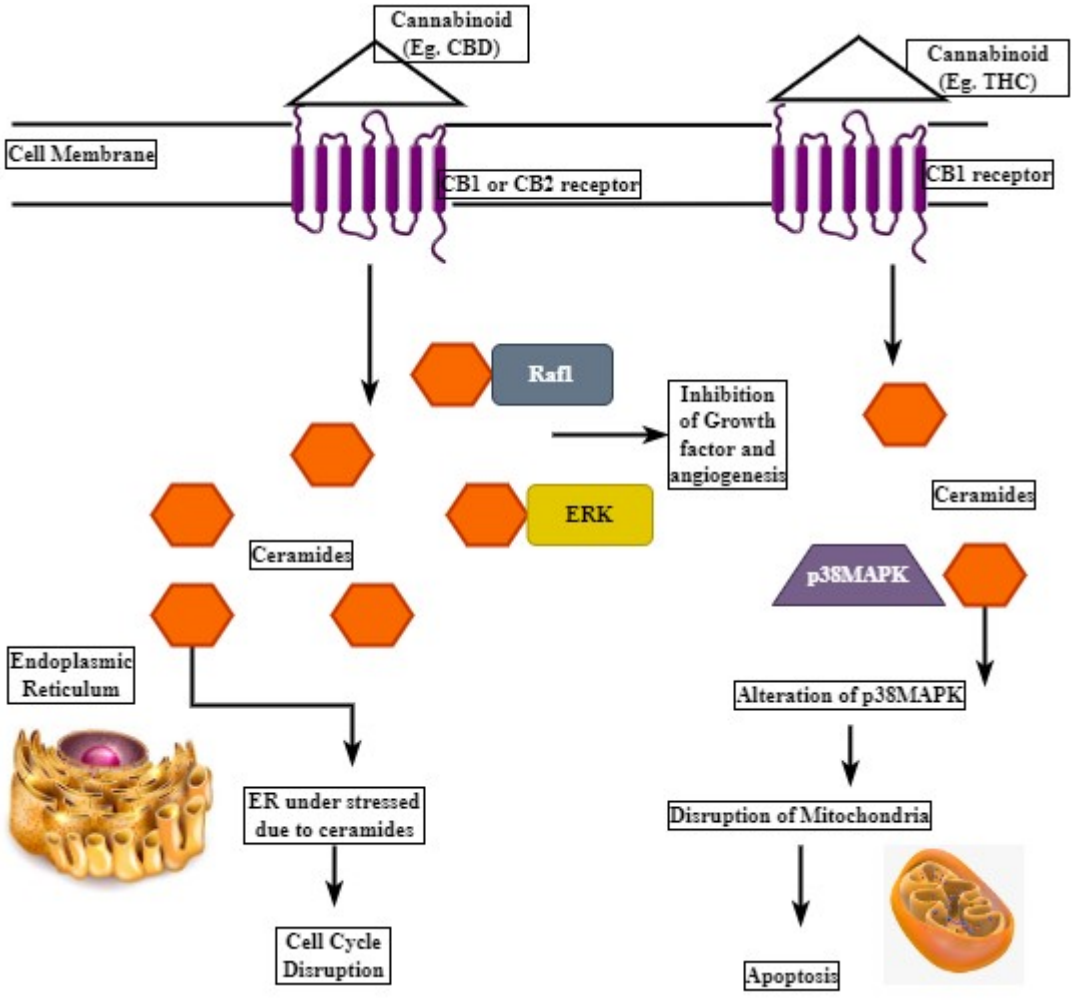

Figure 2. Cannabinoids' anti-cancer effects in cellular ceramide levels.

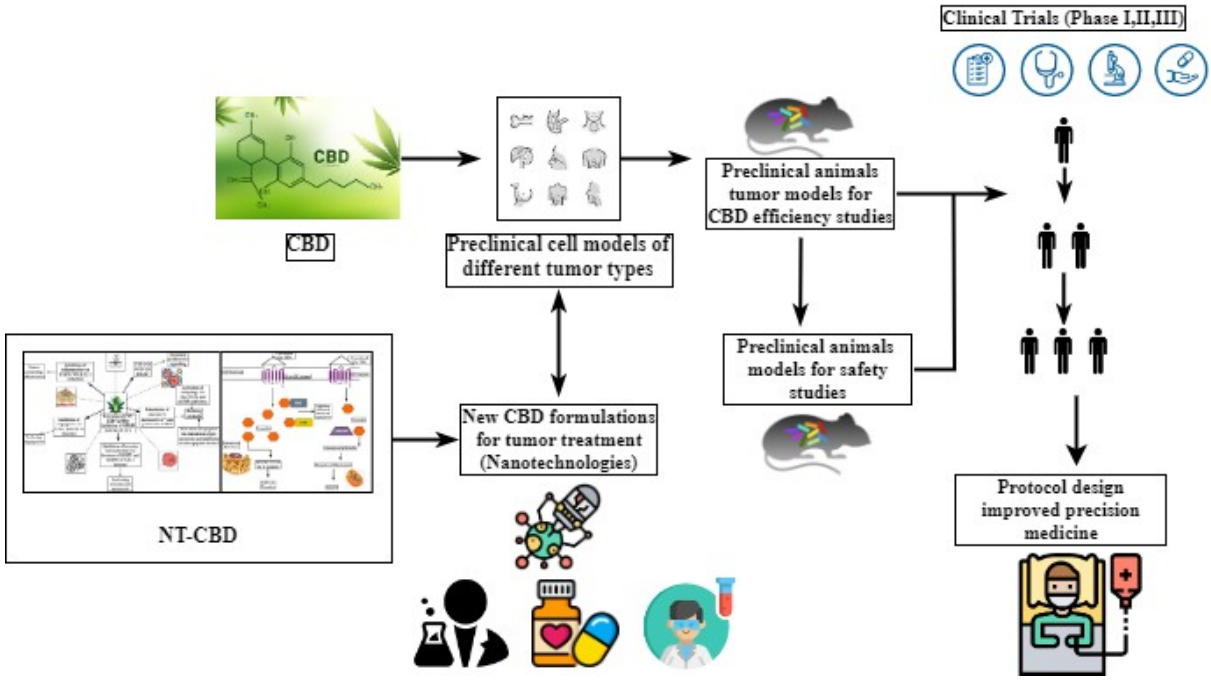

Figure 3. Nanotechnology Tumor therapy with CBD

effects encompass the inhibition of expansion, assault, swelling, chemoresistance, as well as the activation of apoptosis and autophagy (Mukhopadhyay et al,2015). Moreover, cannabinoids contribute to the enhancement of tumor immune surveillance. Numerous studies highlight their potential to impede tumor cells' growth, movement, adhesion, invasion, and angiogenesis, showcasing direct anti-tumor actions (Preet et al,2011). In addition to their standalone anti-tumor properties, cannabinoids have shown promise in synergizing with traditional anti-tumor medications, enhancing their effectiveness. This makes cannabinoids a compelling treatment option for common cancer types, including prostatic and others. While cannabinoids have predominantly been employed for palliative care in cancer patients, noteworthy anti-tumor effects have been observed in cell culture and animal experiments. These findings underscore the multifaceted impact of cannabinoids on cancer-related processes and their potential as a therapeutic avenue in addressing cancer progression (Freund et al,2016).

Furthermore, cannabinoids play a crucial role in signaling cell death in C6 glioma cells through a pathway involving cannabinoid receptors, induction of Raf1/extracellular signaling-regulated kinases, and ceramide accumulation (Chakravarti et al,2014). The structural analog of anandamide, R(p)-methanandamide, and the synthetic CB2 agonist JWH-015 have demonstrated the ability to inhibit the proliferation of PC-3 cells, with JWH-015 additionally triggering de novo production of ceramide (Zhao et al,2012). This process contributes to the induction of cannabinoid-mediated cell death. Notably, JWH-015 has shown a significant reduction in tumor development in mice by activating the JNK pathway and inhibiting the Akt pathway. Medicinal-grade synthesized cannabidiol has been proposed as a potential therapy for tumors, showcasing promising outcomes (Malfitano et al,2011). In 92% of cases involving malignant tumors, researchers observed a clinical response, characterized by tumor shrinkage and a decrease in the quantity of circulating tumor cells, with no adverse effects. WIN55,212-2 has exhibited apoptotic effects on various human tumor cell lines, including those originating from the lungs, testes, and neoplasm (Velasco et al,2015).. Figure 3 illustrates the mechanism through which ceramide triggers cancer cell death. Moreover, natural cannabinoids like JWH015 and BML190, selective CB2 receptor agonists, partly suppressed keratinocyte reproduction, and this inhibition was further observed with another cannabinoid, HU210, an insensitive CB receptor agonist. As CB1/CB2 receptor inhibitors were unable to impede the action of these cannabinoids, it becomes evident that they hold therapeutic benefits against diseases characterized by excessive epidermal keratinocyte growth. These findings contribute to the growing understanding of cannabinoids' potential in targeting specific pathways for cancer treatment (Caffarel et al,2012).

The past decade has witnessed the emergence of new theranostic potential in drug creation, owing to advancements in effective nano-synthesis technologies. Nanotechnology-based drug-delivery techniques have paved the way for authorized medicines, prodrugs, and diagnostic materials in various therapeutic areas (Andre et al,2016). These innovations leverage nanosized arbitrary, chemical, structural, and photonic features of active substances, enhancing efficacy and minimizing unwanted side effects.

The unique characteristics of nanoscale systems enable precise targeting of specific cells and tissues throughout the body, revolutionizing diagnostics and treatment. A notable development in this realm is the utilization of nanoparticles enveloped with cell membranes, representing a promising yet underdeveloped biomimetic technology for efficient medication delivery (Romano et al,2016).. This approach holds potential for further advancements in enhancing the precision and effectiveness of therapeutic interventions, marking a significant stride in the evolution of drug delivery and theranostic applications (Grotenhermen et al,2012).

Advanced therapeutic approaches, including the utilization of cannabinoid nano-delivery devices, have been employed in both in vitro and in vivo settings. Ongoing research initiatives are actively developing nanoparticles for the nano-delivery of cannabis, cannabinoids, and endocannabinoid system (ECS) components (Hong et al,2015). A noteworthy strategy involves cannabinoid nanoconjugates within a versatile nanocarrier, offering a tailored approach depending on specific needs and intended routes of administration. These nanostructured carriers may encompass biological, inorganic, or hybrid compositions, such as liposomes, microbial polyplexes, polymersomes, and ceramic nanoparticles. Their attributes, including enhanced stability, protection against degradation, and taste concealment, are crucial considerations for the evolving cannabis industry (McAllister et al,2015).

While progress in nanoengineering is ongoing, managing medication solubilities by modifying nano object surfaces holds promise. This approach extends the beneficial movement time of medications, reduces biodistribution, and enables gradual drug release, mitigating hypersensitivity. An effective strategy involves coupling the nano object's surface with biologically relevant molecules like amines, carbohydrates, and peptides specific to the target environment and its receptors (Cridge et al,2013)..

Investigations into the systemic consumption of THC and CBD, utilizing a free-moving rat paradigm, have explored the impact of lipid elements in self-emulsifying systems for drug delivery. Results highlight the complexity of predicting how different lipid types affect cannabis absorption. Notably, Type I formulations showed consistent absorption effects between long- and middle-chain lipids, while Type II preparations demonstrated a considerable increase (Shrivastava et al,2011).

Cannabinoids, particularly cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), have undergone intensive study as potential cancer therapies. Despite THC's psychotropic limitations, CBD has emerged as a focus due to its absence of such effects and a robust anti-cancer impact, surpassing that of THC (Solinas et al,2013). For those interested in delving deeper into CBD's biological effects in various tumor types, recent comprehensive studies provide valuable insights. CBD's antitumoral efficacy, examined across diverse tumor cells, underscores the necessity of considering causal relationships in understanding its anti-cancer activity (Sharma et al,2014).

Recent research focuses on cannabinoids like CBD and THC for their anti-tumor efficacy. CBD, in particular, has shown strong anti-cancer effects without the psychotropic characteristics of THC. Mathematical models are being developed to understand the dynamic interactions between tumors and the immune system, providing insights into tumor recurrence and dimension fluctuations (Hanlon et al,2016).

Equations (1), (2), and (3) in the model describe the antigenicity, immunological death rate, antibody cell growth rate, and various factors influencing tumor dynamics. The mathematical framework helps visualize key tumor concepts, providing a theoretical basis for understanding the complex interactions between tumors and the immune system (Castaneto et al,2014).

A theoretical framework has been developed by integrating (PM-2) kinetics with tumor-immune factors, providing a comprehensive understanding of the dynamic interplay between tumors and the body's defenses. The model's straightforward structure facilitates the visualization of key tumor concepts, including tumor recurrence and dimension fluctuations (Debruyne et al,2015).. The conceptualization is expressed through the following set of mathematical equations:

$$\frac{qE}{qt} = fS - \mu_2 E + \frac{n_1 E P_M}{d_1 + P_M} + w_1 \quad (1)$$

$$\frac{qS}{qt} = b_2(1 - vS)S - \frac{cES}{d_2 + S} \quad (2)$$

$$\frac{qP_M}{qt} = \frac{n_2 ES}{d_2 + S} - \mu_3 P_M + w_2 \quad (3)$$

Where in Equations (1), (2), and (3), f represents the antigenicity, d_2 -Half-sat. for tumor elimination, μ_2 Rate of immunological death of cells n_1 -Rate of antibody cell growth, Tumor incidence rate (b_2) Tumor dynamical growth in capacity (v), Tumor elimination period d_3 Half-sat. of growth rate n_2 The halfway point of the activator chemical d_1 Half-sat. for propagation period When E is the number of receptor cells, S is the number of malignant cells, and PM-2 is the concentration (Otrubova et al,2011). To simulate the tumor's antigenicity, the paper uses the parameter f. n_1 is the maximum quantity produced by the receptor cell, and d_1 is the semi-saturation point; the following Equation in (1) indicates natural death (Ravi et al,2014). Third, IL-6's impact on promoting cell proliferation. Lastly, w_1 lymphokine-activated killer (LAK), lymphocytes, and lymphocytes that invade tumors (TIL) are receptor cells originating tumor development represented by the first component in Equation (2) (Winkler et al, 2016). In contrast, clearance by immune response cells is meant by the second term, both at a rate of c. This constant pace, d_1, means the robustness of the body's defenses. The rate of change in PM concentration is given by Equation (3), where d_2, d_3 c, and n_2 have equivalent meanings as d_1 and n_1. Degradation of PM-2 at a rate of μ_3 is indicated by the number 3. Last, w_2 represents an extracellular source of receptor cells like LAK or TIL cells (Kaur et al, 2016).

4. Cannabinoids, Nanocarriers, and Cancer Treatment Innovations

This review explores THC and CBD in tumor treatment, seizures, chemotherapy, and neurological diseases, highlighting diverse cannabinoid effects and nano-delivery advancements. Various therapeutic approaches, including the utilization of cannabinoid nano-delivery devices, have been employed in both in vitro and in vivo settings (Wang et al,2012). Numerous research teams are actively developing nanomaterials designed for the nanotherapeutic administration of cannabis, cannabinoids, and components of the endocannabinoid system. Within these methodologies for cannabinoid delivery system development, cannabinoid nanoconjugates housed in multifunctional nanocarriers play a crucial role. These nanocarriers, which can be metallic and adopt either inorganic, organic, or hybrid compositions, are tailored based on patient requirements and the intended delivery route (Čufar et al,2016).

In pre-clinical tests, nanoparticles and nanoemulsions derived from hemp oil have exhibited promise as a viable alternative to traditional formulation methods, offering a solution for administering medications with challenging bioavailability. Notably, the encapsulation of CBD, a non-psychoactive cannabinoid found in cannabis, in lipid nanocapsules (LNCs) resulted in the successful in vitro elimination of a human tumor cell line (Slovenia et al,2016). Consequently, drug-delivery mechanisms employing nanostructured phospholipid carriers, with adaptations of nanoparticle techniques, are preferred over conventional methods for cannabis and cannabinoid applications.

Regarding the dataset, the paper compiled information from the leafly.com/strains database, accessible on www.kaggle.com (Slovenia et al,2017). The dataset includes both raw and cleaned CSV files, with the data dictionary outlining the sorted columns. The exploration of cannabis varieties aims to identify common characteristics. Additionally, there is a suggestion to scrape photos of strains, particularly popular ones, from the website and

potentially train a Convolutional Neural Network (CNN) to assess strain characteristics based on the images (Ferlay et al,2019).

a) Resistance to drugs in tumor patients treated with cannabinoids:

Cancer patients confront various challenges, and among them is the development of resistance to chemotherapy regimens (Sung et al,2021).. The emergence of resistance in tumors, even to medications with no shared molecular or structural characteristics, can significantly hinder the effectiveness of treatment plans. The endocannabinoid system (ECS) has been implicated in the regulation of drug resistance observed during chemotherapy (Perdana et al,2016).

Notably, research has revealed that in the case of brain tumors, the susceptibility to THC (tetrahydrocannabinol) is not solely dependent on cannabinoid receptors (CBRs) but is instead influenced by variations in gene patterns (Rawla et al,2019).. In response to THC's anti-cancer effects, scientists have demonstrated that Midkine activates the anaplastic carcinoma tyrosine receptor (ALK), thereby counteracting the impact of cannabinoids on autophagy—a process critical for cell survival (Leitzmann et al,2012).. Furthermore, the study showed that THC-resistant glioblastoma cell-derived tumor xenografts became more responsive to cannabinoid therapies after the inhibition of Midkine or ALK. These findings suggest that the activation of the Midkine-ALK axis promotes tolerance to the therapeutic effects of cannabis. As a result, the study proposes a rationale for a combination treatment approach involving Midkine antagonists along with THC, aiming to enhance the efficacy of cannabinoid therapies and overcome resistance in cancer treatment (Cattrini et al,2019).

b) Evidence-based Cannabinoid and cannabis-related clinical studies:

Ongoing and completed clinical studies are actively exploring the safety and efficacy of cannabis in patients with tumors. One trial is specifically investigating the effects of CBD monotherapy in individuals diagnosed with solid tumors. Concurrently, research is underway to assess the side effects and efficacy of dronabinol, a synthetic cannabinoid, at various dosages in individuals with solid tumors and brain malignancies. The risk profile and metabolism of its oral formulation are also being examined in healthy subjects (Makowiecka et al,2014).

Observational research is being conducted with Dexanabinol in combination with traditional chemotherapy drugs like gemcitabine, nab-paclitaxel, and sorafenib for pancreatic tumors. The goal is to determine the optimal dosage of dronabinol for maximal effectiveness in combination with standard chemotherapy (Andre et al,2016).

Furthermore, a randomized, controlled experiment is set to investigate the effects of smoking cannabis on discomfort and swelling in individuals with lung cancer undergoing radiation therapy. This study aims to contribute valuable data to the growing body of evidence supporting the viability of cannabis formulations as a potential option for individuals grappling with the challenges of cancer.

c) Improvement in cannabinoid delivery using nanoparticles:

The potential enhancement of anti-cancer medications through CBD's efficacy has sparked interest in utilizing nanocarriers to simultaneously deliver multiple pharmaceuticals, presenting a compelling avenue for incorporating CBD into chemotherapy protocols (Bridgeman et al,2017).. Liposomal formulations of various anti-cancer drugs are already in clinical use as integral components of chemotherapy regimens. The adaptability of nanocarriers (NC) allows for surface modifications to enhance tumor specificity (Citti et al,2019).

Engineered alterations to the surface of nanocarriers can be achieved through various methods, including the incorporation of different ligands or antibodies targeting antigens specific to cancer cells. Notably, for leukemia treatment, the suggestion involves utilizing CXCR4-targeting liposomes to deliver drugs while concurrently blocking the CXCR4/CXCL12 axis. In a comparative study using transgenic mice models with lung tumors, the efficacy of both inhalation and intravenous injection routes was assessed (Makowiecka et al,2014).

To optimize circulation duration and tumor uptake, the particles were designed to be as small as 100 nm. This strategic size selection aims to maximize the presence of nanocarriers in the bloodstream while facilitating efficient delivery to tumor sites (Kocis et al,2020).. This research direction holds promise in advancing the precision and effectiveness of cancer treatment by leveraging nanocarriers for multi-pharmaceutical delivery, potentially improving therapeutic outcomes.

In essence, this review offers insights into the evolving landscape of cannabinoid applications in cancer treatment, leveraging nanotechnology for enhanced delivery and therapeutic precision. Ongoing clinical studies and innovative nano-delivery strategies hold promise for the future of cannabinoid-based therapies.

5. Conclusion

The widespread legalization of cannabis and cannabinoids has given rise to concerns regarding safety and clinical outcomes, prompting a need for innovative preparation and administration methods that overcome previous challenges. Nanotechnology, already revolutionizing various aspects of medication delivery in healthcare, holds significant promise for harnessing the therapeutic potential of cannabis and cannabinoids in nanomedicine to address a diverse array of diseases.

Hydrophilic cannabinoids present specific delivery challenges, including water insolubility, poor cell penetration, and

susceptibility to degradation. Recent advancements in the development of cannabinoid-nanocarrier (NT-CBD) delivery methods using diverse substances and techniques offer encouraging avenues to address these challenges. Various carrier systems, such as liposomes, polyamide microorganism spheres, and nanotechnology, have been explored, with the selection depending on the molecular target. Solid lipid nanoparticles, in particular, offer notable advantages, including prolonged release, enhanced bioavailability, efficient drug incorporation, and versatile applications.

Given that central nervous system (CNS) diseases are significant targets for cannabis and cannabinoids, there is a notable emphasis on developing nanoformulation systems for cannabinoid nanoconjugates. These systems aim to facilitate effective transportation across the blood-brain barrier while minimizing side effects. Biomedical applications of selected cannabis nanoconjugates have shown promise, demonstrating improved absorption and bio-efficacy.

Despite these advancements, the challenge remains in delivering nano compounds directly to diseased areas. Clinical study findings assessing the efficacy and potential side effects of these innovative formulations are anticipated, marking a crucial step in understanding the full therapeutic potential of nanomedicine in the realm of cannabis and cannabinoids.

Author Contributions

P.S. and L.S. conceptualized, wrote, and reviewed the article.

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Competing financial interests

The authors have no conflict of interest.

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