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A REVIEW ON CANNABINOIDS AS MEDICINE: CANCER

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ABSTRACT –

Recently, cannabis and related compounds have received wide interest for their potential benefits in cancer treatment. Cannabinoids, the active components of Cannabis sativa L. and their hybrids, have various effects that may be useful in treating cancer, from tumor growth inhibition via apoptosis or autophagy up regulation to reduce angiogenesis of these tumors. Based on preclinical studies, cannabinoids may be among those elements capable of selectively killing cancer cells without systemic toxicity, thus suggesting their therapeutic potential in the treatment of many types of cancers. It has been demonstrated that cannabinoids as THC and CBD, along with additional terpenes can cause cancer cell death in the glioblastoma, lung cancer, thyroid cancer and colon cancers complete CRC. It inhibited tumor growth and induced cell death. Moreover, the expression of cannabinoid receptors, including CB2, has been reported to be upregulated in more aggressive breast cancer subtypes, which argues for the use of cannabinoids as beneficial therapeutic options. The endocannabinoid system (responsible for mediating physiological processes) is also affected by different pathophysiological states, such as cancer and neurological disorders. Cannabinoids activate CB1 and CB2 receptors, which modulate various downstream signalling pathways. Moreover, the expression of cannabinoid receptors including CB2 has been reported to be up-regulated in more aggressive breast cancer subtypes which argue for the use of cannabinoids as beneficial therapeutic options.

KEYWORDS - Cannabis, Cannabinoids, Anticancer, Endo-cannabinoid system, colorectal cancer, Apoptosis, Angiogenesis

INTRODUCTION –

In recent years, both the general public and scientific community have become increasingly interested in the medicinal applications of plants in the Cannabis genus, or hemp. Many nations are working to relax their drug laws to make cannabis-based drugs more widely available. Furthermore, a wealth of preclinical and clinical research data has accumulated over the past ten years, indicating that a variety of compounds derived from cannabis plants have medicinal potential, including anticancer effects.[1] In the middle of the 19th century, French psychiatrist Jacques-Joseph Moreau and Irish physician William B. O'Shaughnessy made significant contributions to Western medicine by describing the beneficial effects of cannabis preparations, such as hashish (the compressed stalked resin glands), on rheumatism, tetanus, pain, vomiting, convulsions, and mental abilities. In 1851, the United States Pharmacopoeia recognized cannabis as a medicine in the form of tinctures, extracts and resins. However, cannabis use declined in Western medicine at the start of the 20th century for several reasons, including increased recreational use, the possibility of abuse, variations in the quality of herbal material, the inability to identify individual (active) compounds, and the introduction of alternative medications with proven efficacy to treat the identical symptoms.[2] However, cannabis continues to be classified by the federal government as a Schedule I substance, meaning it has no recognised medical purpose and a high potential for misuse. Despite the large variety of products accessible at sites selling cannabis in areas where it is legal, the National Institute on Drug Use remains the only legal source of marijuana for clinical study.[3]

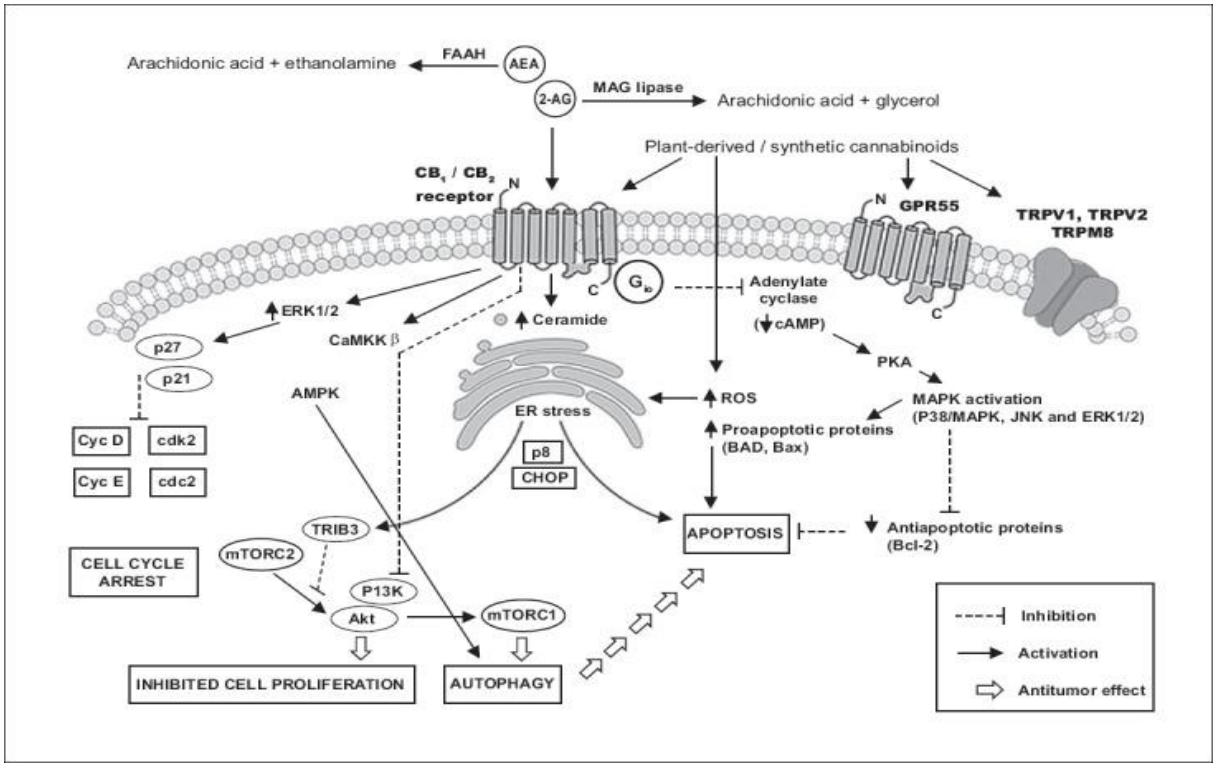
Figure no. 1 Cannabis plant and cannabinoids oil [4]

There are many different hypotheses regarding how cancer starts and spreads. Although there is currently no treatment for the majority of tumors, tremendous advancements have been made in the development of immunotherapy and chemotherapy. Cancer treatment includes palliative care, which attempts to lessen a patient's suffering and side effects, and primary care, which is focused on eliminating the tumor. Cannabinoids are chemicals that may be used in cancer treatment as endogenous homeostasis regulators. They may be especially helpful in palliative care.[5] Selecting the appropriate treatment requires a thorough understanding of the pathophysiology of colorectal cancer. The accumulation of acquired epigenetic and genetic alterations that transform healthy epithelial cells into cancerous cells is part of the complicated etiology of colorectal cancer. There are three primary steps in the formation of the polyp-carcinoma sequence, which is the traditional tumor progression model. The development of benign neoplasms, such as sessile serrated polyps and adenomas, is the initial stage. In the second stage, benign tumors develop into more histologically advanced neoplasms, and in the last stage, they turn into carcinoma.[6] The majority of cannabinoids' actions on neural and non-neuronal tissues depend on the CB1 receptor being activated. The central nervous system regions involved in the regulation of motor behaviour, memory, learning, emotions, perception, and endocrine processes have been found to have high expression.[7]

Antitumor Effects of Cannabinoids –

Although still in its infancy, research on cannabis as a possible anticancer drug has grown in recent years. There is some promise in the body of evidence, which is restricted to a few human investigations, including three experimental studies and one phase I/II clinical study. One of these studies stood out because of its meticulous methodology, which closely matched the evaluation standards of the Cochrane Collaboration Manual. This attention to detail allowed for a more trustworthy interpretation of the experimental procedures and results, highlighting the necessity of additional excellent research to support the anticancer benefits of cannabis. Cannabinoids have the potential to be primary or supplemental antineoplastic agents in cancer treatment, going beyond their use as palliative drugs.[8] Recent developments have focused especially on the antiproliferative properties of the non-psychoactive cannabinoid, CBD. In a targeted in vitro investigation, CBD significantly decreased mitochondrial oxidative metabolism and cell viability in U87 and U373 human glioma cell lines. Within 24 h of exposure to CBD, an antiproliferative effect was observed, and certain substances, such as SR144528 and α-tocopherol, partially mitigated this effect. Interestingly, the effects of CBD were not reversed by other cannabinoid antagonists. Cytofluorimetric analysis and single-strand DNA staining were used to demonstrate the first association between CBD's antiproliferative action of CBD and the activation of apoptosis.[9] They focused a lot of emphasis on the medicinal potential of Cannabis sativa, especially its bioactive constituents, such as terpenes and cannabinoids. THC demonstrated both anti inflammatory and antitumor effects in a study using female C57BL/6 mice administered azoxymethane (AOM) and dextran sulfate sodium (DSS). Hematoxylin and eosin staining of colonic tissue revealed that THC administration significantly decreased the degree of inflammation and tumor growth. THC was also found to reduce the production of interleukin 22, a cytokine linked to inflammation-driven colon cancer. In colorectal cancer (CRC), terpenes and cannabinoids, including myrcene, limonene, and β-caryophyllene, have shown promise in reducing angiogenesis, preventing cell proliferation, and triggering apoptosis.[10] Additionally, extracts with high CBD content have demonstrated a variety of antitumor effects against human neuroblastoma cells. These effects seem to occur through several mechanisms, including increased oxidative stress, disrupted mitochondrial electron transport, and altered cannabinoid receptor activity. Remarkably, the study indicated that whole-plant extracts might have better antitumor benefits than separated cannabinoids. However, the potential mitigating effect of antioxidants, such as α-tocopherol, was not considered in this investigation. They can stop tumor cell growth, migration, and angiogenesis, induce cell cycle arrest, and encourage apoptosis. This is a significant omission because α-tocopherol, a well-known antioxidant that is frequently used to reduce chemotherapy side effects, may reduce the antitumoural effectiveness of cannabinoid-based therapies.[11]

Figure no 2 – Mechanism of Cannabinoids [11]



AEA: Anandamide
Akt: Protein Kinase B;
AMPK: 5' adenosine monophosphate-activated protein kinase;
Bad: Bcl-2-associated death promoter;
2-AG: 2-Arachidonoylglycerol;
Bax: regulator of apoptosis;
Cdk 2: Cyclin-dependent kinase 2;
CHOP: C/EBP homologous protein;
CycD: Cyclin D; CycE: Cyclin E;
CaMKK: Calcium/calmodulin-dependent protein kinase kinase;
ERK: extracellular signal-regulated kinase;
ELK1: protein containing the ETS domain;
MAG lipase: monoacylglycerol lipase;
MAPK: mitogen-activated protein kinase;
p8: Candidate of metastasis 1;
p21: Cyclin-dependent kinase inhibitor 1;
p27: Cyclin-dependent kinase inhibitor 1B;
FAAH: fatty acid amide hydrolase;
GPR55: orphan G-protein coupled receptor 55;
ROS: Reactive oxygen species;
PKA: Protein kinase A;
PI3K: Phosphoinositide 3-kinase;
TRPM8 is transient receptor potential melastatin 8;
mTORC1 is the mammalian target of rapamycin complex 1;
mTORC2 is the mammalian target of rapamycin complex 2;
TRIB3 is Tribbles homolog 3.
TRPV1 and TRPV2 are transient receptor potential vanilloid receptors 1 and 2, respectively.

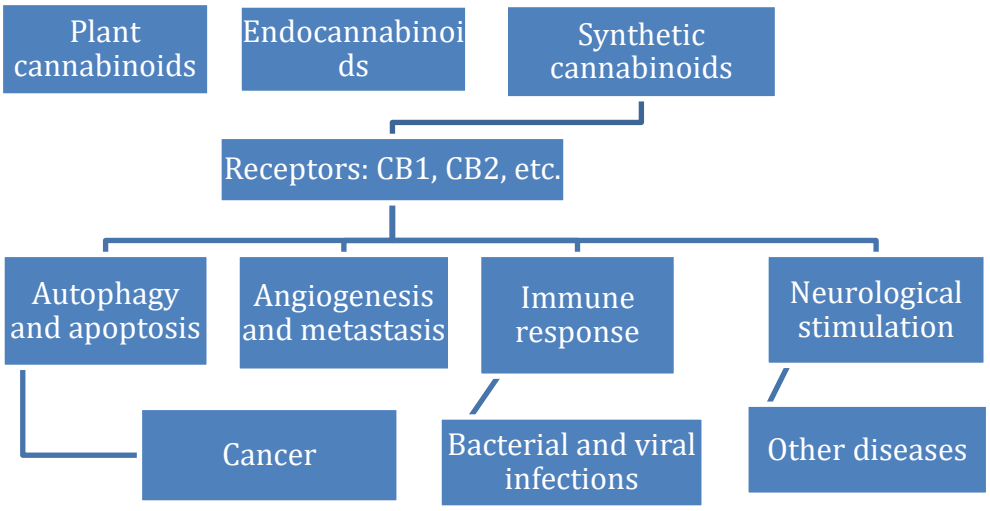
Cannabinoids in Cancer Therapy –

Microarray technology study has shed light on the expression levels of cannabinoid receptors (CB-Rs), specifically CB1-R and CB2-R, in breast cancer tissues. The results show that 72% of cancer samples showed CB2-R positivity, whereas 28% showed CB1-R immunoreactivity. Non-transformed mammary tissues, on the other hand, exhibited very little immunoreactivity for either CB1-R or CB2-R. It is noteworthy that there is a correlation between increased tumour aggressiveness and greater CB2-R expression. For example, CB2-R levels are often higher in tumours lacking oestrogen and/or progesterone receptors, which typically have a worse prognosis. Triple-negative tumours, which are distinguished by the absence of both HER2/neu receptors and steroid hormone receptors, also exhibit this tendency. These tumours frequently have elevated CB2-R levels, which are linked to poor differentiation, a higher risk of distant metastasis, and an earlier local recurrence. Targeting CB-Rs, especially CB2-R and CB1-R, has the potential to completely change the therapeutic landscape for breast cancer. For individuals who have recurrence after anti-HER2-targeted treatments, this pathway may provide helpful therapy alternatives. Other CB-Rs, such as GPR55, are also worthy of consideration in addition to CB1-R and CB2-R. Extracellular signal-regulated kinase (ERK) activation and the consequent production of the c-FOS proto-oncogene are believed to be linked to the proliferative effects of GPR55, which has been found to have higher expression in metastatic MDA-MB-231 cells. Additionally, cannabinoids (CBs) offer therapeutic compounds that may be used to treat breast tumours that express HER2. CBs may increase anti-tumoural effects and improve synergy with traditional chemotherapy medicines like cisplatin when combined with targeted therapies like lapatinib, a tyrosine kinase inhibitor. Empirical studies have corroborated the synergistic effect between CBs and other oncologic agents including cisplatin.[12, 13, 14]

Cannabinoids in Medicine –

The ES is a subject of significant interest due to its involvement in the control of several processes, including pathological ones (Figure 1). Numerous clinical illnesses, including as malignancies and neurological disorders like Parkinson's disease, Huntington's chorea, and multiple sclerosis (MS), have been found to have significant alterations in ES activity.[15] Cannabis increases hunger via activating CBR1. Dronabinol is authorised to treat anorexia and weight loss in adult HIV (human immunodeficiency virus) patients, but not in anorexia and weight loss associated with cancer.[16] These effects could have a variety of underlying mechanisms and multiple modes of action, including altering bioavailability, influencing cellular transport mechanisms, inactivating active components or activating precursors to produce products with a particular action,
contributing to different parts of the same signalling pathway by multiple components, or preventing a ligand from binding to its target receptor. Two theories have been put up to explain how CBD affects THC pharmacokinetics: cytochrome P450 inhibition, which postpones THC decomposition, and increasing fluidity in the membrane, which makes it easier for THC to enter muscle tissue.[17] The euphoric effects of cannabinoids may be impacted by secondary metabolites, which may alter THC's affinity for the receptor known as CB1 and communicate with neurotransmitter receptors. By inhibiting cytochrome P450, flavonoids may also have an impact on the pharmacokinetics of THC. According to certain findings, a Phyto-cannabinoid-terpenoid action includes distinct molecular processes in the neural circuits rather than being dependent on the amount of CB1/CB2 receptor.

Figure no. 3 - The involvement of the endo cannabinoid system in a variety of modulatory



Cannabinoid Receptors (CBRs) –

Animal tissues have so far been found to contain two receptors for cannabinoid (CBR1 and CBR2) with around 44% of their amino acid sequence identity.[18] When each of these receptors is activated, adenylyl cyclase is inhibited, which lowers the concentration of cytoplasmic cyclic adenosine monophosphate (cAMP), closes Ca2+ channels, opens K+ channels, and stimulates protein kinases that are important for several signalling pathways, such as the phosphoinositide 3-kinase (PI3K), cyclooxygenase-2 (COX-2), or mitogen-activated protein kinase (MAPK).[19] The effects seen following THC administration or marijuana usage are explained by the fact that the CBR1 gene is especially highly expressed in areas of the brain linked to the modulation of motor processes, memory, emotion, perception, and endocrine functions.[20] It has also been documented that neurotransmitter that and exogenous cannabinoids interact with other receptor types, particularly TRPV1 (a member of the rapid receptor potential (TRP) family) and GPR55 and GPR18 orphan receptors. Although it has been suggested that some of these receptors should be reclassified as CB receptors since they are essential to the ES, this notion is refuted by the fact that they interact as well with intrinsic and exogenous substances besides cannabinoids, and it is still unknown exactly what part they play in ES functions.[21, 22]

Clinical Applications and Challenges

A. **Clinical Trials and Evidence Based Medicine -** Research on the impact of marijuana on mental health during the prepubertal phases has been sparse and inconsistent up until now. Research has shown that administering CBD to peripubescents may lessen the behavioural impairments observed in animal models of schizophrenia. Additionally, preclinical research suggests that mice exposed to both THC and stress during peri-adolescence may have reduced fear extinction as adults; however, this effect was not observed in animals that received only THC or stress.[23] People living with HIV (PWH) receiving antiretroviral medication (ART) were the target of a historic intervention pilot study that was the first of its type to report anti-inflammatory effects after cannabis delivery in humans. Eight trial participants who received oral cannabinoids completed their treatments satisfactorily. The findings showed notable decreases in surrogate indicators associated with cellular senescence, tiredness, immune cell activation, systemic inflammation, and damage to the gut mucosa. These preliminary findings support more thorough research through bigger clinical trials to ascertain whether employing cannabis capsules to reduce ongoing inflammation in the PWH on ART is feasible.[24]

B. **Safety Considerations and Adverse Effects -** Notable cautions about THC and cannabis centre on their mental side effects, which can lead to discontinuation and frequently determine the highest acceptable dose. DRO has been shown in clinical research to have the ability to worsen illnesses like schizophrenia, depression, and mania. Recent marijuana meta-analyses showed that the risk of negative effects on the mental and nervous system was nearly three times higher than that of comparator groups, but there were no statistically significant differences in

specific symptoms like anxiety or sadness.[25] Participants in clinical trials have reported adverse reactions like disorientation, disassociation, joy, and illusions, which can be especially dangerous for medically vulnerable populations like older adults. Casual users may especially seek out certain effects to THC use.[26] Notably, problems reported have shown a rise over time due to the growing variety of marijuana-derived goods, both prescriptions and OTC (over-the-counter) THC/CBD for both medicinal and recreational purposes. One case report has suggested link between concurrent use of prescription SSRI medicine and cannabis hyperemesis syndrome, however direct clinical interactions are still a developing field of study.[27]

C. **Cannabinoids as Therapeutic Agents -** Growing interest in using cannabis botanicals to treat glioblastoma (GB) has been sparked by new combination cancer treatments. Compared to existing treatments, its polypharmaceutical character provides clear advantages. By fully using their anticancer characteristics, they may more successfully supplement standard-of-care treatments. Furthermore, compared to conventional chemotherapeutics, their off-target effects are less harmful. For many GB patients, the use of cannabis as palliative therapy has already shown promise. Numerous scholarly papers have documented the anticancer properties of cannabinoids, which have been shown to exhibit tumor-specific harmful and cytostatic benefits in both clinical and experimental models, including those involving GB patients.[28] Before developing into aggressive cells that cause tumour regrowth in other parts of the brain, therapy-resistant CSCs that are may lie latent in protected niches. According to the results of Lah et al., with their respective the IC50 concentrations, all three cannabinoids significantly reduced the apoptotic rate of GB cancer stem cells by about 30%. This suggests that the cannabinoids significantly inhibit cell viability processes as cytotoxins, which with this inhibition being an important aspect of both their cytotoxicity and viability mechanisms. The induction of caspase-3/7 is a noteworthy signalling action of CBG, and it is further enhanced by temozolomide (TMZ) and CBD. [29]

Action of cannabinoids on humans

A. **Acute effects -** The immediate toxic effects of cannabis is very small. Although there have been no documented deaths from direct poisoning, comas have occasionally happened from unintentional absorption by kids. Cannabinoids have a wide range of intricate pharmacological effects, including a special fusion of the properties of alcohol, opioids, tranquillizers, and hallucinogens like LSD. Nearly every bodily system is impacted.[30]

B. **Sedative and anxiolytic effects** - Cannabis has a generalised nervous system sedative effect that causes tiredness and sleep near the close of an overdose phase, following an initial time of joy following an acute intake.[31]

C. **Effects on perception** - Most of the senses are impacted by the sensory shifts brought on by cannabis and THC.[31] There could be an increase in our understanding of colour, sounds, and
song. Distorted chronological and spatial perception impairs evaluation of time and distance. Even at moderate amounts (four puffs of a tobacco product containing 3.6% THC, for example), participants routinely underestimate the passage of time, according to experimental studies on time perception.[32, 33]

D. **Effects on motor function** - A form of mental stasis with ataxia, dysarthria, and general incoordination follows an initial phase of excitation and enhanced motor skills following acute cannabis consumption. This state may persist for several hours, depending on the dosage. Measures of body wobble, track capacity, chase rotor performance, eye-hand coordination, reaction time, physical strength, and many other aspects have all demonstrated impaired motor skill in human beings.[34, 35, 36]

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