The Role of Cannabis in the Treatment of Colon Cancer

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “The Role of Cannabis in the Treatment of Colon Cancer” submitted by Shariar Shuvo Rahman (18146001)] of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.)

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Ethics Statement

Over the course of this study, no biological organisms were damaged.

Abstract

Cannabis as a treatment for colon cancer is an increasingly researched topic. This study assessed the effectiveness of cannabis in treating colon cancer. We searched PubMed, Research Gate, and Google Scholar for scholarly articles written in English. The investigation revealed that cannabis, namely CBD and THC, has the potential to heal colon cancer. According to research, THC and other cannabis components inhibit development and death of colon cancer cells. Current research indicates that THC and other cannabinoid chemicals may enhance treatment for colon cancer. These benefits are given by unidentified mechanisms that need more research.

Despite promising outcomes, cannabis treatment for colon cancer remains limited. In the absence large-scale clinical trials studies, the safety and effectiveness of cannabis as a colon cancer therapy remain unknown. The federal designation as a Schedule I controlled substance, which restricts financing for research and clinical studies, has further hindered advancement in this industry. This research indicates that cannabis and THC may be helpful therapy for colon cancer. Additional research is required to completely understand the mechanisms of action, safety, effectiveness, and therapeutic role of cannabis. The dosage, administration, and long-term effects of cannabis in patients with colon cancer need more large-scale, high-quality clinical study. It is vital to address the possible negative effects and drug interactions of cannabis and to standardize cannabis-based therapies. The significance of cannabis in the treatment of colon cancer is complicated and expanding, and continued study into its potential therapeutic advantages is essential for developing innovative therapies for colon cancer patients.

Dedication

Dedicated to my parents

Acknowledgement

First of all, I am most grateful to Allah for giving me the opportunity to choose and study Pharmacy. Without His grace, I would not have been able to finish and submit my Bachelor of Pharmacy project paper. The paper could not have been completed without the aid of the various persons acknowledged below. Without my esteemed supervisor, Dr. Raushanara Akhter, I would not have been able to work. on such a fascinating topic. Thanks to her persistent effort and motivation for my project, I was able to work with more diligence. Her insights have always motivated me to improve my ability to communicate effectively. I am absolutely thrilled to have the opportunity to express my deepest gratitude to my thesis supervisor for her unwavering support, invaluable guidance, and unmatched expertise throughout my review and writing journey. Without her constant encouragement, tireless dedication, and genuine belief in my abilities, I wouldn't have been able to accomplish the paper. In regard to supervision and instruction, she consistently and convincingly showed sincerity, which motivated me to finish this assignment. I am also grateful to all the faculty and members, teaching assistants and students at the school of Pharmacy, Brac University, who have helped me whenever I have needed assistance throughout my journey. Finally, I would want to thank my parents for their constant support and encouragement throughout my whole life. They give me the courage and fortitude to work more diligently and patiently. Their unreserved love and prayers have helped me reach this stage. I convey my gratitude to everyone who aided me with this quest.

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List of Acronyms

CRC - Colorectal Cancer

HC - Tetrahydrocannabinol

CBD - Cannabidiol

CBG - Cannabigerol

CBN - Cannabinol

THCV - Tetrahydrocannabivarin

CBC - Cannabichromene

CBDV - Cannabidivarin

CBDA - Cannabidiolic acid

THCA - Tetrahydrocannabinolic acid

CBGA - Cannabigerolic acid

CBNA - Cannabinolic acid

CBGVA - Cannabigerovarinic acid

CBCA - Cannabichromenenic acid

THCV-A - Tetrahydrocannabivarinic acid

CBDVA - Cannabidivarinic acid

Δ9-THC - Delta-9-Tetrahydrocannabinol

Δ8-THC - Delta-8-Tetrahydrocannabinol

Δ9-THCV - Delta-9-Tetrahydrocannabivarin

Δ8-THCV - Delta-8-Tetrahydrocannabivarin

11-OH-THC - 11-Hydroxy-Tetrahydrocannabinol

11-nor-9-Carboxy-THC - 11-nor-9-Carboxy-Tetrahydrocannabinol

HU-210 - (6aR,10aR)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol

JWH-018 - 1-Pentyl-3-(1-naphthoyl) indole

TRPV1 - Transient Receptor Potential Vanilloid 1

PPARγ - Peroxisome proliferator-activated receptor gamma

GPR55 - G protein-coupled receptor 55

ECS - Endocannabinoid System

FAAH - Fatty acid amide hydrolase

COX-2 - Cyclooxygenase-2

IBD - Inflammatory Bowel Disease

COX-1 - Cyclooxygenase

ROS - Reactive Oxygen Species

FDA - Food and Drug Administration

IND - Investigational New Drug

Chapter 1

Introduction

1.1 History

Cannabis sativa L. was the original and most important source of cannabinoids, and It is being utilized a herbal treatment for millennia. The earliest archaeological evidence of cannabis medicinal usage goes back to ancient China's Han Dynasty, when it was prescribed for rheumatic pain, constipation, female reproductive system diseases, and malaria, among other ailments. (Dariš et al., 2019). Cannabis first appeared during the mid-1500s, South America and subsequently, in the early 1600s, North America. (Tomko et al., 2020). While cannabinoids have aroused the interest of researchers for millennia, the last few decades have offered significant and scientifically based insights into their medicinal potential. (Stella et al., 2021). In the 20th century, cannabis was marginalized and criminalized primarily as a result of misinformation resulting from Western medicine's growing understanding of its medical and recreational benefits.

1.2 CBD in Colon Cancer

According to a new publication from Izzo's team, CBD itself is a strong for both inhibition of cancer development and spread (Aviello et al., 2012). This compound's anticancer action appears to be selective towards cancer cells, at least in vitro, as it has no impact on normal cell lines. CBD's effectiveness is connected to its capacity to target several cellular pathways that govern tumor genesis via regulation of distinct intracellular signaling pathways depending on the cancer type under consideration. The most frequent impact of CBD is an increase in ROS generation, which appears to be a factor for activating its positive activity in all cancer cell types studied. It is unclear what role cannabinoid receptors play in mediating CBD's effects. Through the use of particular antagonists, these receptors have made a significant impact

proven in some cases (lung, leukemia, colon), while in other cancer types (glioma and breast), their importance appears to be negligible or missing(Massi et al., 2013). In addition to the in vitro evidence, the efficacy of CBD in suppressing tumor development and, in certain cases, metastasis was validated in animal models. The potential therapeutic appliance of CBD for cancer treatment, on the other hand, requires considerable thought. Its low toxicity is unquestionably a wonderful place to start. CBD is a nontoxic chemical; fact, oral administration of CBD 700 mg day-1 for 6 weeks did not reveal any overt toxicity in humans (Consroe, Laguna, et al., 1991), indicating that it might be used for long-term therapy. Because CBD oral absorption is sluggish and variable, the route of delivery looks to be more difficult. However, 6 weeks of oral CBD therapy at a dose of 10mg kg-1 day-1 resulted in a mean plasma concentration of CBD ranging from 6 and 11 mg ml-1 (approximately 0.036 μM) (Consroe, Kennedy, et al., 1991), which did not alter substantially during the course of the treatment (Massi et al., 2013).

1.3 An overview on cannabis components with anticancer effects

The cannabinoids, which are a group of terpenophenolic chemicals consisting of 21 carbon atoms, are exclusively produced by the Cannabis sativa and Cannabis indica plant species.. Phytocannabinoids are plant-derived compounds that are distinguished from pharmaceutical chemicals and endogenous cannabinoids. This distinction follows the identification of endogenous cannabinoids. Whilst delta-9-THC serves as the primary active constituent in cannabis, there exists a diverse range of non-THC cannabinoids and non-cannabinoid molecules that also demonstrate biological activity. A number of cannabinoids, including cannabidiol (CBD), cannabichromene, cannabinol, tetrahydrocannabivirin, cannabigerol, and delta-8-THC, have been discovered. (Abrams & Guzman, 2015).

1.3.1 Cannabinoids

The Cannabis sativa plant has generated over one hundred different cannabinoids (ElSohly et al., 2017). Cannabinoids are derived from cannabigerolic acid and vary mostly in how this precursor is cyclized. Other plant species outside cannabis contain phytocannabinoids as well. Because of its psychotropic properties, tetrahydrocannabinol (THC) is the most recognized phytocannabinoid and the principal psychoactive component of cannabis(Tomko et al., 2020). Cannabinol also has euphoric properties. Other nonpsychoactive phytocannabinoids include cannabigerol, cannabivarin, and cannabichromene, with cannabidiol being the most well-known. Here, we will focus on some of the cannabinoids' impacts on cancer, although they have also been studied for other disorders. Consider the evidence, what suggests that compared to the other cannabinoids, THC and cannabidiol (CBD) have stronger anticancer properties. (obtained in vivo, in vitro, and even in a few clinical studies) (Bauer et al., 2008).

1.3.2 Delta9-tetrahydrocannabinol (THC)

The primary association between the psychoactive effects of Cannabis sativa L. cultivars and the central nervous system is attributed to THC, which interacts with CB1 receptors. (Siddiqui et al., 2017) The mechanism of action of THC involves binding to CB1 receptors located in the central nervous system (CNS), causing cannabis intoxication. THC may be ingested, injected intravenously, injected intramuscularly, or inhaled. The widespread administration technique in humans is commonly observed is oral administration, and because of its significant affinity for lipids, the compound exhibits a high degree of binding affinity to plasma proteins and undergoes rapid distribution to highly vascularized organs, including the liver, heart, and lungs. (Tomko et al., 2020). THC accumulation has also been shown to occur in fat tissues. Because of the psychoactive properties of THC are modulated within the central nervous system, there

are matters regarding suggesting THC for therapeutic purposes in individuals with malignance. Other negative side effects of THC use include reliance, tolerance, and misuse problems (Afrin et al., 2020; Tomko et al., 2020).

1.2.3 Pharmacology

Oral bioavailability is modest from 6 to 20 percent and varied. The highest concentrations of plasma are observed within 1-6 hours and stay increased for 20-30 hours. When taken orally, The hepatic metabolism of delta-9-THC results in the formation of 11-hydroxy-delta-9-tetrahydrocannabinol, another strong psychoactive metabolite. When cannabinoids are breathed, they exhibit a swift absorption into the circulation system., reaching the highest concentrations in 2-10 minutes and rapidly declining over the following 30 minutes. Inhalation provides a greater peak concentration with a shorter duration of action. Less of the hallucinogenic 11-OH-THC metabolite is generated (Karschner et al., 2011) Endocannabinoids, comparable N-arachidonoyl ethanolamide and 2-arachidonoyl glycerol, alongside their corresponding receptors, are of significant interest in the field of research may be found throughout the body, consisting of the nervous system, connective tissue, internal organs, glands, and immune cells (Sawtelle & Holle, 2021; Turgeman & Bar-Sela, 2019) Such endocannabinoids are generated according to needs and when the endogenous system is stimulated this system regulates mood, hunger, memory, and pain sensitivity (Birdsall et al., 2016). Phytocannabinoids interact with the endogenous cannabinoid system through the two primary cannabinoid receptors present in the human body CB1 and CB2. The CB1 receptors are largely located within the central nervous system (CNS), where they are credible for the psychological and behavioral effects (Kraft, 2012). CB2 receptors are found on immune cells, hematopoietic cells, and the spleen in peripheral tissues, but they are also found in the CNS, where they contribute to extra mental and behavioral effects (Limebeer et al., 2012; Rubin, 2017). Cannabinoid receptors are also known as G-coupled protein receptors. The interaction

of a ligand activates the G-coupled protein inhibitory (Gi) pathway, which inhibits adenylate cyclase (Birdsall et al., 2016) Due to the restricted distribution of CB2 receptors within the central nervous system/, they constitute an attractive pharmaceutical target, as selective CB2 compounds may not have psychotropic 2 effects (Brown, 2007; Dariš et al., 2019) Different kinds and isoforms of CB receptors, as well as different pharmacological targets of cannabinoids have been defined, including peroxisome proliferator-activated receptors (PPARs), transient receptor potential melastatin 8 (TRPM8), TRP vanilloid 2 (TRPV2), and TRP ankyrin 1 (TRPA1) channel.(De Petrocellis et al., 2011; Latorre & Schmidt, 2015; Pugazhendhi et al., 2021)

1.4 Rationale of the study

The study of cannabis in colon cancer aims to explore the possible therapeutic benefits of cannabis and its derivatives for the treatment of colon cancer. This research is important because colorectal cancer is a prevalent cause of mortality associated with cancer on a global scale, and there is a growing interest in the usage of cannabis for cancer treatment.

The practical application of cannabis in cancer treatment is grounded on the presence of compounds known as cannabinoids that have been demonstrated to have anti-tumor effects in preclinical studies. The goal of this study is to determine whether these effects translate to the clinic and if cannabis and its derivatives can be used as an effective treatment for colon cancer.

This study will likely involve the study of the mechanism of action of cannabinoids in colon cancer cells and the evaluation of the effectiveness and safety of cannabis-based products treatments in both animal models and human clinical trials. The results of this research will help to determine the potential of cannabis as a therapeutic option for colon cancer patients and the future directions for this field of study.

Overall, the rationale of this study is to evaluate the potential benefits and limitations of cannabis in the treatment of colon cancer and to provide a basis for the development of new and improved treatments for this devastating disease.

1.5 Aim of Study

The project's objective is to investigate whether or not compounds produced from cannabis, such as THC and CBD, is possible that it could be utilized in the therapeutic intervention of colon cancer. The objective of the study is to evaluate their safety as well as their effectiveness in killing colon cancer cells in vitro and in vivo, as well as to identify the most effective dose and delivery method, and to gain an understanding of the processes that are responsible for their anticancer activities. In addition, the study plans to investigate the potential use of compounds produced from cannabis in combination with conventional cancer treatments such as chemotherapy and radiation therapy. In the long run, the goal of this review is to add to the widening collection of knowledge concerning the possible therapeutic applications of substances derived from cannabis and to shed light on the process of developing cannabis-based therapies for the treatment of colon cancer that are both safe as well as efficient.

Chapter 2

Methodology

This review paper has been compiled utilizing the most recent and relevant research papers and articles sourced from journals with high impact factors. A comprehensive inquiry has been carried out through diligent consideration of esteemed scholarly publications, articles and official reports. In order to enhance the comprehensiveness of the review paper, fundamental and supplementary data were gathered from various literary sources. The present study's data was collected through various search engines, namely ResearchGate, PubMed, Google Scholar, Science Direct, Elsevier, and others. The primary publications that were consulted include Nature, ACS (American Chemistry Society), AACR (American Association for Cancer Research), Molecular Cell, Cancer Cell, Journal of Molecular Biology, Journal of Medicine, Science, e.t.c.To construct a high-quality review of the role of cannabis in the treatment of colon cacner the extensive scan of the journals was followed by filtering down to the most current (within the previous fifteen years) and relevant ones.

Chapter 3

3.1 Types of cannabis components with anticancer effects.

CBD Exhibits Anticancer Activity in Preclinical In Vitro and In Vivo Studies

Using cannabinoids in the treatment of different forms of cancer has gained increasing attention in the past several years. Anticancer action has been established in pre-clinical studies using CBD and D-9-tetrahidrocannabinol (THC). CBD, a non-psychoactive cannabinoid that has been shown to have a higher anticancer impact than THC, is given particular attention because of its psychotropic effects(Kis et al., 2019).

3.3.1 Cannabigerol (CBG)

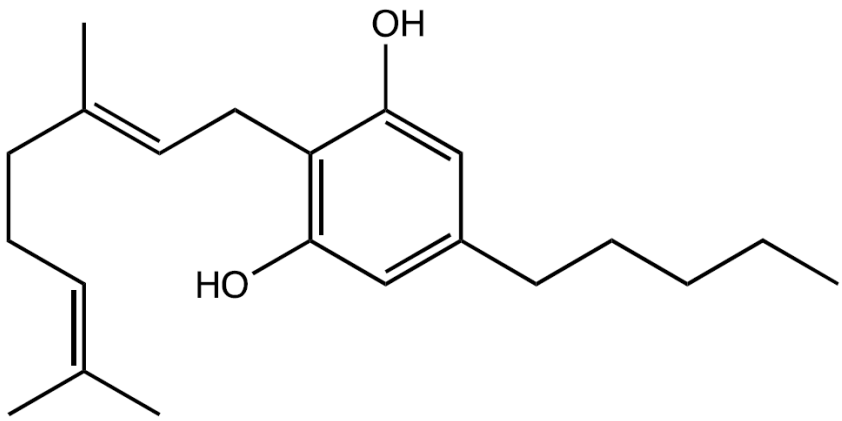

Figure 1: Structure of Cannabigerol (CBG)

Cannabis Sativa Linneas. plants generate cannabigerol (CBG), one of the most potent phytocannabinoids. In spite of this, it is regarded a minor phytocannabinoid in comparison to THC and CBD because of its low quantity. Type IV cannabis refers to cannabis strains with a greater concentration of cannabigerol. CBGA, the acidic precursor, similarly this compound functions as a precursor for the synthesis of tetrahydrocannabinol (THC) and cannabidiol (CBD) synthesis. Increased cultivation of industrial hemp for commercial purposes cultivars

have been created with CBG and CBGA, the primary phytocannabinoids, as the main phytocannabinoids present, in recent years owing to their lack of intoxicating effects (Navarro et al., 2018). According to a study, The CBG compound exhibits binding affinity towards TRPV1, TRPA1, and TRPV2 channels, thereby eliciting their activation. Conversely, it acts as a blocker of TRPM8 channels. Additionally, the TRPM8 channels are known to exert inhibitory effects on 5-HT1A. The findings of an in-vivo study suggest that CBG has the potential to impede colon carcinogenesis through the activation of a pro-apoptotic mechanism. The efficacy of CBG is attributed to the excessive generation of reactive oxygen species (ROS) (Borrelli et al., 2014; Hasan et al., 2022).. Research on cannabigerol's anti-cancer properties has just recently begun, with only a few trials having been conducted (Tomko et al., 2020)

3.3.2 Cannabidiol (CBD)

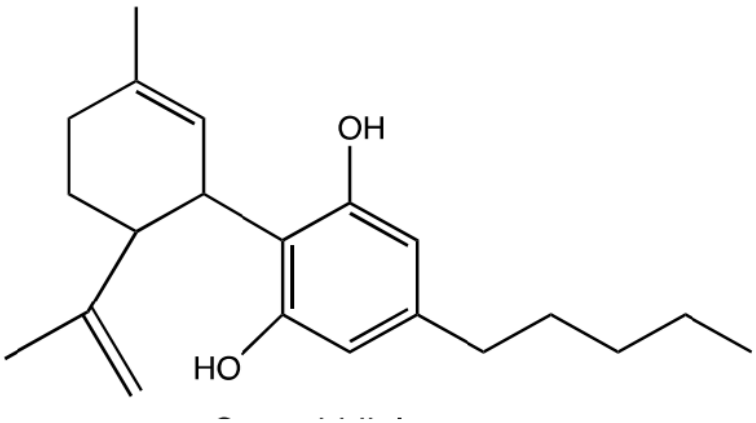

Figure 2: Structure of Cannabidiol (CBD)

Cannabis plants contain cannabidiol (CBD), one of the most important and well-studied Phyto cannabinoids. The endocannabinoid system in the body has a wide variety of receptors that cannabidiol binds to. CBD is most typically used orally and as an oil in medicinal situations. Because it does not produce an intoxication like THC, cannabidiol has a greater appeal as a therapeutic agent because of its absence of intoxicating properties. Cannabidiol's anti-cancer potential has been the subject of several research to date (Tomko et al., 2020) .

3.3.3 Cannabichromene (CBC)

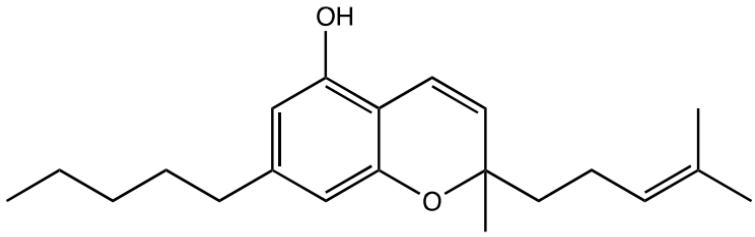

Figure 3 Structure of Cannabichromene (CBC)

Because it is less abundant compared to main cannabinoids THC and CBD, cannabichromene itself is regarded as one among the lesser Phytocannabinoids generated by Cannabis sativa Linnaeus plants(Tomko et al., 2020). Cannabichromene has been identified as the next utmost common form of cannabinoid that is currently in existence in various strains of cannabis in the United States, notably plentiful in dry-type cannabis material. Despite the prevalence of CBC in numerous cannabis strains, there remains a substantial lack of understanding regarding its pharmacological properties. Cannabichromene, like CBD, has no intoxication properties and is hence attractive in terms of its possible therapeutic value to researchers implications in human health and medicine(Tomko et al., 2020). Cannabichromene was discovered to be the second most powerful inhibitor of cell feasibility after CBC inhibited cell proliferation in colorectal cancer Caco-2 cells, but only at a dose of 30 M (Issue et al., 2014). CBC revealed great effectiveness as a cell viability inhibitor in breast cancer cell lines (MDA-MB-231 and MCF-7) (Tomko et al., 2020; Udoh et al., 2019)

3.3.4 Cannabidivarin (CBDV)

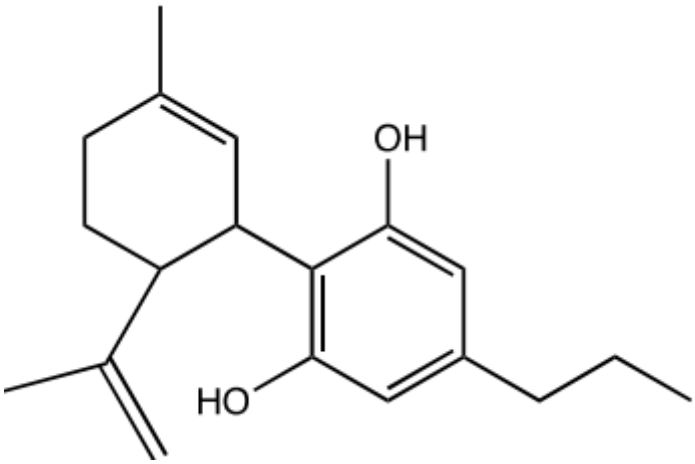

Figure 4: Structure of Cannabidivarin (CBDV)

Cannabidivarin has a similar structure to cannabidiol, and with a shorter side chain. In India and Nepal, CBDV-rich cannabis varieties have been discovered. CBDV was evaluated on numerous human prostate cancer cell lines for suspected cytotoxic effects (Tomko et al., 2020)

3.3.5 Cannabinol (CBN)

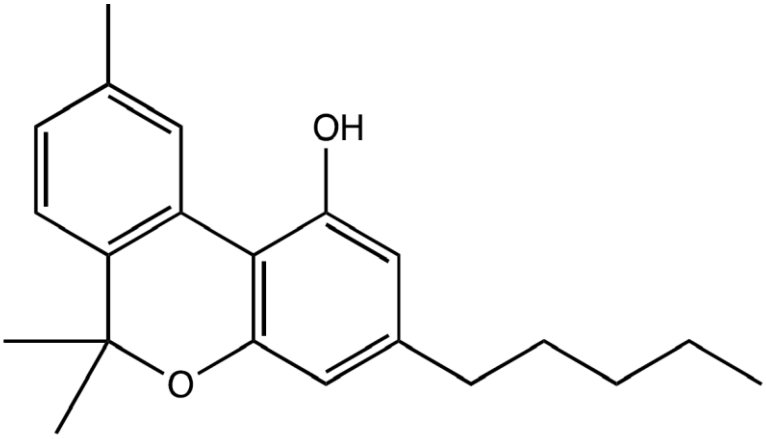

Figure 5 Structure of Cannabinol (CBN)

Cannabinol (CBN) is found within the cannabis plant. and is a degradation result of tetrahydrocannabinolic acid, particularly in mature cannabis. Despite being the first phytocannabinoid to be identified, it has received little attention. The psychoactive effects of cannabinol are believed to be ten times weaker than those of THC (Huestis, 2005). Cannabinol exhibited some cytotoxic effects in prostate cancer cell lines DU-145 and LNCaP(Tomko et al., 2020). In most tests, the measured IC50 was reported to be greater than the maximum dosage tested (25 M) (De Petrocellis et al., 2013). CBN has also been demonstrated to inhibit cell proliferation in aggressive breast cancer cells (McAllister et al., 2007). Because of their propensity to give resistance to numerous anti-cancer medicines, multi-drug transporters are a persistent concern in cancer treatment. CBN hindered the The ABCG2 multidrug transporter has been found to exhibit an augmented capacity for mitoxantrone accumulation, which is a recognized substrate for this particular transporter, in one research (Tomko et al., 2020).

3.3.6 Cannabivarin (CBV)

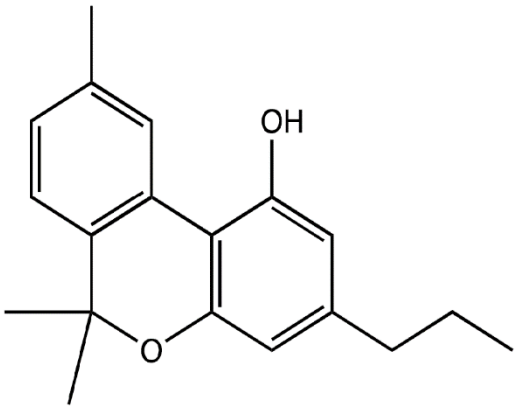

Figure 6: Structure of Cannabivarin (CBV)

Cannabivarin (CBV), better recognized as cannabivarol, is a cannabinoid analog featuring a reduced side chain length that is existing in trace levels in some cannabis cultivars. It is a tetrahydrocannabivarin oxidation product that is seldom observed in new cannabis. There are

no literature on the subject matter at hand material on cannabivarin effects in cancer (Tomko et al., 2020).

3.3.7 Tetrahydrocannabivarin (THCV)

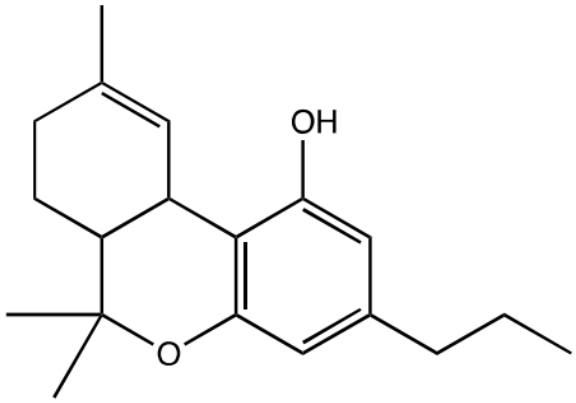

Figure 7: Structure of Tetrahydrocannabivarin (THCV)

Tetrahydrocannabivarin (THCV) is a THC homologue with many side chains that provide effects unique from THC. Maximum cannabis plant species have individual trace quantities of THCV, while specific sativa cultivars originating from mixed It is speculated that African genetics exhibit elevated levels of THCV.. Nothing is known considering the properties of THCV on cancer, as with most other minor cannabinoids. In prostate cancer cell lines (DU-145 and LNCaP), tetrahydrocannabivarin displayed some cytotoxic effects, with IC50 values reaching 17.5 M (De Petrocellis et al., 2013) .

3.3.1. Licensed drugs

Currently, no cannabis-based anticancer medications have been licenced by regulatory organisations such as the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (EMA). Certain cannabis-derived medications, such as dronabinol

and nabilone, have been licenced for additional purposes, including as the treatment of chemotherapy initiated nausea and vomiting (Heider et al., 2022; Society, 2015).

There are currently ongoing clinical studies looking at the anticancer characteristics of cannabis-derived substances including cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) (THC). These trials, however, are still in their early phases, and additional study is required to evaluate their safety and effectiveness in cancer treatment .

3.3.2. Agents in clinical trials

Cancer type: Colon cancer

Table 1: pre-clinical assessment of cannabinoids on tumor development (Ladin et al., 2016)

Cell Line	Animal species/strain	Cannabinoid	Dose (route)	Findings
Azoxymethane-Male ICR mice induced colon cance model	Male ICR mice	CBD	5mg/kg 3x weekly (p)	Reduced aberrant crypt foci (ACF), number of polyps and tumors
Azoxymethane-Male ICR mice Induced colon cancer mode	Male ICR mice	Cannabis extracts rich	5mg/kg (p)	Reduced aberrant crypt loci (ACF), number of polyps and tumors

Xenograft-HCT-116	Athymic nude-female	CBG	3 and 10mg/kg (p)	Reduced the growth
Azoxymethane-induced colon cancer model	Male ICR mice		5mg/kg (p.)	Reduced ACF, number of tumor/mice
Xenograft-HT-29	Nude mice	HU-331	5mg/kg 60)	Reduced angiogenesis
Xenograft-HT-29	Nude mice	HU-331	5mg/kg	Reduced tumor growth
General in vivo	Sabra male mice, SCID-NOD Mice	HU-331	7.5mg/kg 6.3)	Less toxicity than doxorubicin
Xenograft-HT-29		male nude mice	5mg/kg	It is less cardiotoxic than doxorubicin and causes less tumor formation.
Colitisis induced colon cancer model	Male CD1 mice	0-1602	3 mg kg p	reduced inflammation and proliferation.

According to the in vitro studies conducted in the identical research, it was found that the process of cytotoxicity was caused by CB1, TRPV1, and PPARγ (CBD and Cannabis extract) or CB2 (Cannabis extract) ((Aviello et al., 2012; Ladin et al., 2016; Romano et al., 2014a)). Moreover, Cannabigerol (CBG), a phytocannabinoid that does not exhibit psychoactive properties, has been shown to reduce the proliferation and development of HCT-116 xenografts and colon cancer formation induced by AOM(Ladin et al., 2016). Using the HCT-116 cell lines,

cell death was prevented by blocking TRPM8 but not CB1, CB2, or TRPV1 receptors (Romano et al., 2014b) . The quinone compound HU-331, which is derived from cannabidiol, was observed to have a reducing effect on angiogenesis and tumour growth in an HT-29 xenograft model. (Kogan et al., 2004, 2007; Ladin et al., 2016)). A study conducted nude mice xenografts employing HT-29 cells and observed that HU331 exhibited a greater degree of inhibition towards tumour development compared to the conventional chemotherapy agent, doxorubicin (Kogan et al., 2007; Ladin et al., 2016) Furthermore, A study employing several animal models demonstrated that HU-331 exhibit lower levels of cardiotoxicity in comparison to doxorubicin. In an alternative study, O-1662, which is an analog of abnormal cannabidiol, exhibited a reduction in the quantity and size of tumors that were developed through the AOM + dextran sulphate sodium approach in the colon cancer model induced by colitis. The present study observed an associated reduction in inflammation and proliferation, as well as an induction of apoptosis within the cancerous tissue during the course of this action. (Kargl et al., 2013)

3.3.3 Adverse and unwanted, effects of cannabinoids

There are additionally contradictory reports about the effect of cannabis on cancer cells. According to one research, the treatment of THC to immunodeficient mice with a xenograft form of non-small cell lung cancer had antiangiogenic and antiproliferative effects (Preet et al., 2008)(Sawtelle & Holle, 2021). Contrarily, other studies discovered that THC induced tumor development in immunocompetent mice, probably because of its immunosuppressive impact. (McKallip et al., 2005; Zhu et al., 2000). On the other hand, endo- and Phyto cannabinoids' anti-inflammatory properties may be employed to prevent and treat colorectal cancer. (Preet et al., 2008). These data provide compelling evidence that cannabis is not suitable for cancer treatment in each and every circumstances. Due consideration must be given to the molecular subtypes of cancer and prospective medication interactions when analyzing their diverse cellular effects. Otherwise, they may do more damage than good for afflicted cancer patients.

Chapter 4

4.1 Limitations

There is limited research on the efficacy and safety of cannabis in the treatment of colon cancer. Most of the existing studies are preclinical or observational, and lack the large, randomized controlled trials that are needed to establish definitive conclusions about the benefits and risks of cannabis in colon cancer. Additionally, many of the studies have been conducted on animal models, which may not accurately reflect the effects of cannabis in humans. As a result, it is difficult to determine the best dosage and administration method for cannabis in colon cancer patients.

4.2 Potential for cannabis as a treatment for colon cancer

Cannabis has been shown to have anti-inflammatory, antioxidant, and antiproliferative effects that may be beneficial in the treatment of colon cancer. Some preclinical studies have uncovered that certain cannabinoids can prevent the growth of colon cancer cells, while others have shown that they can induce cell death. Additionally, animal studies have suggested that cannabis may enhance the effectiveness of chemotherapy in colon cancer. However, more research is needed to determine the optimal dosages and administration methods for cannabis in colon cancer patients.

Combination therapy with cannabis and chemotherapy: There is evidence to suggest that combining cannabis with chemotherapy may enhance the effectiveness of the chemotherapy in colon cancer (Achuk et al., 2021). Some preclinical studies have found that cannabis can sensitize colon cancer cells to chemotherapy, making them more susceptible to the effects of the chemotherapy(Tomko et al., 2020). Additionally, animal studies have suggested that cannabis may reduce the side effects of chemotherapy, such as nausea and vomiting, in colon

cancer patients. However, more research is needed to determine the optimal dosages and administration methods for combining cannabis and chemotherapy in colon cancer patients.

Safety and adverse effects of cannabis in colon cancer treatment: Cannabis has been associated with several adverse effects, including increased heart rate, dry mouth, and decreased blood pressure (Subramaniam et al., 2019). In addition, long-term use of cannabis can lead to addiction, impaired memory and learning, and decreased motivation(Mhatre V. Ho, Ji-Ann Lee & Dien et al., 2008). In colon cancer patients, the use of cannabis may interact with other medications and can increase the risk of side effects. As a result, it is important to carefully monitor patients taking cannabis for colon cancer, and to adjust the dosage and administration method as needed to minimize adverse effects.

4.3 Recent progress

Cell survival, ROS levels, and apoptosis were lowered by cannabidiol in colon cancer cells in a mouse model of colon cancer, CBD dramatically decreased the amount of abnormal crypt foci polyps and tumor. In colon cancer cells, CBD exhibited a chemo-preventative effect (Aviello et al., 2012; Romano et al., 2014a) because it up-regulated caspase-3. Research has demonstrated the effects of CBD on colon cancer cells in other in vivo experiments to inhibit proliferation, induce apoptosis, and have anti-metastatic and anti-angiogenesis effects (Honarmand et al., 2019). At GPR55, CBD's antagonistic action has been found to play an important role in the decrease and prevention of metastasis of HCT116 colon cancer cells ((Kargl et al., 2016),(Martínez et al., 2020)). Using colorectal cancer in vivo models, researchers discovered that CBD therapy reduced tumor volume by increasing apoptosis and decreasing the expression of pro- and anti-apoptotic proteins (Jeong et al., 2019; Tomko et al., 2020).

Chapter 5

Conclusion and Future Prospects

Greater study in the future may provide further understanding regarding the matter at hand possible immunostimulatory impact of specific cannabinoids or cannabis extracts. This understanding may assist medical experts in incorporating cannabis extracts into cancer targeted treatment, perhaps as an additional therapy. Special extracts with substantial anti-neoplastic properties that are not harmful to normal cells and may sensitize cancer cells to additional treatment without suppressing immune responses should be found. The extracts may then be coupled with immunotherapy, which may have a synergistic effect. The findings of a retrospective study involving patients with melanoma, renal carcinoma, and non-small cell lung cancer who received cannabis in conjunction with the immunotherapeutic drug Nivolumab revealed a reduction in RR but no changes in PFS or OS. More research is required to look at the potential interactions between cannabis and immunotherapy medicines. (Taha et al., 2019)

Conclusion

As emphasized in this review article, Papers of important pharmacological properties and therapeutic potential shown that several of the substances included in cannabis might be part of a treatment approach for particular difficulties encountered during cancer therapy. Cannabis offers a multitude of possible advantages, particularly in the treatment of indications in cancer patients. Cannabis may help with symptoms associated with cancer, such as chemotherapy-induced nausea and vomiting, discomfort, and sleeplessness. Whereas cannabis is less effective than some other antiemetics, from time to time it is the only medication that works, and it is the only antiemetic that also promotes appetite. Treatment with cannabis may be beneficial in experimental forms of intestinal inflammation. CB1 was also found to be protective in CRC

experimental models. However, in terms of modes of action, it is known that cannabinoids can signal through numerous routes, most likely in a ligand-biased manner (Ibsen et al., 2017) Despite an abundance of evidence indicating cannabinoids have anti-carcinogenic activities in vitro, there is a scarcity of evidence to sustain their actions in vivo. Specific receptors that respond to cannabinoids, such as GPR55, have been identified, have even been found to be pro-inflammatory and pro-carcinogenic (Grill et al., 2018)

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