The Role of Cannabis Species on Oxidative Stress in Cancer Cells

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Abstract

Many therapeutic mechanisms kill cancer cells through reactive oxygen species (ROS) generation, ROS plays a vital role in cancer cell signaling and metabolism, which is an irony. Cancer therapies can therefore target oxidative stress through varying mechanisms. The cannabis plant consists of many bioactive compounds with multiple beneficial health properties which have been overlooked for decades. It had been limited to illegal recreational use and legal pharmaceutical exploitation for the manufacturing of medicine. Cannabis consists of derivatives known as cannabinoids which target the endocannabinoid system in the body. Alongside its psychoactive effects, most of the cannabinoid compounds have

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potent therapeutic effects, one of which observed is the induction of oxidative stress in cancer cells, eventually leading to the cell death. This review discusses a brief account of cannabis and its derivatives and how they cause apoptosis in cancer cells by inducing oxidative cellular damage.

Keywords

Cannabis · Cannabinoids · Cannabidiol (CBD) · Tetrahydrocannabidiol (THC) anticancer properties · Cancer cell death

Introduction

Cannabis is a natural compound and a psychoactive drug from the cannabis plant with multiple beneficial health properties which have been overlooked for decades. It had been limited to illegal recreational use and legal pharmaceutical exploitation for the manufacturing of many drugs, textiles fiber, and food. Due to its negative and inaccurate myths, its domestic use has an undesirable view in communities and legal jurisdiction at large. However, recently it has been proven to have healing properties to several ailments. One of its profound elements is linked to its anticancer properties. The cannabis plant produces bioactive derivatives compounds called cannabinoids which have varying properties ranging from psychoactive effects to antitumor properties through various mechanisms. It also shows anti-inflammatory activities leading to pain relief, appetite stimulation, and helps to improve sleeping patterns. More understanding of cannabis and its derivatives needs to be explored. The cannabis plant includes a group of plants belongs to the family cannabacaeae. It has three formally recognized Cannabis species, namely: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Among the three, *C. sativa* is the most commonly cultivated and popular species. It has more than 140 cannabinoids with only two commonly studied cannabinoids such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Pertwee 2006; Hazekamp and Fischedick 2012).

How cannabis derivatives kill cancer cells is a mystery that still needs a whole lot of exploration. However, one of its key mechanisms of activation of cancer cell death is through the increase of oxidative stress (Jeong et al. 2019). This is an interesting phenomenon since cancer cells are well known to escape reactive oxygen species (ROS) induced cell death through the activation of their antioxidant resistance mechanisms (Reczek and Chandel 2018). Cancer cells indeed have the highest ROS levels compared to the normal cells; however, an increase in ROS levels above a certain threshold causes a shift in cancer cell redox balance leading to cytotoxicity and cell death (Massi et al. 2010). The irony of ROS is that it promotes cancer cell survival via cellular calcium ion (Ca^{2+}) channels and causes cell death after reaching the threshold. Cancer cells utilize ROS signaling for migration, proliferation, and survival. Increased ROS levels promote antitumor factors which will induce cell senescence and death. To prevent this, cancer cells upregulate the nuclear factor erythroid 2 related factor 2 (NRF2) which causes antioxidant activation, glutathione peroxidase and

peroxiredoxin enzyme activation for glutathione (GSH) synthesis (Gorrini et al. 2013). The distortion of ROS homeostasis in cancer cells leads to oxidative stress-induced cell death. Hence any cancer therapy that results in ROS increase and antioxidant inhibition is an attractive one if it targets only the diseased cells.

Cannabinoids bind to specific Gαi protein-coupled receptors CB_1-R and CB_2-R on the cell surfaces (Velasco et al. 2016a). However, CBD has shown affinity to different binding targets mainly: CB_2-R, GPR55, and TRPV1/2 protein receptors (Pellati et al. 2018). The binding of cannabidiol to the cannabinoid surface receptors induces cell death via apoptosis and autophagy. This involves the increase in intracellular ROS which leads to endoplasmic reticulum (ER) stress, and thus the activation of the caspases (Jeong et al. 2019).

Cannabis and Cannabinoids

Unlike the *C. sativa, C. indica* is well known for its increased levels of psychoactive compounds mainly THC. The *C. ruderalis* on the other hand contains both psychoactive (THC) and non-psychoactive (CBD) compounds. As mentioned previously, the cannabis plant has derivatives mostly referred to as cannabinoids which function via the stimulation of the cannabinoid receptors (CB1 and CB2) on cells (Grotenhermen and Müller-Vahl 2012). Cannabidiol (CBD) is one of the non-psychoactive cannabinoids associated with several medicinal properties mainly anticancer and antioxidant properties.

For medicinal use, *C. sativa* is the most studied and most applicable because of the properties of its compounds. It contains numerous functional compounds with different conformations that possess varying chemical properties. Over 100 compounds have been extracted from *C. sativa* and one can assume that there is more that is yet to be explored. The term "cannabinoids" is used to refer to many compounds in *C. sativa*, the majority of which include, carbohydrates, fatty acids, and their esters, amides, amines, phytosterols, terpenes, phenolics (Andre et al. 2016). Chemically, these cannabinoids are meroterpenoids derived from the alkylation of alkyl resorcinol with a monoterpene unit. In the plant itself, cannabinoids are biosynthesized in the acid form, upon exposure to light and heat, decarboxylation into their non-acidic form. Although they are varying in chemical orientation, cannabinoids have been well characterized and classified into 11 chemical groups (Hanuš et al. 2016) such as:

1. Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA)
2. Delta-9-Tetrahydrocannabinol (Δ^9-THC)
3. Cannabidiolic acid (CBDA)
4. Cannabigerolic acid (CBGA)
5. Cannabidiol (CBD)
6. Cannabigerol (CBG).
7. Cannabichromenic acid (CBCA)
8. Cannabichromene (CBC)

9. Cannabinolic acid (CBNA)
10. Cannabinol (CBN)
11. Delta-8-Tetrahydrocannabinol (Δ^8-THC produced from the isomerization of Δ^9-THC)

Cannabinoid Receptor System

The cannabinoid receptor system/endocannabinoid system is a very important system in the body that helps to regulate many vital central (CB_1-R) and peripheral (CB_2-R) biological functions. The CB_1-R is much more expressed in the central nervous system (CNS). Because CB2 is expressed more in peripheral tissue, its role is observed in many peripheral effects, e.g., heart rate, blood pressure, lipid metabolism, insulin action, etc. The high expression of CB1 in the CNS on the other hand plays important role in the neural transmitter release and other CNS functions (Zou and Kumar 2018).

Application of Cannabis Species in Medicine

One of the most common applications of cannabis is for recreational purposes. The reason why cannabis is used for recreation and pleasure is that its compounds have a direct effect on brain cells that results in the psychotropic effects (Table 1).

The Endocannabinoid System

The endocannabinoid system was first discovered in 1990 through the discovery of G-coupled receptors. The first receptor to be discovered was CB_1-R followed by the CB_2-R receptor. The discovery of endocannabinoid receptors was driven by the *C. sativa's* psychoactive activity of THC in the brain as a neurotransmitter. Endocannabinoids are lipids produced in the brain and other tissues, they modulate several physiological processes such as pain, mood, appetite, and many other processes by targeting the CB_1-R and CB_2-R cannabinoid receptors (Piomelli 2005). The first endocannabinoid discovered was anandamide, followed by the 2-arachinonylglycerol (2-AG) and many others including arachidonoyldopamin (NADA), homo-gamma-lineleoul ethanolamide, docosatetraenoul ethanolamide (DEA), and noladin ether (2-AGE). Moreover, it was then noted that the endocannabinoid system is one of the most vital physiological systems involved in maintaining human health. The endocannabinoid system is not limited to a certain portion or part of the body but is everywhere in the body bridging between body and mind (Alger 2013). Despite being the most understudied system, it plays an important role in apoptosis, neurotransmission, and homeostasis (Basavarajappa et al. 2009). The cannabinoids of cannabis plant mimic endocannabinoids of course with some undesirable psychoactive effects mainly from THC; however, that does not remove the benefits that come with it such as anticancer properties, pain alleviation, appetite stimulation, etc. (Piomelli 2005).

Table 1 Medicinal properties of cannabis compounds

Compound	Medicinal property	Mode of action	References
Cannabidiol (CBD)	Pain relief	Analgesic and antiemetic properties	Russo (2008) and Baron et al. (2018)
	Weight loss	Regulation of insulin in the body	Bielawiec and Harasim-Symbor (2020)
	Blood sugar control	Regulation of insulin in the body	Bielawiec and Harasim-Symbor (2020)
	Anticancer effects	Decreased cancer cell viability, prevents cancer cell proliferation and invasion	Seltzer et al. (2020)
	Parkinson's disease	Parkinson's disease: Cannabis can help to reduce tremors and pain, promote sleep. It has shown to improve motor skills in patients.	Rieder (2020)
	Epilepsy	Helps to control seizures.	Devinsky et al. (2014)
	Psychogenic effects, e.g., depression management, PTSD, and autism therapy.	Helps in stabilizing moods which can ease depression, violent mood swings. Cannabis helps to control the fight-or-flight response, preventing it from going into overdrive.	Demirakca et al. (2011)
	Anti-inflammatory effects	Cannabis's endocannabinoid contains anti-inflammatories that fight against brain inflammation which leads to Alzheimer's disease.	Ribeiro et al. (2012) and Fouda and Ruben (2021)
	Glaucoma therapy	Helps to reduce the pressure applied on the eyeball providing temporary relief to individuals with glaucoma	Tomida et al. (2004)
Delta-9-tetrahydrocannabinol (THC)	Anti-inflammatory effects	Enhance immune response while also interact with cells that play a vital role in the functioning of the gut in Crohn's disease or ulcerative colitis. Cannabis helps to block bacterial growth and other	Thapa et al. (2018)

(continued)

Table 1 (continued)

Compound	Medicinal property	Mode of action	References
		compounds that cause inflammation in the intestine.	
	Anticancer effects	Induces apoptosis in a CB_1-R dependent binding, inhibits survival signaling cascades while activating the proapoptotic Bcl-2 family member bad.	Greenhough et al. (2007)
Cannabinol (CBN)	Increased appetite	Stimulates appetite without the psychoactive effects.	Farrimond et al. (2012)
	Antibacterial properties	Destroy and suppress bacterial growth.	Stahl and Vasudevan (2020)
	Neuroprotection	Protect the central nervous system from injury and damage.	Pellati et al. (2018)
	Glaucoma therapy	Helps to reduce the pressure applied on the eyeball providing temporary relief to individuals with glaucoma.	Pertwee (2006)
	Anti-inflammatory effects	Like THC, CBN reduces pain, can be used for rheumatoid arthritis treatment.	
Cannabigerol (CBG)	Anticancer effects	Induces apoptosis by stimulation of reactive oxygen species (ROS) production and reduces cancer cell growth.	Borrelli et al. (2014)

Anticancer Properties and Mechanism of Cell Death

Cannabinoids especially CBD and THC, are considered as antineoplastic agents based on the in-vitro and in-vivo studies. The exact mechanisms are not fully known or understood. However, many studies suggest that CBD downregulates the CB_1-R endocannabinoid receptor and rather binds to CB_2-R, while THC binds to CB_1-R. Depending on the type of cancer, CBD induces endoplasmic stress leading to autophagy and decreases mitochondrial membrane potential leading to apoptosis. The autophagic cancer cell death is induced by the inhibition of the AKT and mTOR pathways. While apoptosis is triggered by the reduced mitochondrial potential resulting in Bid translocation to the mitochondria thus leading to cytochrome c release into the cytoplasm, ultimately the stimulation of the apoptotic pathways. Overall, CBD increases ROS production beyond the tumor threshold thus inducing cancer cell death (Shrivastava et al. 2011).

THC has an affinity for the CB_1-R endocannabinoid receptor. It stimulates cancer cell death via the apoptotic pathway by activating Bad, the Bcl-2 family member. Cannabigerol (CBG) has also been associated with apoptotic pathway activation via increased ROS production and decreased cancer cell proliferation and growth (Nallathambi et al. 2018). Generally, the most studied cannabinoids indicate that cancer cell death is mainly triggered by the activation of the ER-stress and mitochondrial potential reduction-related pathways thus leading to autophagy and apoptosis (Velasco et al. 2016b).

Acute Versus Chronic Oxidative Stress in Cancer

Normal cellular metabolic processes result in the production of ROS and Reactive Nitrogen Species (RNS) are inevitable results of the biomolecular reactions in the cells (Chittiboyina et al. 2018). The presence of ROS in normal cells is required for physiological processes, i.e., signal transduction whereas higher level is harmful to the cell macromolecular components. In normal concentrations, ROS regulates several cellular signaling pathways by directly reacting and/or modifying protein transcription factors and genes necessary for cellular processes. Physiologically, ROS concentrations are controlled by redox reactions where the reactive species are antagonized by varying antioxidant systems in the body, resulting in normal levels as per cellular homeostatic requirements. In the presence of disproportionate levels of ROS and/or RNS in correspondence to the capacity of these antioxidant systems to maintain homeostasis, oxidative stress occurs (Hayes et al. 2020).

Genes Involved in Cancer Oxidative Stress

In both normal and pathological conditions, such as stem cell differentiation and cancer, the increased metabolic rate requires high ROS alongside ATP production which may result in acute oxidative stress. During acute oxidative stress, the cell can always adapt to metabolic mechanisms to avoid oxidative damage. In chronic states, however, gene transcription and genetic reprogramming arise to manage the intracellular redox reactions. This results in the expression of various transcription factors as listed in Table 2. In the process of carcinogenesis, these factors play an important role at various stages including initiation, proliferation, and metastasis of cancer (Marinho et al. 2014; Zhang et al. 2018).

At varying stages of cancer cells, including tumorigenesis, proliferation, and the metastatic phase, oxidative stress potentially drives cell senescence and activates cell death via activation of apoptosis. Nonetheless, the presence of ROS in the cells is shown to play a significant role in the initiation of cancer, the proliferation of initiated cells during the promotion to the loss of anchorage dependence, and subsequent metastasis. Cancer cells, therefore, need to maintain their intercellular ROS levels at concentrations necessary for their metabolic activities while avoiding overly stressful conditions that may trigger apoptotic cell death and cancer regression.

Table 2 Transcription factors expressed to regulate redox reactions

Transcription Factor	Function in normal cells	Function/implication in cancer cells	Refs
Tumor protein p53	• Orchestrates apoptosis by stimulating the production of ROS under more severe oxidative stress, induces antioxidant genes to enable adaptation to mild oxidative stress.	• Its deactivation causes accelerated growth of cancer cells by impaired inhibition of cell growth.	Monti et al. (2020)
HIF-1α, heat shock factor 1 (HSF1)	• Activates hypoxia-responsive genes, e.g., VEGF, growth factors, and glycolytic enzymes upon translocation to nucleus and heterodimerization with HIF-1β to form HIF-1 protein.	• Contributes to cancer cell proliferation via hypoxia-mediated angiogenesis.	Ji et al. (2006)
Activator protein 1 (AP-1)	• Aids in the maintenance of cellular homeostasis by binding to DNA regulatory sequences that modulate the rate of gene transcription.	• Varying functions depending on cellular context, i.e., when deregulated, either by overexpression or downregulation, AP-1 factors promote tumorigenesis by acting as transcription factors for most growth factors including oncoproteins, cytokines, and HIF-1α.	Garces de los et al. (2018) and Puigserver and Spiegelman (2003)
Nuclear factor-erythroid 2 p45-related factor 2 (NRF2)	• Regulates the expression of TRPA1, reinforcing. • The link between redox homeostasis and Ca2+ signaling.	• Mediates adaptation to oncogene-stimulated oxidative stress.	Cao et al. (2005)
Peroxisome proliferator-activated receptor ϒ coactivator 1α (PGC-1α),	• Regulates energy metabolism including glucose metabolism and thermogenesis. • Regulates mitochondrial biogenesis by controlling mitochondrial protein production.	*Varying mechanisms:* • Increases antioxidant systems resulting in the inhibition of apoptosis; increases the rate of cancer cell proliferation by induction of the mitochondrial biogenesis pathway;	Puigserver and Spiegelman (2003), Zhang et al. (2004), Alonso-Molero et al. (2017), Yun et al. (2018)

(continued)

Table 2 (continued)

Transcription Factor	Function in normal cells	Function/implication in cancer cells	Refs
	• Stimulates mitochondrial oxidative metabolism.	enhances nutrient uptake, i.e., glucose, reduces glycolysis, and increases oxidative phosphorylation.	
Nuclear factor κB (NF- κB)	• Control mitochondrial function. • Controls cellular resistance to invading pathogens by linking pathogenic signals and immune system.	• Enables cancer cells to resist apoptosis-based tumor-surveillance mechanisms.	Zinatizadeh et al. (2021), Karin (2006), Albensi (2019)
BTB and CNC homology 1 (BACH1)	• Forms a major link between the cellular heme level, the redox state, and the transcriptional response.	• Represses the oxidative. • Stress response by antagonizing NRF2.	Warnatz et al. (2011)

Oxidative Stress in the Tumor Microenvironment

The tumor microenvironment (TME) is a very important element in tumor pathology. The conditions of the TME influences cancer at its varying stages of development. Therefore, the changes in the tumor microenvironment including pH, chemical balance, molecular constituents, and cellular components are very important for tumor cell survival. The oxidative stress in tumors has got a direct influence on the TME by influencing the presence of cellular components including regulatory T (Treg) cells, and tumor-associated macrophages (TAMs) (Nieto et al. 2016). When in the TME, high ROS content would cause chronic oxidative stress that causes the expression of HIF-1a, which in turn promotes the differentiation of cells including cancer-associated fibroblasts (CAFs) in the TME.

Cannabis Derivatives and Oxidative Stress

The suppression of ROS in cancer cells reduces the likelihood of tumor growth (Hayes et al. 2020). The tumor in vivo and in vitro experiments showed, therapies that affect redox reactions influence cancer cell growth and survival. Because of their active role in signal transduction, modulating ROS and their concentration in the cells affects the function of many processes by altering the expression of transcription factors and the signaling pathways involved in oxidative stress responses and maintenance of cellular processes. In cancer, the intracellular oxidative stress that is required for cancer cell metabolism can only be maintained up to a certain level, with

a threshold of which, cell death can still be induced upon exceeding the maximum stress the cancer cell can withstand. Most therapies, therefore, employ the use of mechanisms that are prooxidation by either producing ROS or affecting antioxidant systems to achieve unbearably intracellular ROS levels (Massi et al. 2010).

Cannabis derivatives affect ROS levels in different ways. The action of cannabis derivatives including THC and CBD on oxidative stress is through oxidation that alters the redox balance in favor of increasing ROS levels. This culminates into a state of stress that exceeds the stress threshold and consequently activates apoptosis in cancer cells (Massi et al. 2010; Andre et al. 2016). The link of CBD to high levels of oxidative stress is demonstrated in experiments where added antioxidants to treated cells prevented cell death (Massi et al. 2004; Massi et al. 2006). The production of ROS, combined with the activation of prooxidant enzymes and decreased level of GSH leads to activation of caspase 8 and 9, which activate caspase 3 to induce apoptosis (Fig. 1).

The induction of oxidative stress in CBD-treated cells depends on the role of CB_1-R and CB_2-R on the surface of the cancer cells. Because they mimic endocannabinoids, cannabis derivatives bind to the CB_1-R and CB_2-R on the surface of cancer cells and initiate the pathway that results in apoptosis as shown in Fig. 1. The advantage is that the CB receptors are highly expressed in most tumors and are therefore potential targets for therapy (Sarfaraz et al. 2005). The important role of CB receptors is seen in many instances where inhibition or attenuation of the receptors prevents oxidative stress in normal cells and increases the survival rate, and their high expression is correlated with oxidative stress and apoptosis.

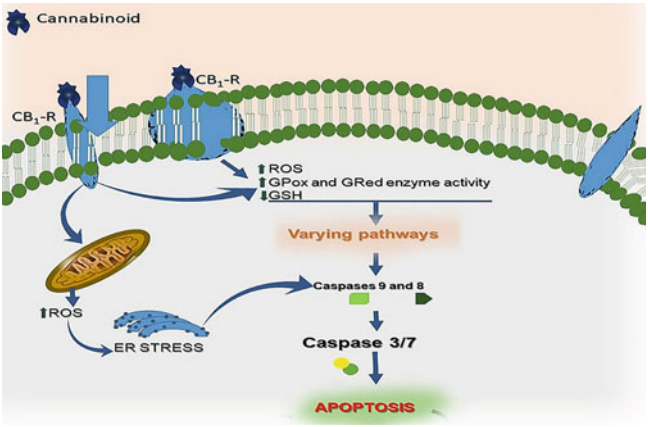

Fig. 1 The binding of cannabinoids in CB receptors leading to the production of ROS, causing ER stress and combined activation of prooxidant enzymes and decrease of GSH resulting in the activation of caspase 8 and 9 which further activate caspase 3 to induce apoptosis

Conclusion

Although oxidative stress is an inherent feature of cancer cells and is required for cancer cell signaling, excessive stress is cytotoxic and can activate apoptosis in cancer cells. There is still a lot to explore with the cannabis plants. Most of its specific cellular and molecular mechanisms are not fully understood, although there have been several in-vitro and in-vivo studies focusing on the effects of cannabinoids on cancer, epilepsy, diabetes, glaucoma, and so forth. The detailed molecular explanations are well documented except for the few abundant ones such as tetrahydrocannabinol and cannabidiol. The discovery of cannabis compounds led to the exploration of the neurotransmitter system and its anticancer activities. The role and influence of cannabis compounds mediated ROS generation in various cancer cell death mechanisms is an important therapeutic target for future research.

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