WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 1, 1686-1696. Review Article ISSN 2277– 7105

CANNABIS & ITS CONSTITUENTS FOR CANCER: HISTORY, BIOGENESIS, CHEMISTRY & PHARMACOLOGICAL ACTIVITIES

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Article Received on
21 Nov. 2020,

Revised on 11 Dec. 2020,
Accepted on 31 Dec. 2020

DOI: 10.20959/wjpr20211-19588

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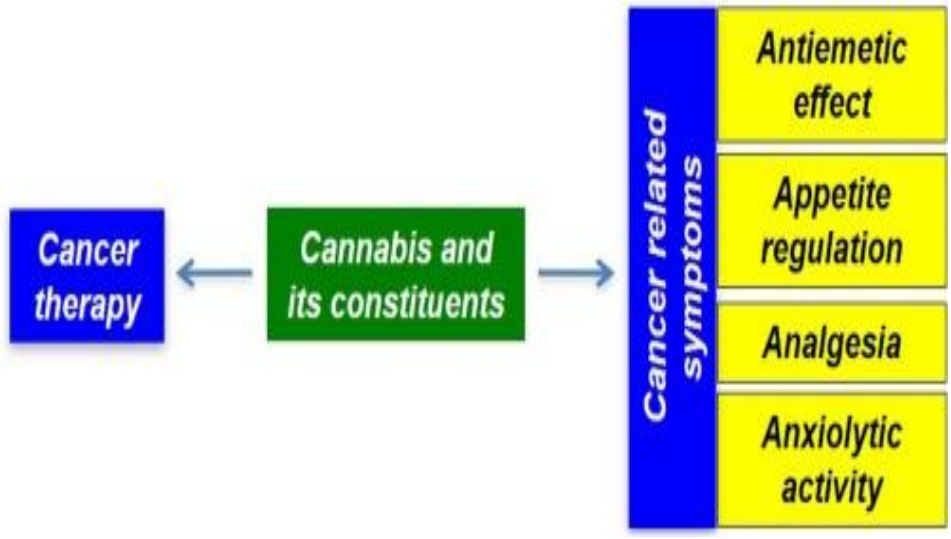
ABSTRACT

Cannabis has long been used for healing and recreation in several regions of the world. Over 400 bioactive constituents, including more than 100 phytocannabinoids, have been isolated from this plant. The non-psychoactive cannabidiol (CBD) and the psychoactive Δ^9-tetrahydrocannabinol (Δ^9-THC) are the major and widely studied constituents from this plant. Cannabinoids exert their effects through the endocannabinoid system (ECS) that comprises cannabinoid receptors (CB1, CB2), endogenous ligands, and metabolizing enzymes. Several preclinical studies have demonstrated the potential of cannabinoids against leukemia, lymphoma, glioblastoma, and cancers of the breast, colorectum, pancreas, cervix and prostate. Cannabis and its constituents can modulate multiple cancer related pathways such as PKB, AMPK, CAMKK-β, mTOR, PDHK, HIF-1α, and PPAR-γ. Cannabinoids can block cell growth, progression of cell cycle and induce apoptosis selectively in tumour cells. Cannabinoids can also enhance the efficacy of cancer therapeutics. These compounds have been used for the management of anorexia, queasiness, and pain in cancer patients. Cannabinoid based products such as dronabinol, nabilone, nabiximols, and epidyolex are now approved for medical use in cancer patients. Cannabinoids are reported to produce a favourable safety profile. However, psychoactive properties and poor bioavailability limit the use of some cannabinoids. The Academic Institutions across the globe are offering training courses on cannabis. How cannabis and its constituents exert anticancer activities is discussed in this article. We also discuss areas that require attention and more extensive research.



KEYWORDS: Cancer, Cannabidiol, Cannabis, Endocannabinoid, Phytocannabinoids, Tetrahydrocannabinol.

INTRODUCTION

Cannabis refers to a group of three plants with psychoactive properties, known as *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.

When the flowers of these plants are harvested and dried, you're left with one of the most common drugs in the world. Some call it weed, some call it pot, and others call it marijuana. As weed becomes legal in more areas, names for it are evolving. Today, more and more people are using the term cannabis to refer to weed. Some argue that it's a more accurate

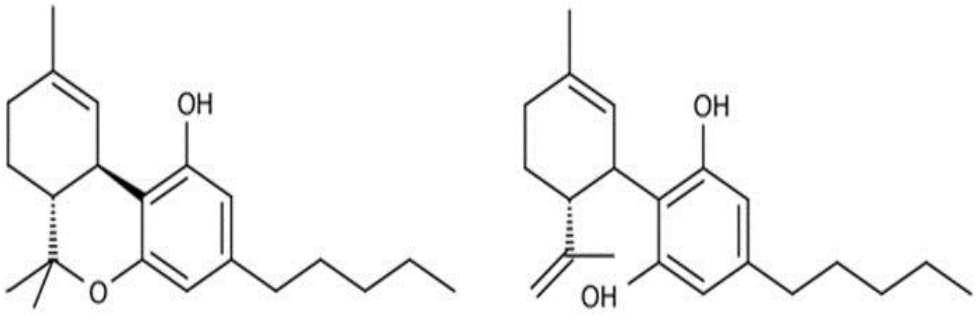
name. Others feel it's more neutral compared with terms like weed or pot, which some people associate with its illegal use. Also, the term "marijuana" is falling out of favor due to its racist history. Cannabis is usually consumed for its relaxing and calming effects. In some U.S. states, it's also prescribed to help with a range of medical conditions, including chronic pain, glaucoma, and poor appetite. Keep in mind that while cannabis comes from a plant and is considered natural, it can still have strong effects, both positive and negative.

History of cannabis use

The history of cannabis and its usage by human's dates back to at least the third millennium BC in written history, and possibly further back by archaeological evidence. For millennia, the plant has been valued for its use for fiber and rope, as food and medicine, and for its psychoactive properties for religious and recreational use.

The earliest restrictions on cannabis were reported in the Islamic world by the 14th century. In the 19th century, it began to be restricted in colonial countries, often associated with racial and class stresses. In the middle of the 20th century, international coordination led to sweeping restrictions on cannabis throughout most of the globe. Entering the 21st century, some nations began to change their approaches to cannabis, with measures taken to decriminalize cannabis; the Netherlands became the first nation to legalize cannabis, and in 2015 Uruguay became the first to legalize recreational cannabis with Canada following in 2018 and South Africa for personal home use only.

Chemical composition of cannabis



Delta-9-tetrahydrocannabinol (THC) Cannabidiol

Delta-9-tetrahydrocannabinol and cannabidiol

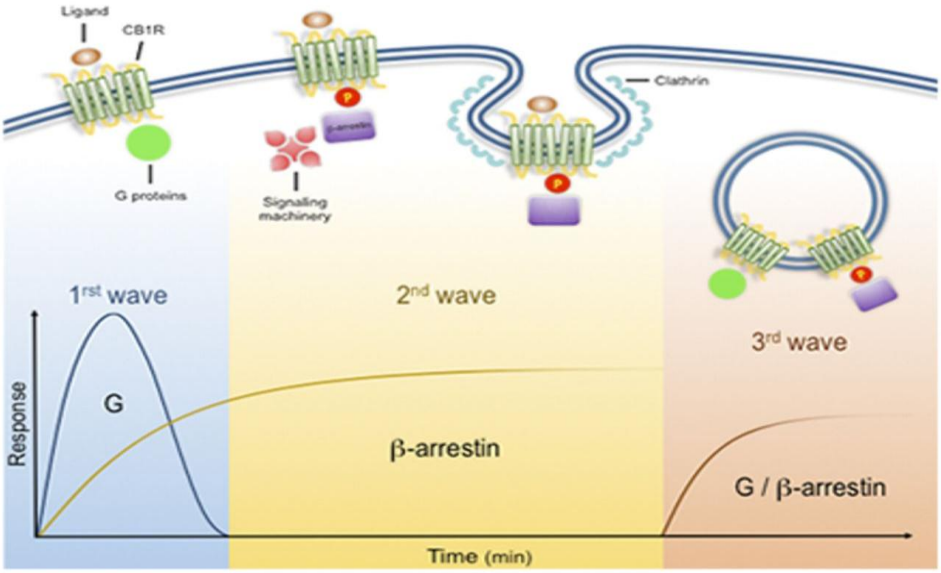
Natural compounds of the cannabis plant are also referred to as phytocannabinoids of which d-9-THC is the main psychoactive ingredient and has been widely researched both in animals

and humans. It characteristically produces, in a dose-dependent manner, hypoactivity, hypothermia, spatial and verbal short-term memory impairment [Hayakawa *et al*. 2007]. However, the second major compound, CBD, does not affect locomotor activity, body temperature or memory on its own. However, higher doses of CBD can potentiate the lower doses of d-9-THC by enhancing the level of CB1R expression in the hippocampus and hypothalamus. The authors suggest that CBD potentiates the pharmacological effects of d-9-THC via a CB1R-dependent mechanism [Hayakawa *et al*. 2007].

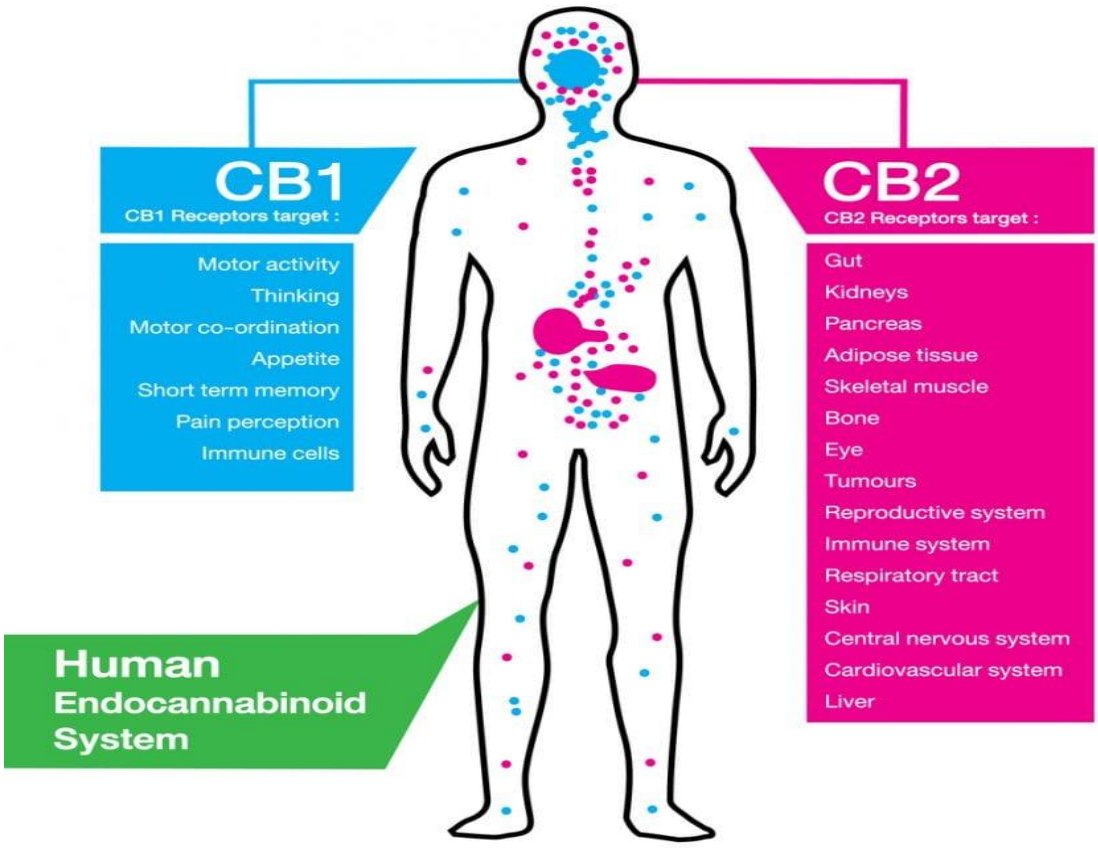
The available research indicates that the main two compounds, d-9-THC and CBD, whilst having similar effects in certain domains, also have almost opposite effects to one another in other aspects.

Receptors of cannabinoids

Cannabinoid receptors, located throughout the body, are part of the endocannabinoid system, which is involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory. Cannabinoid receptors are of a class of cell membrane receptors in the G protein-coupled receptor superfamily. As is typical of G protein-coupled receptors, the cannabinoid receptors contain seven transmembrane spanning domains. Cannabinoid receptors are activated by three major groups of ligands: endocannabinoids, produced by the mammillary body plant cannabinoids (such as Tetrahydrocannabinol, produced by the cannabis plant); and synthetic cannabinoids (such as HU-210). All of the endocannabinoids and phytocannabinoids (plant based cannabinoids) are lipophilic, such as fat soluble compounds. There are currently two known subtypes of cannabinoid receptors, termed CB_1 and CB_2. The CB_1 receptor is expressed mainly in the brain (central nervous system or "CNS"), but also in the lungs, liver and kidneys. The CB_2 receptor is expressed mainly in the immune system and in hematopoietic cells, however further research has found the existence of these receptors in parts of the brain as well. Mounting evidence suggests that there are novel cannabinoid receptors that is, non-CB_1 and non-CB_2, which are expressed in endothelial cells and in the CNS. In 2007, the binding of several cannabinoids to the G protein-coupled receptor GPR55 in the brain was described.



The protein sequences of CB_1 and CB_2 receptors are about 44% similar. When only the transmembrane regions of the receptors are considered, amino acid similarity between the two receptor subtypes is approximately 68%. In addition, minor variations in each receptor have been identified. Cannabinoids bind reversibly and stereo-selectively to the cannabinoid receptors. Subtype selective cannabinoids have been developed which theoretically may have advantages for treatment of certain diseases such as obesity.



Activities of cannabis for cancer

The role of the endocannabinoid system in cancer

Endocannabinoids interact with different types of receptors, including the two $G_{i/o}$-coupled CB receptors, CB_1 and CB_2. While CB_1 receptors are mainly located in the CNS and, to a lesser degree, in some peripheral tissues, CB_2 receptors are primarily expressed on the surface of immune cells. Due to the low expression of CB_2 receptors in the CNS they represent a promising pharmacological target, as selective CB_2 ligands potentially would not have psychotropic effects. In addition, other CB receptor types and isoforms or completely different pharmacological targets of cannabinoids have been described, for example transient receptor potential vanilloid receptor 1 (TRPV1), orphan G-protein coupled receptor (GPR)55, peroxisome proliferator-activated receptors (PPARs) transient receptor potential melastatin 8 (TRPM8), TRP vanilloid 2 (TRPV2) and TRP ankyrin 1 (TRPA1) channel. It is important to note that cannabinoids may also exert their antitumor effects independent of the CB receptors, for example as demonstrated in human pancreatic cancer cell line MIA PaCa-2.

The biological role of the ECS in cancer pathophysiology is not completely clear but most studies suggest that CB receptors and their endogenous ligands are upregulated in tumor tissue and that the overexpression of ECS components (i.e., receptors, ligands, and enzymes) correlates with tumor aggressiveness. However, a tumor-suppressive role of ECS was also indicated by some studies, e.g., the upregulation of endocannabinoid-degrading enzymes was observed in aggressive human cancers and cancer cell lines. Moreover, experimental studies showed that the activation of CB receptors by cannabinoids is antitumorigenic in most cases, i.e., it inhibits tumor cell proliferation, induces apoptosis *in vitro*, and blocks angiogenesis and tumor invasion/metastasis *in vivo*. The effects of CB receptor (over)expression in selected human tumor cell lines are described in more detail in TABLE NO.1

Table no. 1: Expression of cannabinoid (CB) receptors in selected human cancer types.

Cancer cell type	Regulation of CB_1/CB_2	Mechanisms and other relevant circumstances	Reference
Breast cancer	Elevated CB_2 receptor expression in HER2+ breast tumors.	HER2 induces CB_2 expression activating ELK1 (ERK/MAPK cascade); activated pro-oncogenic signaling through tyrosine kinase c-Src.	[28,29]
	Presence of TRPV1 in human breast adenocarcinoma cell line (MCF-7).	TRPV1 agonists/antagonists induce significant inhibition of MCF-7 cell growth.	[30]
	Elevated CB_1 receptor expression.	Activation of Akt signaling pathway was proposed. Increased CB_1 and FAAH levels correlate with severity of the disease.	[31-34] [35,36]
Prostate cancer	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Additionally: Presence of TRPV1 and TRPA1 in all prostate cancer cells (except LNCaP cells). TRPV2 in DU-145 and PC-3 cells only. TRPM8 in AR-dependent prostate cell lines (e.g., LNCaP).	[37-39]
	Expression of CB_1 and CB_2 receptor significantly higher in human prostate cancer.	Expression of GPR55 in PC-3 and DU-145 cell lines has been reported, mediating effects of LPI.	[40]
Chemically induced hepatocellular carcinoma	Upregulation of CB_1 receptors.	Diethylnitrosamine induced liver cancer.	[41]
Hepatocellular carcinoma	Overexpression of CB_1 and CB_2 receptors.	Overexpression of CB_1 and CB_2 receptors is associated with improved prognosis.	[42]
Non-small cell lung cancer	Overexpression of CB_1 and CB_2 receptors.	Activation of Akt signaling pathway; MMP9 expression and activity.	[43]
Chronic lymphocytic leukemia	Overexpression of CB_1 and CB_2 receptors.	CB_1 receptor expression correlated with high-risk markers.	[44]
Pancreatic cancer	CB1 and CB_2 receptors expressed in normal and pancreatic cancer cells (higher expression of CB_1).	Cannabinoids induced apoptosis via CB_1 receptor (ceramide dependent pathway).	[45-47]
Melanoma	CB_2 is overexpressed in human melanoma tissues and cell lines.	Not reported.	[48]

HER2: Human epidermal growth factor receptor 2; ELK1: ETS domain-containing protein; c-Src: Tyrosine-protein kinase Src; ERK: Extracellular-signal-regulated kinase; MAPK: Mitogen-activated protein kinase; TRPV1: Transient receptor potential vanilloid receptor 1; Akt: Protein Kinase B; FAAH: Fatty acid amide hydrolase; TRPA1: Transient receptor potential ankyrin 1; GPR55: Orphan G-protein coupled receptor 55; AR: Androgen receptor; LPI: Lysophosphatidylinositol; MMP9: Matrix metallopeptidase 9

Antitumor effects of cannabinoids

By targeting the ECS, cannabinoids affect many essential cellular processes and signaling pathways which are crucial for tumor development. For example, they can induce cell cycle arrest, promote apoptosis, and inhibit proliferation, migration and angiogenesis in tumor cells. In addition to CB receptor-mediated (CB_1 and CB_2 receptors) cannabinoid effects, it appears that these processes can also be CB receptor-independent (e.g., through TRPV1, 5-hydroxytryptamine [5-HT], or nicotinic acetylcholine receptor [nAChR] among others) suggesting that molecular mechanisms underlying the antitumor activity of cannabinoids are even more complex than originally thought. Moreover, it is expected that future studies will discover novel molecular targets of cannabinoids. The ability of plant-derived and synthetic cannabinoids to control cancer cell growth, invasion, and death has been demonstrated in numerous experimental studies using cancer cell lines and genetically engineered mouse models. Also, different types of cannabinoids may have different modes of action. For example, a phytocannabinoid THC promotes apoptosis in a CB-receptor dependent manner, while CBD exerts this effect independently of CB_1/CB_2 receptors and possibly includes the activation of TRPV2 receptor, at least in some cancer types. Also, some CB receptor agonists are less efficient in promoting cancer cell death although they demonstrate higher affinity for CB receptors than THC, such as synthetic CB receptor agonist WIN-55,212-2. Better understanding of homo- or hetero-oligomerization of CB receptors, their interactions with lipid rafts for example, and mechanisms of selective G-protein coupling may clarify these

differences . Finally, because molecular changes are tumor-specific in most cases (i.e., the presence of intra- and inter-tumor heterogeneity), CB-receptor mediated antitumor effects largely depend on the type of cancer that is being investigated and characteristics of derived tumor cell line, including the donor characteristics, tumor site of origin and hormonal responsiveness.

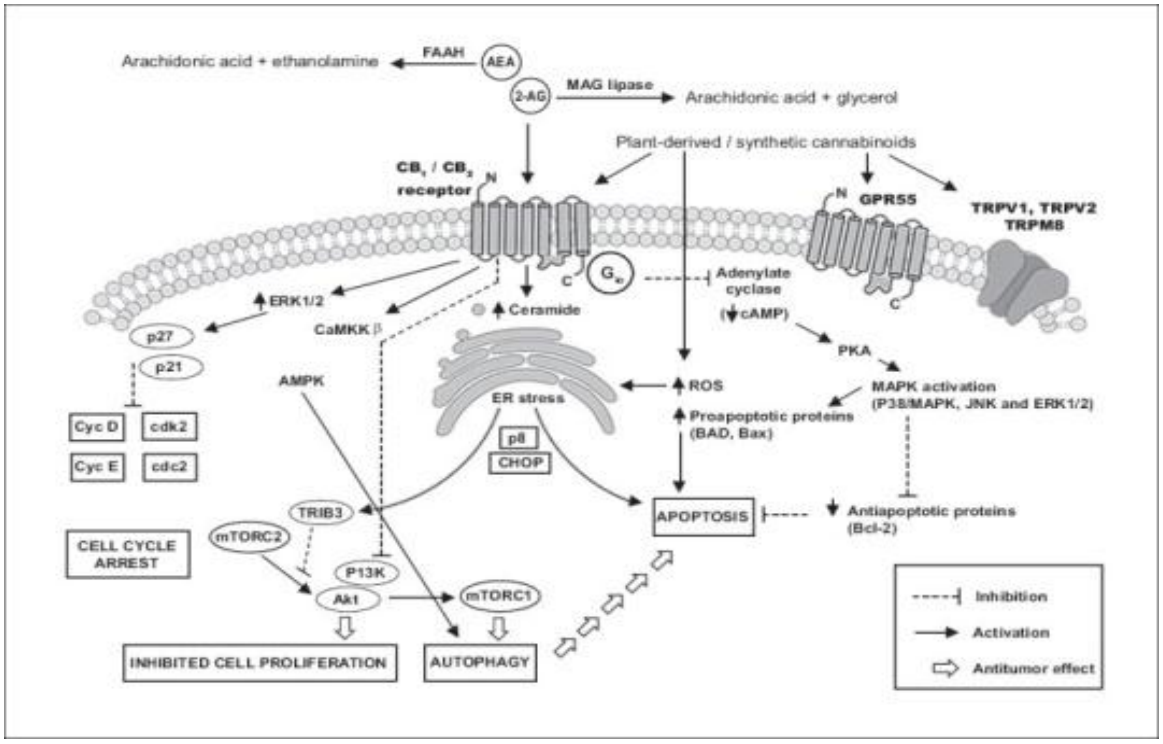


Fig. no. 1: Example of different signaling pathways induced by cannabinoids in cancer cells.

Pharmacology of cannabis

Two separate cannabis receptors have been identified (CB_1 and CB_2), which were cloned in 1990 and 1993, respectively. Both receptors are coupled to G proteins and their activation leads to an inhibition of adenyl cyclase, decreased production of cAMP and modulation of the ion channel activity. At the cellular level, cannabinoids act through CB receptors to hyperpolarise neurones by closing voltage-dependent calcium channels and by activating potassium channels. CB_1 receptors are distributed widely throughout the central nervous system (CNS) and the peripheral nervous system (PNS). They are present in their greatest concentration around the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum and spinal cord. This pattern accounts for the effects of cannabinoids on memory, emotion, cognition and movement. Increased levels of CB_1 receptors are found in the peri-aqueductal grey matter (PAG) and dorsal horn of the spinal cord, regions involved in the modulation of

nociceptive transmission. CB_1 receptors are sparse in the brainstem, which may explain the lack of respiratory depression associated with the administration of these compounds. CB_2 receptors are located peripherally and are closely linked with cells in the immune system, predominantly the spleen and macrophages .Research on endogenous ligands has focused mainly on three ligands:

1. Anandamide (from the Sanskrit word *ananda*, meaning bliss);
2. Arachidonoylglycerol;
3. Palmitoylethanolamide.

Anandamide, first described in 1992, produces similar effects to δ-9THC but is a less potent agonist with a shorter half-life .It is a partial agonist for both CB_1 and CB_2 receptors, with less CB_2 than CB_1 efficacy. 2-Arachidonoylglycerol, originally identified in intestinal tissue, is found at 170-fold higher levels than anandamide in the brain. Palmitoylethanolamide may bind to a yet unidentified 'CB_2-like' receptor With regard to the fate of released endocannabinoids, there is evidence that anandamide and 2-arachidonoylglycerol are removed from the extracellular space by a carrier-mediated, saturatable uptake process that is present in neurones and astrocytes (the anandamide transporter). Once within the cell, anandamide is thought to be hydrolysed to arachidonic acid and ethanolamine by the microsomal enzyme, fatty acid amide hydrolase (FAAH). Anandamide is a vanilloid receptor (VR_1) agonist. Recent advances include the development of inhibitors of the anandamide transporter and FAAH, and the capsaicin analogue Olvanil, which is a potent inhibitor of the anandamide transporter and is also a CB_1 receptor agonist The endogenous cannabinoid system is involved in analgesia, cognition, memory, locomotor activity, appetite, vomiting and immune control.

A series of synthetic compounds has been developed that act on the cannabinergic system, e.g. WIN55212 and CP55940. Recent developments include the synthesis of new ligands that have CB_1 and CB_2 receptor selectivity. Another significant advance is the development of a cannabinoid receptor agonist (δ8 THC-11-oic acid) that is soluble in water. The removal of the need for a solubilizing agent will facilitate cannabinoid delivery, not only *in vitro* but also clinically, particularly when administration to patients is to be by injection or aerosol. Specific antagonists to both CB_1 and CB_2 receptors have been developed. SR141716A is a selective CB_1 receptor antagonist and SR144528 is a selective CB_2 receptor antagonist .Both these compounds also exhibit the properties of an inverse agonist. Thus, as well as

attenuating the effects of CB receptor agonists, it can by itself elicit responses in some CB receptor-containing tissues that are opposite to those elicited by CB receptor agonists. Experiments in animal models have shown that addition of the cannabinoid antagonist SR141716A produces abnormal nociceptive behaviour, indicating that the cannabinergic system is tonically active.

CONCLUSION

Cannabinoids are a large and important class of complex compounds that have a promising therapeutic potential for the treatment of variety of diseases, including cancer. In this review, we focused on studies that provided evidence for anticancer effects of plant-derived and synthetic cannabinoids and their potential mechanisms of action. Cannabinoids were able to effectively modulate tumor growth in different *in vitro* and *in vivo* cancer models, however, these anticancer effects appears to be dependent on cancer type and drug dose. Understanding how cannabinoids are able to modulate essential cellular processes involved in tumorigenesis, such as the progression through the cell cycle, cell proliferation and cell death, as well as the interactions between cannabinoids and immune system are crucial for improving existing medications and developing new therapeutic approaches.

Although still strict, the legislation on the use of cannabis-based medications has been improved, especially following the promising results of related basic research. The Republic of Slovenia established a legal basis for the use of cannabinoids in the years 2016 and 2017. The increasing popularity of cannabis and cannabis-based medication should lead to clear regulatory guidelines on their use, in the near future.

REFERENCES

1. Touw M. The religious and medicinal uses of cannabis in China, India and Tibet. J Psychoactive Drugs, 1981; 13(1): 23–34.
2. Robinson SM, Adinoff B. The classification of substance use disorders: Historical, contextual, and conceptual considerations. Behav Sci (Basel), 2016; 6(3): 18.
3. Zuardi AW. History of cannabis as a medicine: A review. Rev Bras Psiquiatr, 2006; 28(2): 153–7.
4. American Herbal Pharmacopoeia®[Internet] Scotts Valley: American Herbal Pharmacopoeia®; 2018.

5. Bifulco M, Pisanti S. Medicinal use of cannabis in Europe: The fact that more countries legalize the medicinal use of cannabis should not become an argument for unfettered and uncontrolled use. EMBO Rep, 2015; 16(2): 130–2.
6. Ko GD, Bober SL, Mindra S, Moreau JM. Medical cannabis - The Canadian perspective. J Pain Res, 2016; 9: 735–44.
7. Birdsall SM, Birdsall TC, Tims LA. The use of medical marijuana in cancer. Curr Oncol Rep, 2016; 18(7): 40.
8. Davis MP. Cannabinoids for symptom management and cancer therapy: The evidence. J Natl Compr Canc Netw, 2016; 14(7): 915–22.
9. National Cancer Institute [Internet] USA: National Cancer Institute; 2018. [cited 2018 May 30].
10. Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA. Antineoplastic activity of cannabinoids. J Natl Cancer Inst, 1975; 55(3): 597–602.
11. Müller L, Radtke A, Decker J, Koch M, Belge G. The synthetic cannabinoid Win 55,212-2 elicits in human cancer cell lines. Anticancer Res, 2017; 37(11): 6341–5.
12. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther, 1997; 74(2): 129–80.