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Cannabis and its constituents for cancer: History, biogenesis, chemistry and pharmacological activities

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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.

Abbreviations: Δ^8-THC, Δ^8-tetrahydrocannabinol; Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; 2-AG, 2-arachidonoylglycerol; 5HT, 5-hydoxytryptamine; ACPA, arachidonoyl cyclopropamide; AEA, N-arachidonoyl ethanolamine; AIDS, acquired immunodeficiency syndrome; ALL, acute lymphoblastic leukemia; AMPK, adenosine monophosphate activated kinase; Ang-2, angiopoietin-2; ATP/AMP, adenosine triphosphate/Adenosine monophosphate; BAD, Bcl2-associated agonist of cell death; Bcl2, B-cell lymphoma 2; CAMKK-β, calmodulin-dependent protein kinase kinase-beta; CBC, cannabichromene; CBD, cannabidiol; CBDA, cannabidiolic acid; CBG, cannabigerol; CBGA, cannabigerolic acid; CBN, cannabinol; CBND, cannabinodiol; CBs, cannabinoids; Cdc2/25A, cell division cycle2/25A; Cdk2, cyclin dependent kinase 2; COX-2, cyclooxygenase-2; CTCL, cutaneous T-cell lymphoma; ECS, endogenous/endo cannabinoid system; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal regulated kinase1/2; FAAH, fatty acid amide hydrolase; FAK, focal adhesion kinase; GPR55, G protein coupled receptor 55; HIF-1α, hypoxia-inducible factor-1 alpha; IL-1β, interleukin-1 beta; IL, interleukin; JNK1/2, c-Jun N-terminal kinase1/2; MAG lipase, monoacylglycerol lipase; MAPK, mitogen activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; NF-1, neurofibromatosis type-1; $p27^{kip1}$, $p27^{kinase\ inhibitor\ protein\ 1}$; PA, pilocytic astrocytoma; PAI-1, plasminogen activator inhibitor-1; PDHK, pyruvate dehydrogenase kinase; PGE2, prostaglandin E-2; PI3K, phosphatidylinositol-3-kinase; PIGF, placental growth factor; PKB, protein kinase B; PPAR-α/γ, peroxisome proliferator-activated receptor alpha/gamma; pre-THC, pre-tetrahydrocannabinol; Rb, retinoblastoma; RhoA, Ras homolog gene family member A; ROS, reactive oxygen species; SEA, stearoyl ethanolamide; TIMP-1, tissue inhibitor of matrix metalloproteinases-1; TNF-α, tumor necrosis factor-alpha; TRB3, tribbles homolog 3; Trk, tropomyosin receptor kinase; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential cation channel subfamily M (melastatin) member 8; TRPV1/2, transient receptor potential vanilloid ½; VEGF, vascular endothelial growth factor.

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1. Introduction

Cannabis sativa (commonly called cannabis, marijuana, bhang, ganja or hemp) is an important source of cannabinoids (CBs). The cannabis plant is known to contain more than 400 medicinally important molecules, about one-fourth of which are CBs. Phytocannabinoids and endocannabinoids are the two main categories of CBs. While phytocannabinoids are produced by plants, endocannabinoids are produced by mammals. Humans have cultivated and used cannabis over thousands of years for medicinal and recreational purposes. Terpenoids, flavonoids, fatty acids, amino acids, sugars and vitamins are the other common chemical constituents isolated from cannabis. Amongst various constituents of cannabis, cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (Δ^9-THC) are the common and widely studied CBs. While Δ^9-THC is psychoactive, CBD is non-psychoactive in nature.

CBs exert their pharmacological activities through the endogenous cannabinoid system (ECS) that comprises CB_1 and CB_2 receptors [1–4]. Apart from binding to CB receptors, CBs also bind to non-CB_1/non-CB_2 receptors such as G protein-coupled receptor 55 (GPR55) [5] or the transient receptor potential (TRP) channels [6] and exert the effects. ECS modulates various physiological functions including immunological and neurological processes. CBs can also modulate numerous physiological conditions and processes such as memory, mood, appetite and pain. Thus, researchers and clinicians have explored the potential of CBs as a potential agent for clinical use in various disorders including cancer [7].

In the past few decades, significant studies have investigated the safety, efficacy and clinical utility of cannabis and CBs in preclinical and clinical cancer models. These have been exploited both for therapy and management of cancer associated symptoms. Most clinically available cancer drugs are non-selective and induce systemic toxicity in patients. The undesirable side-effects limit the therapeutic utility of many cancer drugs. However, CBs such as Δ^9-THC can preferentially induce cell death in tumour cells over normal cells. Additionally, in healthy rat models, Δ^9-THC exhibited very little toxicity and did not affect any haematological parameter, overall health and survival of the animals [8]. These findings make Δ^9-THC a potential candidate for therapeutic use in cancer chemotherapy [9]. Although the underlying mechanisms for antineoplastic activity are still under investigation, cannabinoids are reported to inhibit cell growth, induce apoptosis, modify signalling molecules, inhibit angiogenesis and reduce invasion and metastasis [10].

Besides established and demonstrated antineoplastic activity in preclinical studies, very few clinical investigations have been performed to examine the efficacy of CBs in cancer patients. For instance, CBs have shown significant efficacy in reducing tumour volume in patients with solid tumours. However, some studies have reported inconsistent results due to high variability in pharmacodynamics and lack of specific formulations. Additionally, due to complex tumour biology and associated microenvironment, further clinical investigations are warranted [9]. Also, more stringent studies on dosage forms and route of administration which modulate the overall efficacy of the drug are required. In patients, CBs are more effective in relieving cancer associated pain. In this article, we summarize biogenesis, structural aspects and chemical composition, classification and various signalling pathways involved in the anti-cancer activities of cannabis and CBs. We have covered both pre-clinical and clinical studies for therapy and symptom management. Key aspects that require further investigation before cannabis can be prescribed as a treatment modality for patients are highlighted.

2. History of cannabis use

The uses of cannabis and its constituents as an herbal medicine date back several thousand years [11]. To our knowledge, the medical use of cannabis was reported in the 28th century BCE by the Chinese Emperor Shen Nung [12]. Originally, cannabis and its constituents were used in the Central and Northern regions of Asia. It was widely used for medicinal purposes in the form of resin, marijuana, hashish and flower buds [13,14]. Cannabis was introduced to Western medicine in the 1840s [15]. The interest in cannabis research has grown exponentially after Δ^9-THC was identified from a group of more than 60 cannabis constituents [7]. As of 13 June 2020, 22,497 articles are listed on the National Institutes of Health PubMed database, out of which 903 are related to cancer.

More than 500 unique compounds have been identified from various species of Cannabis [16]. Due to the psychoactive effects including addictive and abusive potential, cannabis and its products are included in the category of controlled drug substances and their possession is illegal in many countries. Δ^9-THC, cannabinol (CBN) and cannabinodiol (CBND) are the main psychotropic components of *C. sativa* that are listed in controlled substances act under schedule I since 1970. Despite being recognised as a medicinally valuable agent, cannabis received little attention in the scientific community because of its status as a controlled drug substance [17]. The chemical inventory of cannabis is experiencing a revival from the past few decades [18,19].

Over the years, some CBs have been approved for human use. For example, in 1986 dronabinol (synthetic Δ^9-THC) was approved for the management of chemotherapy-induced conditions such as emesis. Later, it received approval for the therapy of weight loss in AIDS patients. Epidiolex (CBD) has also been approved by the Food and Drug Administration for severe epileptic conditions, Dravet syndrome and Lennox-Gastaut syndrome. Nabiximols (Sativex) oromucosal spray was approved in Europe and Canada for various clinical conditions including neuropathic pain, spasticity and multiple sclerosis in 2010. However, these products are available only with a prescription from a licensed medical practitioner.

The pharmacological activity of CBs is reported for several diseases including cancer [20]. To our knowledge, the antineoplastic potential of cannabinoids was first reported in 1975 [21]. The group demonstrated a dose-dependent anti-proliferative action of Δ^8-tetrahydrocannabinol (Δ^8-THC) and CBN. The oral administration of the agents retarded the tumour growth in mouse models of Lewis lung adenocarcinoma. Since then, a number of cell lines and animal studies demonstrated the impressive therapeutic potential of CBs [10,22].· The first human-interventional study to assess the anti-tumour action of CBs was reported in 2006 [23]. The pilot-scale investigational study was a phase I trial performed on patients with recurring glioma who had failed in previous radiotherapy and chemotherapy. The intracranial administration of Δ^9-THC to the cohort resulted in 24 weeks of median survival (95 % confidence interval: 15–33). However, the study also demonstrated that Δ^9-THC is not the first choice agent for cancer therapy due to its high hydrophobicity and CB_1 mediated psycho-activity [23]. Nonetheless, the study paved the way for further clinical and pre-clinical testing of other natural and synthetic cannabinoids to assess their anti-cancer potential. However, complete pharmacological profiling of all the compounds of cannabis extract remains to be fully explored. Currently, Epidioloex (containing CBD) marketed by GW Pharmaceuticals is prescribed as an adjuvant for the treatment of glioma [24].

3. Biogenesis and chemical composition of cannabis

Distribution of phytocannabinoids in nature is restricted but highly variable. These compounds are found in different taxonomic groups such as plants [16], fungi [25] and liverworts [26,27]. Traditionally, phytocannabinoids are related with cannabis species and related plant analogues. *C. sativa* contains more than 500 chemical compounds including Δ^9-THC and CBD as shown in Fig. 1 [16].

In the cannabis plant, CBs are biosynthesised from cannabigerolic acid (CBGA). CBGA is derived from its aromatic precursor olivetolic acid, which forms the resorcinyl core (Fig. 2). The resorcinyl core surrounded by carbon skeletons of varying length contribute to structural hallmarks of phytocannabinoids. CBGA is the key precursor in the biosynthesis of most CBs (Fig. 3) [16]. The biosynthesis of CBs typically

comprises of thermal and irradiation reactions, oxidation and enzyme catalysis [28]. For example, synthases perform conversion of CBGA into cannabidiolic acid (CBDA) and Δ^9-Tetrahydrocannabinolic acid (Δ^9-THCA) [29,30]. Further, oxidation and photochemical reactions of Δ^9-THC forms CBN and CBND, respectively [29,31]. Similarly, cannabigerol (CBG) and CBD are formed via photochemical reaction of CBGA and CBDA, respectively. When a dried extract of cannabis is subjected to heat or sunlight, phytocannabinoids loose the carboxylic acid moiety leading to the formation of compounds that exhibit high binding affinity towards CB_1 and CB_2 receptors over the carboxylated ones [32,33].

CBs can be divided broadly into 3 major classes: i) phytocannabinoids, ii) endocannabinoids, and iii) synthetic cannabinoids.

3.1. Phytocannabinoids

The structural diversity of phytocannabinoids can be attributed to the vast variation in the resorcinyl core, isoprenyl moiety, and the side-chain (Fig. 4). Based on the structural diversity in isoprenyl moiety, major skeletons of phytocannabinoids have been classified into nine topological arrangements (Fig. 5). For example, in CBG-type compounds, the carbon chain remains linear whereas it cyclises in cannabicyclol-type compounds. Further, ring formation connected to the resorcinyl moiety generates cannabichromene (CBC)-type, cannabielsoin-type, and cannabifuran-type compounds. Ring-aromatisation generates CBND-type and CBN-type compounds [16].

The resorcinyl core of phytocannabinoids remains carboxylated in raw extracts of cannabis and undergoes decarboxylation when subjected to heating or smoking. These compounds are known as acidic phytocannabinoids or pre-cannabinoids. Acidic CBs are not decarboxylated in biological milieu and therefore, they are subjected to heat before use. Nowadays, pre-cannabinoids are gaining interest in the arena of drug discovery. A notable example is pre-tetrahydrocannabinol (pre-THC) which is not a narcotic due to its poor efficiency in crossing the blood-brain barrier. However, it retains the binding affinity towards CB_1 and CB_2 receptors [34].

Native or raw extract of cannabis contains a variety of compounds including phytocannabinoids, flavonoids, terpenes and fatty acids. Representative compounds of various classes are listed in Table 1 [28]. Among phytocannabinoids, Δ^8-THC, Δ^9-THC, and CBN bind to CB receptors with significant affinity (Fig. 6) [16]. Δ^9-THC, the major chemical component of cannabis, is a partial agonist of CB_1 and CB_2 receptors [35,36]. It is unstable in pure form (amorphous gum) and turns brown due to oxidative conversion into CBN. However, its crude form is stable and can be stored in alcoholic solutions under refrigeration [37,38]. It is an interesting candidate for drug-discovery due to reduced toxicity compared to CBN and other CBs [39].

Similar to Δ^9-THC, Δ^8-THC also exhibits a decent binding affinity towards cannabinoid receptors [36]. Also, it has greater stability over Δ^9-THC which makes a better lead for exploration of its biological activity [36,40]. However, it is slightly less active compared to Δ^9-THC [36]. CBN was the first CB isolated from the extract of cannabis in 1896 in the UK [41]. It exhibits a weak binding affinity towards CB_1 and CB_2 receptors as compared to THC [42]. However, it is highly stable towards oxidative degradation compared to Δ^9-THC. Upon storage, the concentration of CBN in cannabis products such as marijuana and hashish increases due to oxidative degradation of Δ^9-THC [37,38].

3.2. Endocannabinoids

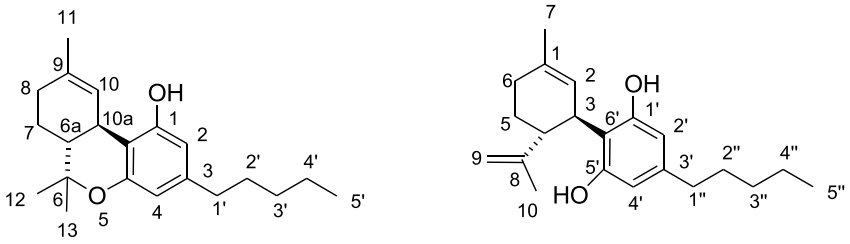
Endocannabinoids (endogenous cannabinoids) are basically endogenous ligands that were discovered in the early 1990s as part of ECS. Major endocannabinoids found in mammals are anandamide or N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). Other components of ECS are discussed in the later sections of this manuscript.

2-AG and AEA are lipid-based derivatives of arachidonic acid (Fig. 7). For instance, AEA is the amide derivative of arachidonic acid and ethanolamide [43–45]. ECS modulates various physiological processes of the body including cellular growth and proliferation [46–48]. Several reports have demonstrated their anti-tumorigenic activity in various cell lines. The molecular mechanism of action of CBs depends on various factors such as the site and the type of cancer. For instance, AEA inhibits cell growth and proliferation in MCF-7 cell lines by binding to CB_1 receptors [49], while in CHP100 human neuroblastoma cells, it induces apoptosis through vanilloid receptors, leading to caspase activation [50]. However, some studies have also reported its protective action against apoptosis [51]. The synthetic analogue of AEA, arachidonyl-2′-chloroethylamide reduces the invasiveness of breast cancer stem cells via binding to CB_1 receptor [52] but is inactive in Kaposi's sarcoma cell lines [53]. Likewise, several derivatives of linolenic acid and arachidonic acid have demonstrated efficacy in enhancing the cytotoxic activity of AEA in cancer cell lines including glioma [54].

3.3. Synthetic cannabinoids

Synthetic CBs encompass a diversified group of compounds. The synthetic molecules are developed to explore the therapeutic potential of CBs. In contrast to the raw extract of cannabis, which contains a mixture of CB receptors agonists as well as antagonists, synthetic cannabinoids come in pure form with selective receptor binding affinity and pharmacological activity. The widespread popularity of synthetic CBs among users can be attributed to their powerful effects and lack of detectability in simple urine tests. They often exhibit greater potency and higher binding affinity towards CB_1 receptors compared to psychoactive Δ^9-THC. Furthermore, synthetic CBs have shown improved pharmacological profile over Δ^9-THC in several analgesic and anticancer preclinical studies [55,56]. However, like Δ^9-THC, synthetic CBs also show adverse effects such as severe psychotic symptoms, arrhythmias and shortness of breath.

Synthetic CBs belonging to various classes have demonstrated a wide range of pharmacological activities including anticancer activity. For example, JWH-015, a naphthoyl indole derivative, induced apoptosis and reduced metastasis in breast cancer cell lines. Further, in non-small lung cancer cell lines, JWH-015 reduced the tumour growth and



Δ^9-Tetrahydrocannabinol (Δ^9-THC) Cannabidiol (CBD)

Fig. 1. Numbering system of phytocannabinoids.

inhibited the recruitment of macrophages [57,58]. JWH-133, a pyran derivative and a scheduled substance, inhibited tumour progression and metastasis in breast cancer cell lines [59]. Among quinone based synthetic CBs, which have demonstrated *in-vitro* apoptotic activity include HU-331 and PM-49 [60–63]. HU-331 is an oxidation product of CBD and exhibits anti-tumour activity via inhibition of topoisomerase-II. In *in-vitro* experiments, it exhibited anti-tumour activity against leukemia, lymphoma, and colon cancer cell lines [60–62]. PM-49 exhibits apoptotic activity by acting on CB_1 receptor and cellular oxidative stress mechanisms [63]. Recently, anti-tumour activity of naphthaquinone derivatives were reported against breast cancer cell lines of triple-negative origin [64].

4. Receptors of cannabinoids

Cannabinoid receptors are transmembrane proteins that mediate the action of CBs. Two common cannabinoid receptors are CB_1 and CB_2 that belong to the class A family of G-protein coupled receptors. Both receptors contain a glycosylated amino-terminal (extracellular) and carboxy-terminal (intracellular) domain connected by 7 transmembrane domains, 3 extracellular loops and 3 intracellular loops [3,65].

Cannabinoid receptors are found in both central and peripheral tissues of the body [66]. CB_1 is predominant in the regions of brain such as cerebral cortex and cerebellum. CB_2 is mostly located in peripheral tissues including lungs, leukocytes, liver, and spleen [66]. CB_1 and CB_2 receptors along with endogenous CBs and endocannabinoid metabolic enzymes [monoacylglycerol lipase (MAG lipase) and fatty acid amide hydrolase (FAAH)] constitute ECS of the body. Natural and synthetic CBs play important roles in different pathophysiological conditions, including cancer, by modulating ECS [67].

The ability of CBs to modulate tumorigenic properties depends on various factors including the type of cancer, binding affinity between the ligand and the pharmacological target (e.g., cannabinoid receptor) and the site of the tumour [10,68,69]. For instance, binding affinity of WIN-55,212−2 with cannabinoid receptors is higher compared to its natural analogue, THC [10]. However, WIN-55,212−2 is less efficient in promoting cell death as compared to THC [10]. WIN-55,212−2 is a schedule I controlled substance and illegal to use. The anti-tumorigenic action of CBs is attributed to the modulation of various signalling pathways crucial for cancer pathogenesis (Fig. 8) [10,69–71].

CBs exert their apoptotic action by binding to CB_1 and CB_2 receptors. For instance, cannabinoid receptor agonists when bind to receptors enhance pro-apoptotic molecules such as sphingolipid ceramide which in-turn modulates various signalling pathways involved in the pathogenesis of cancer. In leukemic cells, CBs act through ceramide which induces apoptosis by modulation of the p38 mitogen-activated protein kinase (MAPK) pathway. In glioma cells, CBs induces apoptosis by upregulating endoplasmic reticulum stress-related genes [72]. Furthermore, in lung cancer, CBD is reported to up-regulate the expression of cyclooxygenase-2 (COX-2) and pro-apoptotic prostaglandin E-2 (PGE2) which contribute to cellular apoptosis [73].

A pathway by which Δ^9-THC promotes apoptosis is via upregulation of Tribbles homolog 3 (TRB3) protein. Upregulation of TRB3 leads to cellular autophagy and inhibition of protein kinase B (PKB) leading to increased synthesis of Bcl2-associated agonist of cell death (BAD), which is a pro-apoptotic protein [73,74]. Autophagy either acts as an alternate to apoptosis causing cell death or acts together with the apoptotic pathway leading to cell death. For instance, Δ^9-THC and JWH-015, when bind to CB_2 receptors, induced cellular autophagy and reduced cellular viability in HepG2 and HuH-7 hepatocarcinoma cell lines and tumour models [75]. Here, JWH-015 and Δ^9-THC upregulated TRB3. This resulted in the suppression of the PKB/mammalian target of rapamycin Complex1 (mTORC1) axis and stimulation of adenosine monophosphate-activated kinase (AMPK). Further, calmodulin-dependent protein kinase kinase-beta (CAMKK-β) induced AMPK phosphorylation leads to cellular autophagy [75].

CBs have also been reported to downregulate glycolysis which is a novel target for cancer therapy (Fig. 9) [76–78]. Cancer cells, in order to survive in a hypoxic environment, undergo metabolic reprogramming and make aerobic glycolysis their preferred pathway irrespective of the status of oxygen levels in the cell (Warburg effect) [78]. On the other hand, normal or healthy cells undergo mitochondrial Krebs' cycle and oxidative phosphorylation after formation of pyruvate from glucose in the process of glycolysis. Anaerobic glycolysis is preferred only in unusual conditions such as stress and limited oxygen supply. This distinctive feature of cancer cells could be further explored for CB mediated cell killing.

Arachidonoyl cyclopropamide (ACPA) and GW405833 (GW), upon binding to CB_1 and CB_2 receptors respectively, release reactive oxygen species (ROS) which inhibit glycolysis, Krebs' cycle and oxidative phosphorylation in pancreatic cancer cells (Fig. 9) [76,77]. Additionally, inhibition of oxidative phosphorylation changes the Adenosine Triphosphate/Adenosine Monophosphate ratio of cells and induces AMPK, the enzyme responsible for maintaining the intracellular homeostasis and energy regulation of cells. Activation of AMPK leads to inhibition of mTORC1, a key regulator of protein synthesis and cell growth. All these events eventually trigger the cell towards autophagy. mTORC1 inhibition also downregulates its downstream targets, hypoxia-inducible factor-1 alpha (HIF-1α) and pyruvate dehydrogenase kinase (PDHK) resulting in cell death (Fig. 9) [76].

5. Non-cannabinoid receptors

CBs are also reported to exhibit anticancer activity independent of cannabinoid receptors [79,80]. The non-cannabinoid receptors include GPR18, GPR55, and TRP ion channels among others [81]. The TRP family members are commonly upregulated in several cancers [82]. The role of TRP channels in pathogenesis of cancer is highly heterogeneous and their oncogenic or tumour-suppressive activity depends on various factors including the location and the cancer type. For instance, transient receptor potential vanilloid type-2 (TRPV2) is reported to be over-expressed in both adenocarcinoma and U87MG glioma. In the case of adenocarcinoma, TRPV2 contributes to cancer invasion and metastasis. However, TRPV2 plays a tumour-suppressive role and negatively controls glioma cell proliferation and apoptosis [83,84]. On binding with TRPV2 receptors, Δ^9-THC is reported to trigger calcium influx inside the cells altering the transmembrane potential of mitochondria and induce apoptosis. In addition, calcium ions also promote autophagy and increase the ROS concentration promoting cell death. CBD upon binding with TRPV2 promotes cell death in glioma [85]. Likewise, AEA

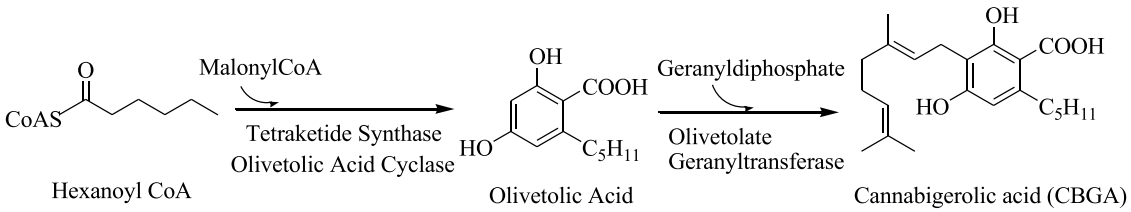


Fig. 2. Biosynthesis of cannabigerolic acid (CBGA).

promotes apoptosis in malignant cells by binding to TRPV1 receptors [50].

Moving ahead in the list of non-cannabinoid receptors, GPR18 and GPR55 have been reported to be targets of several phytocannabinoids, synthetic cannabinoids and endocannabinoids. GPR18 and GPR55 receptors are predominantly dispersed in central and peripheral systems of the body such as brain and vascular system. GPR18 and GPR55 have been reported in the modulation of various signalling pathways involved in pathogenesis of cancer and other metabolic disorders. CBD acts as an antagonist of GPR55 and exerts anti-proliferative effects through PKB and ERK inhibition [73,86,87].

6. Activities of cannabis for cancer

Cannabis and its constituents have been explored for therapy and management of cancer- associated symptoms [88]. CBs are active against several cancers of both benign and malignant in nature. In the following section, we provide evidence from both preclinical and clinical studies for the anti-cancer potential of cannabis and CBs.

6.1. Cancer therapy

CBs have been reported to be active against various cancers including breast ([89], gastric [90], colon [91], and leukemia [92]. The phytocannabinoids have also shown cytotoxic activity against Sézary syndrome which is a rare type of cutaneous T-cell lymphoma (CTCL) [93]. The study demonstrated the cytotoxicity of mixtures of active cannabis compounds. The mixtures induced cell-cycle arrest and apoptosis in CTCL cell lines [93]. The terpenoids found in cannabis are known to potentiate the cytotoxic activity of phytocannabinoids [94].

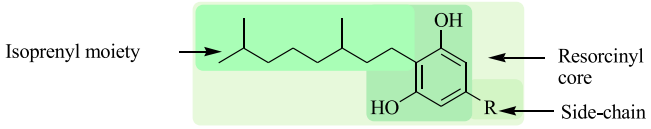


Fig. 4. Structural moieties of phytocannabinoids.

CBs have also been reported for selective targeting of malignant cells. For example, in glioma and acute lymphoblastic leukemia, the cannabinoid selectively targeted malignant cells over healthy ones [95,96]. CBs are also under investigation as early-stage non-invasive biomarkers in cancer. For instance, the levels of AEA and stearoyl ethanolamide (SEA) increases in the urine of bladder cancer patients [97]. Some noteworthy preclinical and clinical studies performed on CBs are discussed below.

6.1.1. Preclinical studies

Phytocannabinoids, endocannabinoids and synthetic cannabinoids are reported to modulate multiple aspects of tumour development (Table 2). Other constituents of cannabis can also modulate the process of tumorigenesis. In this section, we provide evidence from preclinical studies on the anti-tumorigenic potential of cannabis and its constituents.

The common phytocannabinoids reported to exhibit anti-cancer activity include Δ^9-THC, CBD, CBG and CBC. For instance, in a study [98] performed on B16 and A375 melanoma cell lines with high levels of CB_1 and CB_2 receptors, Δ^9-THC selectively inhibited the growth of melanoma cell lines over normal melanocytes. The cannabinoid-induced cell-cycle arrest through hypophosphorylation of the tumour

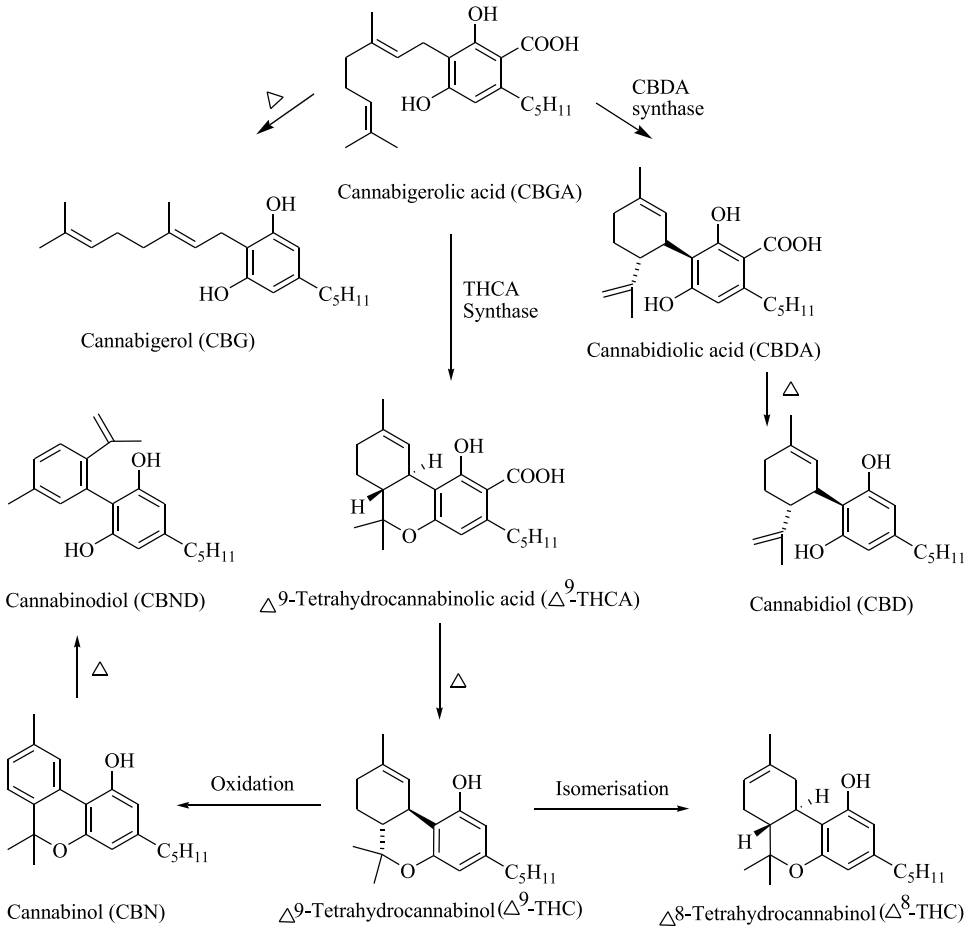


Fig. 3. Biosynthetic pathway of major phytocannabinoids.

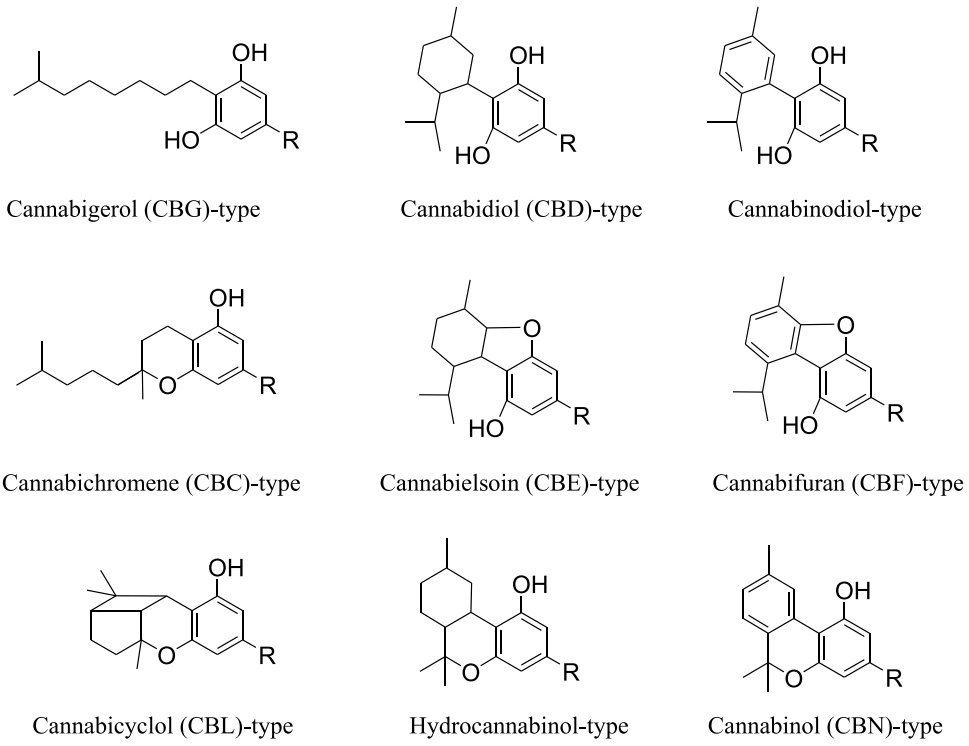


Fig. 5. Major skeletons of phytocannabinoids.

Table 1
List of selected compounds from the raw extract of Cannabis.

Compound Class	Chemical constituent(s)
Neutral cannabinoids and their derivatives	Δ^9-THC, Δ^8-THC, CBD, cannabitriol, cannabicyclol
Cannabinoid acids	Cannabicitran, cannabidivarinic acid, cannabielsoin, cannabigerolic acid, cannanbigerolic acid, cannabidiolic acid
Flavonols	Quercetin, cannabigerol
Flavones	Orientin
Chlorophyll	Chlorophyll (decarboxylated)
Fatty acids	α-Linolenic acid, stearidonic acid
Sterol	Acetyl stigmasterol
Sesquiterpene	*β*-caryophyllene oxide
Terpenoids	Limonene, terpinolene, pinene

Abbreviations: Δ^8-THC: Δ^8-tetrahydrocannabinol; Δ^9-THC: Δ^9-tetrahydrocannabinol; CBD: cannabidiol.

suppressor retinoblastoma (Rb) protein and inhibition of PKB. Additionally, in mice tumour models, cannabinoid inhibited tumour progression and metastasis [98]. CBs are also reported to inhibit tumour invasion and metastasis by modulating multiple pathways. For instance, Δ^9-THC upon binding to CB receptors, inhibited Ras homolog gene family member A (RHOA)- focal adhesion kinase (FAK) and protein kinase Src (RHOA-FAK-Src) axis. Further, Δ^9-THC downregulated angiopoietin-2 (Ang-2), vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) in cancer cells [74,99]. In human colon adenocarcinoma Caco-2 SEA cells, palmitoyl-ethanolamide reduced proliferation, angiogenesis and migration via peroxisome proliferator-activated receptor alpha (PPAR-α) activation and inhibition of AKT/mTOR axis [99]. Δ^9-THC and CBD induced apoptosis and reduced invasion and tumour growth in mice. For example, CBD reduces invasiveness and self-renewal in glioblastoma cell lines [100]. Similarly, Δ^9-THC and CBD, alone, and in combination with radiation are reported to reduce the viability of glioma cell lines such as U87MG, T98 G, and GL261 [101]. CBD has also shown anti-proliferative activity on glioma stem cells and U373 glioma cell lines [102,103]. In human T lymphoblastoid leukaemia CEM/VLB100 cell line, Δ^9-THC and CBD have proven efficacy in reversing multidrug resistance [104]. CBD also produced apoptosis inducing effects in murine lymphoma (EL-4) and the human leukemia (MOLT-4, Jurkat) cell lines [105]. Similarly, Δ^9-THC has also proven efficacy in reducing the viability of leukemia cell lines [106,107]. In lung cancer A549 and H460 cell lines, CBD induced apoptosis by upregulating PPAR-γ and COX-2 [108]. In A549 cells, CBD also reduced invasion and metastasis via an increase in tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) and suppression in plasminogen activator inhibitor-1 (PAI-1) [109,110]. In A549 and SW-1573 cell lines, Δ^9-THC inhibited phosphorylation of extracellular-signal-regulated kinase (ERK)1/2, c-Jun N-terminal kinase (JNK)1/2) and AKT induced by epidermal growth factor (EGF) [111].

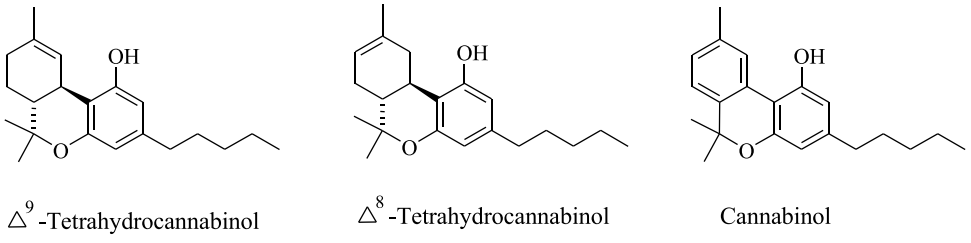


Fig. 6. Phytocannabinoids with high binding affinity towards CB1 and CB2 receptors.

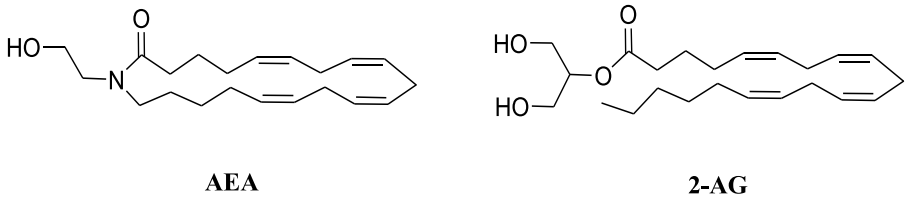


Fig. 7. Structure of anandamide (AEA) and 2-arachidonoyl glycerol (2-AG).

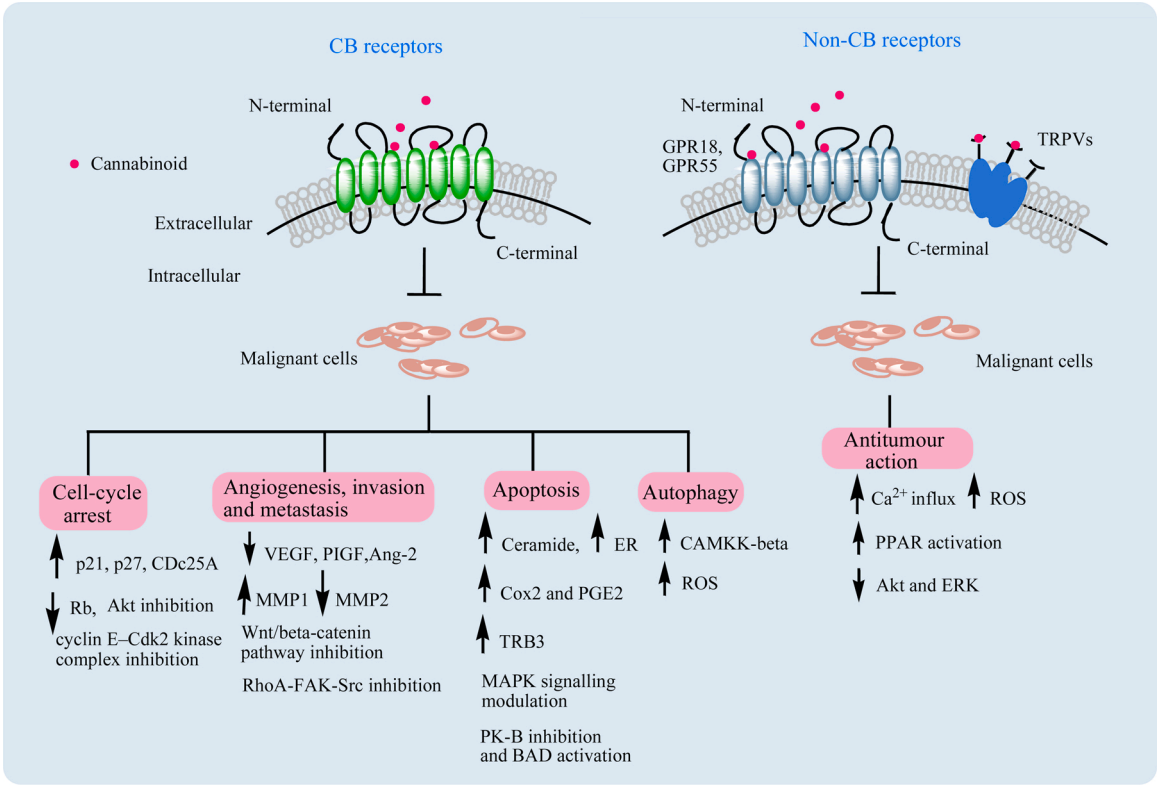


Fig. 8. Key signaling pathways modulated by cannabinoids in cancer cells.

Δ^9-THC also inhibited the growth of both SW-1573 and A549 cell lines [111].

CBs have shown significant antiproliferative actions in breast cancer cell lines. For instance, both Δ^9-THC and CBD reduced cell proliferation and induced apoptosis in human MDA-MB231-luc-D3H2LN cells [112]. Furthermore, both CBs also reduced invasion and metastasis in tumour bearing mice models [112]. CBD significantly inhibited proliferation and chemotaxis in triple-negative breast cancer cells induced by EGF [113]. In breast cancer cells, CBD reduced Id-1 protein expression, cell proliferation and invasion [114]. CBD and CBG also reduced tumour volume and induced apoptosis in athymic nude mice model bearing breast cancer cells [115]. The antineoplastic activity was reported through the activation of CB_2 and TRPV1 receptors contributing to oxidative stress and apoptosis [115]. Δ^9-THC is also reported to reduce the proliferation of breast cancer cell lines induced by 17β-estradiol [116].

CBs have also shown efficacy in gastrointestinal system related cancers including pancreatic and colorectal cancers. CBG reduced the viability in colorectal cancer cells through enhanced generation of ROS [117]. Similarly, Δ^9-THC suppressed the proliferation in pancreatic cancer cells through ER stress [117,118]. In HeLa and C33A cervical cancer cell lines, CBD impeded invasiveness via upregulation of TIMP-1 [109]. CBD also induced apoptosis in HeLa and ME-18 cervical cancer cell lines [119]. CBD also suppressed proliferation and induced apoptosis in SGC-7901 gastric cancer cells by increasing ROS production and inducing cell-cycle arrest [90]. Δ^9-THC reduced cell cycle progression by inducing G2-M arrest and down-regulating cell division cycle 2 (Cdc2) in breast cancer cells [120]. In prostate cancer, Δ^9-THC and CBD inhibited cell proliferation and induced apoptosis [121,122].

Other constituents of cannabis such as quercetin and β-Caryophyllene have also shown anticancer properties. Quercetin exhibited an anti-proliferative effect in colon adenocarcinoma cell lines Caco2 and DLD-1 [123]. It modulated major signalling pathways including down-regulation of Phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR and upregulation of JNK pathway contributing to apoptosis and cell death [123]. β-Caryophyllene has shown anti-proliferative properties against various tumour cell lines including ME-180 and PC3 [124]. Morin, a pentahydroxy flavone obtained from cannabis extract suppressed astrocyte activation in bone cancer pain rat model [125]. The flavone also reduced pro-inflammatory cytokines [interleukin-6 (IL-6), IL-1β, tumour necrosis factor-alpha (TNF-α)] and induced anti-inflammatory IL-10 cytokine [125].

Apart from phytocannabinoids, endocannabinoids also exhibit anti-carcinogenic activities. For instance, AEA induces cell-cycle arrest in G1-S phase via increased synthesis of p27 kinase inhibitor protein 1 ($p27^{kip1}$), $p21^{waf}$, proteolysis of Cdc25A and suppression of the cyclin E-cyclin dependent kinase 2 (Cdk2) kinase [72,73]. AEA has shown anti-tumorigenic properties in various tumour models including breast,

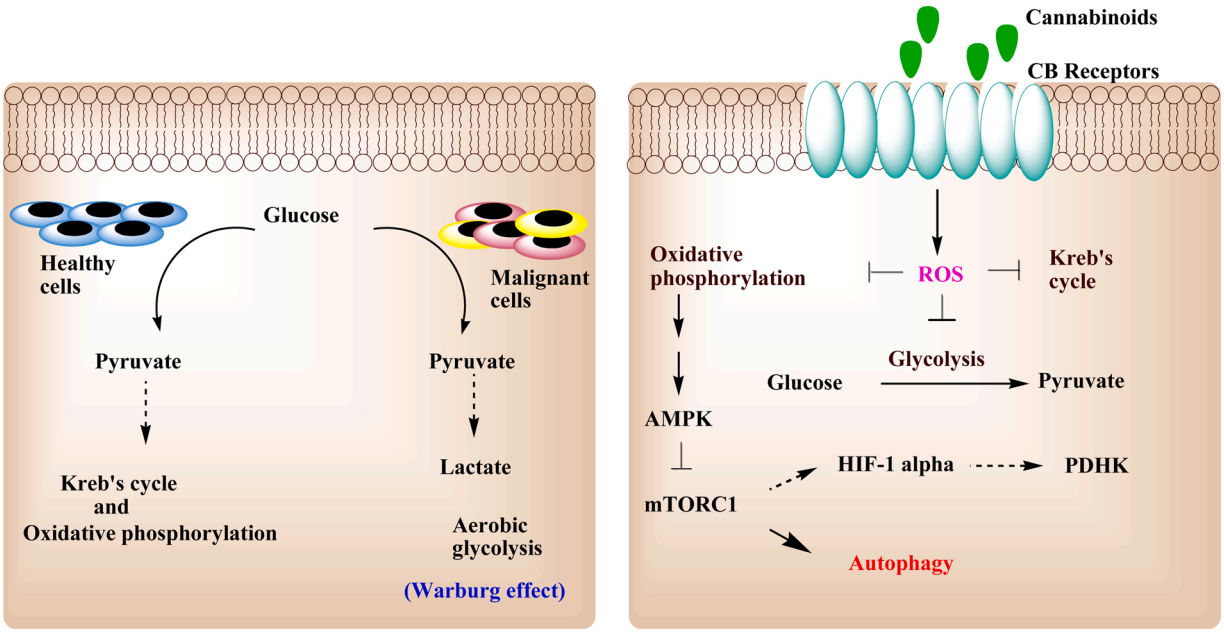


Fig. 9. Schematic representation of energy metabolism in healthy and malignant cells along with effect of cannabinoids on key pathways involved.

prostate and lymphoma. In T-47D and MCF-7 breast cancer cell lines, AEA inhibited proliferation via suppression of tropomyosin receptor kinase (Trk) and prolactin receptors [126]. AEA also reduced proliferation in prostate cancer cell lines [126]. In mantle cell lymphoma lines, AEA reduced cell viability and induced apoptosis [127].

6.1.2. *Clinical studies*

Whilst the therapeutic potential of cannabis has been examined by preclinical studies on a wide range of cancers, the clinical studies are limited to very few tumours. To our knowledge, the first human clinical trials of Δ^9-THC were performed on nine terminally ill patients of recurrent glioma resistant to chemotherapy and radiotherapy [23]. The intracranial administration of the CBs extended the survival time of two patients for approximately 1 year. Additionally, the dose was optimal and induced apoptosis without any psychoactive effects. However, few patients did not respond to Δ^9-THC and tumour progression continued with worsening of symptoms. The study revealed a need for a better route of administration and drug delivery system in order to increase the efficacy of the agent [23]. Another interventional study (NCT01812603) was performed on 6 patients of recurrent glioma. The trial was performed to assess the safety, tolerability and pharmacodynamics of Sativex (2.7 mg Δ^9-THC and 2.5 mg CBD). However, the outcomes of this study are yet to be published.

Moving ahead, a similar study (NCT01812616) was performed on 21 patients with recurrent glioma. The goal of the investigation was to examine the tolerability, safety and pharmacodynamics of Sativex in combination with temozolomide in recurrent glioblastoma patients. CBD has also been studied to evaluate its impact on patients with solid tumour (NCT02255292). The study was performed to evaluate the efficiency of oral CBD for recurrent solid tumours. The study was projected to be completed by 2015; however, no outcome has been published as yet.

Implications of cannabis in paediatric oncology are limited to case reports. A case study was conducted on a 14-year-old boy with a severe form of acute lymphoblastic leukemia (ALL) [128]. A standard bone marrow transplant, chemotherapy and radiotherapy were revoked. Subsequently, CB extract was administered to the patient orally. The patient responded to the extract leading to a stable disease after cannabis administration. In another case study, cannabis was found to produce satisfactory results in two children with pilocytic astrocytoma (PA) tumours in the absence of neurofibromatosis type-1 (NF-1) [129].

In addition to phytocannabinoids, synthetic CBs have also been tested in cancer patients. For example, three clinical trials (NCT01489826, NCT01654497 and NCT02054754) are evaluating the safety and therapeutic potential of dexanabinol in patients with solid tumour. Initially investigated as a neuroprotective agent, dexanabinol is expected to destroy tumour cells by reducing the level of control on networks that keep the cancer cells alive and prevent from dying. To our knowledge, the observations of these clinical trials are yet not published.

Overall, cannabis and its extract appear to be promising for cancer therapy. However, more double-blind clinical studies are required to prove the efficacy of cannabis and its constituents in cancer patients.

6.2. *Cancer-related symptoms*

As the disease progresses, the cancer patients develop multiple symptoms. The symptoms common in cancer patients are anorexia, anxiety, cachexia, cognitive impairment, delirium (acute confusion state), depression, fatigue, neuropathic pain and sleep disorders. These symptoms are caused either by the disease itself or by the treatment. In this section, we provide evidence from preclinical and clinical studies on the uses of cannabis and its constituents for cancer-related symptoms.

6.2.1. *Preclinical studies*

In preclinical studies, CBs have shown high efficacy in the management of cancer related symptoms. They are particularly beneficial in the management of cancer-associated symptoms such as nausea, vomiting and weight loss. Some significant preclinical studies of CBs are discussed in this section.

6.2.1.1. Antiemetic effect. Emesis refers to the action or process of vomiting. Antiemetic drugs are used to ease the symptoms of nausea or vomiting. The antiemetic action of CBs is mediated through CB_1 and 5-hydoxytryptamine (5HT-3) receptors. Preclinical research suggests that CBs are useful in managing the symptoms and side effects of toxic chemotherapeutic agents. For instance, in shrews, Δ^9-THC reduced the cisplatin-induced emesis in a dose-dependent manner [130]. Previous studies on animals have already demonstrated the potential of Δ^9-THC, Δ^8-THC, Nabilone and HU210 in preventing emesis [131–133]. Further, Δ^9-THC and CBD are also reported to reduce the effect of lithium

Table 2
Activity of phytocannabinoids and endocannabinoids in preclinical cancer model.

Phytocannabinoid	
Δ^9 -THC	• Selectively inhibited the growth of melanoma cell lines over normal melanocytes [98]; induced hypophosphorylation of the Rb protein, cell-cycle arrest and suppression of PKB [98]. • Inhibited RhoA-FAK-Src axis and downregulated VEGF, PlGF and Ang-2 in cancer cells [74,99]. • Increased radiosensitivity and induced apoptosis in glioma cell lines [101]. • Reversed multidrug resistance in T lymphoblastoid leukaemia CEM/VLB100 cell line [104]. • Exhibited cytotoxicity in leukemic cell lines [106]. • In combination with cannabidiol, inhibited the viability in leukemia cell lines [107]. • Inhibited phosphorylation of ERK1/2, JNK1/2 and AKT induced by EGF [111]; inhibited growth of lung cancer cell lines (A549 and SW-1573) [111]. • Induced apoptosis and reduced proliferation in human breast cancer cell lines [112]; reduced invasion and metastasis in tumor bearing mice models [112]. • Reduced the proliferation of MCF-7 breast cancer cell line induced by 17β-estradiol [116]. • Induced apoptosis in MiaPaCa2 and Panc1 pancreatic cancer cell lines through ER stress [118]. • Induced cell cycle arrest by inducing G2-M arrest and down-regulating Cdc2 in breast cancer cells [120]. • Reduced cell growth and induced apoptosis in prostate cancer cells [121,122].
Cannabidiol	• Downregulated Id-1 gene expression, glioma cell invasion and self-renewal [100]. • Increased radiosensitivity and induced apoptosis in glioma cell lines [101]. • Reduced survival of glioma stem cells by augmenting levels of ROS [103]. • Exhibited antiproliferative activities in glioma cell lines [102]. • Reversed multidrug resistance in T lymphoblastoid leukaemia cell line [104]. • Induced apoptosis in murine lymphoma (EL-4) and the human leukemia (MOLT-4 and Jurkat) cell lines [105]. • Induced apoptosis in A549 and H460 lung cancer cell lines by upregulating the expression of PPAR-γ and COX-2 [108]. • Inhibited invasion in human lung and cervical cancer cell line by upregulating the expression of TIMP-1 [109]. • Reduced invasion in human A549 lung cancer cells by decreasing expression and secretion of PAI-1 [110]. • Reduced proliferation and induced apoptosis in human breast cancer cell lines [112]; reduced invasion and metastasis in tumor bearing mice models [112]. • Inhibited proliferation and chemotaxis in SUM159 cell line by modifying EGFR signaling [113]. • Inhibited Id-1 protein expression and suppressed cell proliferation and invasion in MDA-MB231 cell line [114]. • Reduced cell growth in mice model bearing MDA-MB-231 breast cancer cell line [115]. • Induced apoptosis in HeLa and ME-18 cervical cancer cell lines [119]. • Induced apoptosis and suppressed proliferation in SGC-7901 gastric cancer cell line by increasing ROS production and inducing cell-cycle arrest [90]. • Induced apoptosis and reduced cell proliferation in prostate cancer cells [121,122].
Cannabigerol	• Inhibited the growth of colorectal cancer cells by enhancing ROS generation [117].
Other constituents	
Quercetin	• Reduced cell growth, migration and induced apoptosis [123]; inhibited PI3K/AKT/mTOR and upregulated JNK pathway in Caco-2 colon cancer cell line [123].
β-Caryophyllene	• Exhibited antiproliferative properties against ME-180 and PC3 cancer cell lines [124].
Morin	• Suppressed astrocyte activation, reduced pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) and upregulated anti-inflammatory cytokine (IL-10) in bone cancer pain rat model [125].
Endocannabinoids	
AEA	• Reduced proliferation in breast cancer cell lines by suppressing prolactin and Trk receptors [126]. • Reduced proliferation in prostate cancer cell lines [126]. • Reduced viability and induced apoptosis in mantle cell lymphoma cell lines [127]. • Induced apoptosis in human neuroblastoma CHP100 cell lines that was protected by cannabinoid receptors [50].

Abbreviations: AEA: N-arachidonoyl ethanolamine; Ang-2: angiopoietin-2; CBC: cannabichromene; CBD: cannabidiol; CBG: cannabigerol; COX-2: cyclo-oxygenase-2; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; ERK1/2: extracellular-signal-regulated kinase 1/2; FAK: focal adhesion kinase; IL: interleukin; IL-1β: interleukin-1 beta; JNK1/2:c-Jun N-terminal kinase1/2; mTOR: mammalian target of rapamycin; PAI-1: plasminogen activator inhibitor-1; PI3K: phosphatidylinositol-3-kinase; PKB: protein kinase B; PlGF: placental growth factor; PPAR-γ: peroxisome proliferator-activated receptor gamma; Rb: retinoblastoma; RhoA: Ras homolog gene family member A; ROS: reactive oxygen species; TIMP-1: tissue inhibitor of matrix metalloproteinases-1; TNF-α: tumor necrosis factor-alpha; Trk: tropomyosin receptor kinase; VEGF: vascular endothelial growth factor.

chloride-induced vomiting in musk shrew [134].

6.2.1.2. Appetite regulation. The endogenous cannabinoid system of the body regulates the eating behaviour and can stimulate the food-intake via acting on CB receptors of the brain. Endocannabinoids modulate appetite through central and peripheral mechanisms of the body via acting on hypothalamic, limbic and intestinal systems [135]. Δ^9-THC stimulates the appetite and is efficacious in cancer-related anorexia, which refers to the loss of the desire to eat. The first evidence of the involvement of endocannabinoids in the regulation of food intake was demonstrated by Kirkham and colleagues in 2002 [136]. It was reported that in fasting rats, the levels of 2-AG increased in limbic forebrain and hypothalamus. Further, the levels of 2-AG were sensitive to variations in fasting and feeding [136].

6.2.1.3. Analgesia. Analgesics are used as a pain reliever. Analgesic activity of CBs has widely been reported. Various animal studies have demonstrated the analgesic action of Δ^9-THC [137,138]. Cannabinoids produce an analgesic effects through the brainstem circuits [139]. Several preclinical investigations have demonstrated the role of cannabinoid receptors in modulating the analgesic effect of CBs [140]. CBs are also reported to reduce chemotherapy-induced neuropathy in various animal models. For instance, WIN55,212−2 through binding to CB_1 and CB_2 receptors reduced the allodynia induced by vincristine in rats [141]. WIN55,212−2 can also reduce paclitaxel-induced hyperalgesia and allodynia in rats [142]. Likewise, anandamide was found to reduce cisplatin induced neuropathic pain in mice [143]. ACPA and AM1241 are agonists for CB_1 and CB_2, respectively. These agonists promote analgesia in tumour-bearing mice [144].

6.2.1.4. Anxiolytic activity. The anxiolytic agents are used to inhibit anxiety. Cannabinoids possess antipsychotic, antidepressant, and anxiolytic activities which are valuable in the management of cancer and chemotherapy-related anxiety disorders in patients. Δ^9-THC and CBD have shown anxiolytic properties in various animal models [145–148].

6.2.2. Clinical studies

CBs are highly efficient in managing cancer-related symptoms in patients. Several cohort-studies have demonstrated the efficiency of natural and synthetic cannabinoids in cancer patients. They are highly effective in reducing drug-induced nausea and vomiting in cases where first-line antiemetic agents fail. Additionally, they act synergistically with several other agents in reducing chemotherapy-induced adverse effects. In this section, we discuss the clinical studies performed on

cancer patients using cannabis and CBs.

6.2.2.1. Antiemetic effect. CBs are highly effective in reducing the impact of cancer-related symptoms which often arise at the time of chemotherapy. For instance, in cancer patients, nabilone was found to be more superior in controlling emesis compared to classical antiemetic agents such as domperidone and alizapride [149]. Another randomised controlled trial was conducted between 1975 and 1991 on cancer patients to investigate the antiemetic effect of nabilone or dronabinol compared to conventional dopamine antagonists. The study revealed a higher performance of CBs with complete absence of chemotherapy induced emesis in patients [150]. Similarly, a combination therapy of dronabinol with ondansetron has been found to be highly effective in preventing delayed-onset of chemotherapy induced emesis [151].

The antiemetic effect of CBs also varies with the anticancer agent administered. For instance, Δ^9-THC is effective in reducing emesis in patients receiving high-dose methotrexate. However, it is not effective on emesis induced by adriamycin and cytoxan [152,153]. In another study conducted on oromucosal spray formulation of THC:CBD (1:1) revealed its effectiveness in reducing chemotherapy-induced emesis in patients [154].

6.2.2.2. Appetite stimulation. Appetite associated problems such as anorexia and weight loss commonly arise with patients who receive chemotherapy. CBs have shown effectiveness in improving appetite stimulation in cancer patients [155]. For instance, Δ^9-THC has produced a variable effect in stimulating appetite in advanced-stage cancer patients with HIV infection [149]. In a randomised double-blind trial, oral preparations of cannabis extract (1 mg CBD and 2.5 mg Δ^9-THC) improved appetite and overall quality of life of patients receiving chemotherapy in advanced cancer [156]. Among synthetic CBs, dronabinol and nabilone have shown a significant effect in improving appetite and chemosensory perception of cancer patients [157,158].

6.2.2.3. Analgesia. Cancer pain originating from inflammation of tissues is often resistant to treatment with classical anti-inflammatory agents and opioids. However, several studies have reported the efficacy of CBs in reducing cancer pain. For instance, Δ^9-THC is reported to reduce cancer-associated pain in cancer patients [159]. However, in one study, it induced side effects including ataxia, dizziness and reduced sharpness of vision indicating a need of further dose formulation and standardisation [160]. In a double-blind investigational study conducted in patients with advanced stage cancer, Δ^9-THC:CBD extract was found effective in reducing pain compared to Δ^9-THC alone [161]. In another study, long-term use of the oromucosal spray of cannabinoids (Δ^9-THC: CBD) helped in reducing cancer-associated pain without increasing the dose in patients. Additionally, the spray was found to be effective in patients refractory to opioid analgesics [162]. In an observational study, nabilone improved the problem of pain, nausea, and anxiety in advanced cancer patients when compared with untreated ones. Further, it also decreased the use of other drugs including anti-emetics, non-steroidal anti-inflammatory drugs, antidepressants and opioids [163].

CBs act synergistically with opioids and reduce the effective dose of opioids when given in combination. In a randomised controlled trial, vaporised cannabis augmented the analgesic effect of opioid and reduced the pain significantly in patients [164]. In an another randomised, placebo-controlled investigation on nabiximols, an oromucosal whole cannabis-based spray containing Δ^9-THC, CBD, terpenoids along with other minor CBs was studied. The spray significantly reduced chemotherapy induced neuropathic pain with very little side effects [165].

6.2.2.4. Anxiolytic activity. CBs have demonstrated a significant effect in elevating mood and reducing anxiety in cancer patients. In a pilot study, 15 mg and 20 mg doses of Δ^9-THC produced an anxiolytic effect in cancer patients [166]. Similarly, in a case-series study on 5 patients, inhaled cannabis produced anxiolytic effect and improved the state of well-being [167]. In a randomised, double-blind, placebo controlled trial, Δ^9-THC improved taste perception and sleep quality in advanced cancer patients [155]. Another study was conducted in Canada to evaluate the effect of cannabis on 74 patients newly-diagnosed with head and neck cancer. The study revealed the efficacy of cannabis in improving the sense of well-being, reduced anxiety and less tiredness in patients [168].

7. Conclusions

Cannabis and its constituents are reported both for therapy and management of cancer symptoms. Most evidences on the use of cannabinoids for cancer therapy are based on preclinical studies. CBs can selectively modulate tumour growth both in cell lines and in animal models. Cohort studies and surveys suggest that cancer patients on cannabis are less vulnerable to cancer associated symptoms such as pain, nausea, and anxiety. The relatively favourable toxicity profile of cannabis compared to classical anticancer agents makes it a potential candidate for further exploration. Although cannabis has demonstrated potential in cancer models, it is not considered as a first-line agent. Its utility as an adjunct for management of cancer related symptoms is more convincing as compared to treatment. The use of cannabis is not completely devoid of risks. For example, use of THC is associated with impairment in attention, associative learning, and motor coordination. It also causes red eyes, dryness of the mouth, increased appetite, and tachycardia. Unlike opioids, death from cannabis overdose is reported to be highly unlikely [12]. The use of cannabis for investigative research and medical purpose is legalized only in very few countries. Several academic Institutes across the globe have already included cannabis related courses in their curricula. Future studies on cannabis should be focussed more on the dosage, drug combination and route of administration. This will generate solid evidence for the use of this molecule in cancer patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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