REVIEW ARTICLE

Cancer Signaling Pathway and Anti-Cancer Mechanism of Cannabidiol

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Cannabidiol (CBD) is one of the major ingredients found in Cannabis. It has become of medical value due to containing various pharmacological properties such as analgesic, anti-hypertensive, anti-inflammatory, and especially anti-cancer effects. For a more in-deep understanding of the CBD mechanism associated with cancer, the authors had demonstrated the potential of CBD against various cancer types, especially the signaling pathway underlying of CBD's potential as an anticancer agent based on *in vitro* and *in vivo* studies. The present article provided information on how CBD can interact with many forms of cellular targeting that contributed to the modulation of the notable cancer pathway, such as MAPK, PI3K, and Wnt signaling pathways. These would lead to inhibiting cell survival, inducing apoptosis, exerting a cytotoxic effect, or arresting the cycle of cancer cells. Furthermore, the present article had been carried out on the pre-clinical data possibility of CBD as a natural plant for their anticancer property. However, demand further scientific research is needed.

Keywords: Human Cancer Signaling; Cannabidiol (CBD); Chemopreventive agent

Received 7 October 2022 | Revised 26 December 2022 | Accepted 3 January 2023

J Med Assoc Thai 2023;106(2):217-27

Website: http://www.jmatonline.com

Cancer is one of the leading causes of death in the world[1,2]. The number of reported cancer cases in 2020 had risen to 19,292,789. It is important to note that this is a significant increase on the 9,958,133 patients who died from cancer annually just a few years ago[2,3]. The causes of cancer are wide-ranging, with environmental, genetic or epigenetic factors all potentially leading to the initiation of cancer[3,4]. Carcinogenesis is driven by a multi-step sequential mutation processes that takes many years[5]. The prevention and cure of cancer are a major challenge for medical professionals. Treatment by conventional therapy, including surgery, radiotherapy, and chemotherapy can cure cancer if it was detected in its early-stage or metastasis[6]. When treated with a chemotherapeutic drug, cancer will relapse due to compensatory mutation or the activation of an alternative signaling pathway for the cancer cells[7]. However, certain cancer drugs are also toxic to normal cells and cause multidrug-resistance[8-10]. Therefore, anticancer drugs are a demanding issue and there is a need to develop drugs with fewer side effects and higher efficacy.

Recently, the medical use of natural products is becoming increasingly popular due to the improved efficacy and reduced toxicity[11,12]. Several natural products not only contain nutrients but also represent a good source of bioactive phytochemicals[11,13]. Emerging evidences indicate that several bioactive compounds occurring in natural products possess anticancer properties that work by targeting multiple oncogenic signaling pathways[12,14]. Previous studies had shown a variety of bioactive compounds, including lycopene, astaxanthin, lutein, fiber, and Omega-3 possess potential antioxidative activity[15,16]. This function can reduce not only oxidative damage to DNA but also the risk of cancer[17-19]. Among the natural products currently being considered for medical usage, *Cannabis sativa* L. is drawing increasing interest due to its use as a medicinal agent

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How to cite this article:

Praphasawat R, Klajing W, Palipoch S, Wimuttiyanon J, Wutti J, Saypeark N, et al. Cancer Signaling Pathway and Anti-Cancer Mechanism of Cannabidiol. J Med Assoc Thai 2023;106:217-27.

DOI: 10.35755/jmedassocthai.2023.02.13749

to provide relief for neuropathic pain[20,21]. Cannabis contains more than 500 components, of which 104 cannabinoids exist in the *Cannabis sativa* L. plant[20]. Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) are the two major cannabinoids that have been utilized in the treatment of cancer since the 1970s[22-24]. Both THC and CBD can inhibit the growth of various types of cancer cells and of angiogenesis as well as reducing metastasis[23,25,26]. Despite the multiple antigrowth effects of THC-related cannabinoids in cancer research, the clinical use of these compounds is limited due to their psychoactive side effect. Compared to THC-related cannabinoid, CBD has non-psychoactive effects[27-29].

Therefore, the present research focused the importance of CBD, which could be very useful in fighting cancer cells as well as reducing their proliferation and progression. Based on the present study, the authors suggested that CBD may be one of the more promising potential treatments for cancer in the future.

Cancer

Cancer is defined as the abnormal growth of cells, which has no functional purposes and has the potential to spread to adjacent cells or organs in other parts of the body. There are many causes of cancer and these can be divided to environmental and genetic factors[4,30]. The genetic factors are characterized by an alteration directly to genes or epigenetics that are linked to the cell growth, survival, and progression[31]. The environmental factors appear in daily life, such as unhealthy food habits, occupational stress, exposure to radiations or toxins, infections, or inflammations[30].

Recently, the World Health Organization (WHO) reported that there had been more than 19.29 million new cancer cases worldwide in 2020, with 9.9 million cancer-related deaths in the same year. The incidence and death rates for cancer are growing at alarming rates for both genders. The incidence of all cancer type is 22.60% and 18.55% for males and females, respectively. The mortality rates for cancer are 12.59% and 8.86% for males and females, respectively. Among the total incidences of cancer, breast cancer was found to be the most commonly-occurring cancer in the world, accounting for 11.7% of all cases following by lung at 11.4% and colorectal cancers at 10%, which have the second and third highest prevalence, respectively. However, lung cancer had the highest mortality rate worldwide at 18%. Colorectal cancer and liver cancer then have

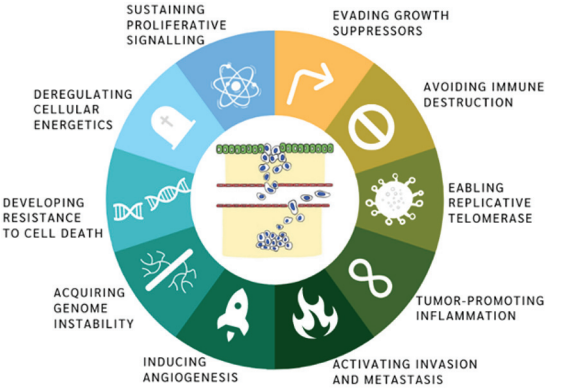

Figure 1. The hallmarks of cancer: evading growth suppressors, avoiding immune destruction, enabling replicative telomerase, tumor-promoting inflammation, activating invasion and metastasis, inducing angiogenesis, acquiring genome instability, developing resistance to cell death, deregulating cellular energetics.

the second and third highest mortality rates at 9.4% and 8.3%[32].

The phenomena of cancer is the collectively unregulated proliferation of abnormal cells[33,34]. The characteristics of cancer have been presented in the earlier publication that have explained the capabilities or hallmarks of cancer, such as described by Hanahan and Weinberg in 2000[35]. A decade later, there had been many updates and revisions to these descriptions with the addition of the marked characteristics of cancer[36-38]. The hallmark of cancer is that it is a multistep development in human tumor. The authors summarized ten representative hallmarks of the cancer cell model as shown in Figure 1.

Cancer pathways

MAPK signaling pathways

The mitogen-activated protein kinases (MAPK) play the most important role in the physiological body by regulating the dephosphorylation of kinases. These functions include eliciting signals that control physiological response in mammalian systems, such as cell proliferation, differentiation, transformation, migration, apoptosis, and survival. There are four main groups of MAPK pathway that have been identified in human, extracellular signal-regulated kinase (ERK1/2), Jun N-terminal kinase (JNK), p38 MAPK, and ERK5[39,40]. In pathologic response, a defect in a MAPK signal is associated with many diseases including the development and progression of cancer. Excessive activation of the ERK1/2 signaling is found to be closely related to one-third of all occurrences and development of all

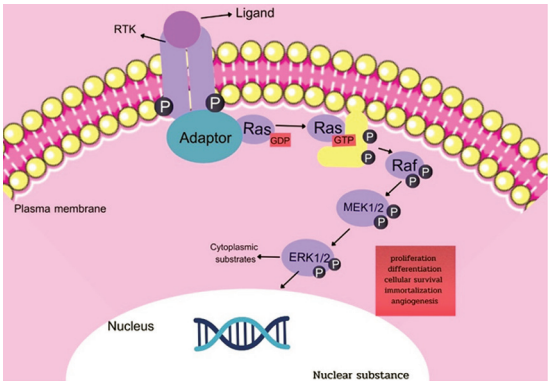

Figure 2. Mechanism of MAPK signaling pathway.

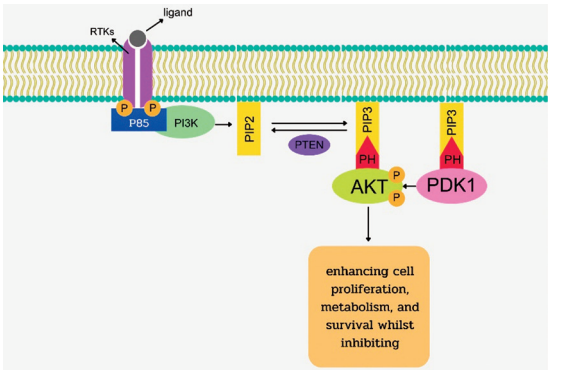

Figure 3. Mechanism of PI3K signaling pathway.

cancers in humans[41,42]. Accordingly, the authors of the present study understood that the ERK1/2 is a very important signaling cascade among all MAPK signal transduction pathways (Figure 2).

The ERK1/2 signaling cascade includes Ras, Raf, MEK, and ERK, which carry extracellular signals to intracellular targets. In response to stimuli, such as growth factors and hormones, these signals bind to the receptors of tyrosine kinase (RTK). The amount of Ras-guanosine triphosphate (GTP) increases in cells, which then promote Ras-GTP kinase activation. In this conformation, Ras can attach to the plasma membrane and directly activate its effectors. Activated Ras can induce the sequential phosphorylates and activate Raf MEK1/2 and ERK1/2. The activated ERK1/2 phosphorylates the number of substrates, in both the nucleus and cytoplasm, such as cytoskeletal proteins, kinases, and transcription factors, including nuclear factor (NF)-κB, AP-1, ETS-1, c-Myc, and members of the signal transducer as well as activators of transcription family. Consequently, phosphorylated ERK1/2 triggers several changes in cells, such as cellular motility, promoting proliferation, differentiation, cellular survival, immortalization, and angiogenesis[43,44]. Therefore, ERK1/2 activation is an important signal and activated ERK1/2 must be tightly controlled[45,46]. However, mutation and dysregulation of ERK1/2 signals have been found in the development of tumors. The mutation of Raf occurred frequently in many types of cancers including pancreatic cancers in 90%, colon cancers in 30% to 50%, and lung cancers in 20%[47]. Driver mutations in B-Raf account for approximately 7% of all cancers with the highest incidence found in skin cancer, thyroid cancer, colon cancer, leukemia, lung cancer, and brain cancer[48].

Blocking of ERK1/2 signal has been challenging as a target for cancer therapy. In cancer research, there are various studies on the inhibitor of ERK1/2 signaling. Varga et al. used GDC-0994 ERK1/2 inhibitors through oral administration on patients with locally advanced and metastatic solid tumors. Forty-seven patients were included in their studies. The result revealed that the MAPK pathway was inhibited by up to 51% with the greatest overall response being stable disease in 15 of 45 (33%) of the patients. However, two patients with BRAF-mutant colorectal cancer had a confirmed partial response. The authors suggested that the combination of MEK, BRAF, and EGFR inhibitors would further suppress MAPK pathway activity[49].

Another study showed that inhibiting of p-ERK1/2 levels led to the reduced viability of pancreatic stellate cells (PSCs) as well as inhibiting cancer–stromal interactions. This ERK inhibitor, on the other hand, promoted autophagy and may have protected the activated PSCs from senescence. The authors further investigated the effect of ERK1/2 inhibitors on in vivo cases. These data also showed that inhibiting ERK1/2 and autophagy together reduced the number, volume, and weight of liver metastases substantially. The authors proposed that combination therapy could inhibit both ERK1/2 and autophagy suggesting it would be of interest in the treatment of pancreatic cancer[50].

PI3K signaling pathways

Phosphoinositide 3-kinase (PI3K) signaling is important for glucose homeostasis, protein synthesis, cell proliferation, and survival[51-53]. The PI3K/AKT signaling pathway is activated when growth factors bind to receptor tyrosine kinases (RTKs) on the extracellular cell membrane (Figure 3). This

binding then leads to the recruitment and binding of PI3K, directly or through adaptor proteins, to its cytoplasmic domain through its regulatory subunit (P85). Activated PI3K catalyzes the conversion of PIP2 to PIP3. Consequently, PIP3 recruits and shares a subset of pleckstrin homology (PH) domain and other lipid-binding domains for a variety of signaling protein such as kinase AKT and PDK1. Then, activated Akt phosphorylates several downstream protein targets with the overall effect of enhancing cell proliferation, metabolism, and survival whilst inhibiting apoptosis. Therefore, control of PI3K/AKT pathway signaling output is indispensable for the maintenance of tissue homeostasis. Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) function as a negative regulator of PI3K signaling by dephosphorylating PIP3 to PIP2. Thus, PTEN is a strong characteristic of a tumor suppressor[54-56].

In various type of cancers, many proteins of the PI3K/AKT signaling pathway are more easily affected via amplification, mutation, and translocation. The uncontrolled activation of this system, particularly the overactivation of AKT and inactivation of the tumor suppressor PTEN, frequently results in aberrant signal transduction and finally uncontrolled proliferation-related disorders[57]. Therefore, ATK and PTEN are important in the genetic alterations of the PI3K/AKT pathway in cancer. It has been shown that aberrant of AKT contained AKT1 at 5% and AKT2 at 8%, are the most observed in breast and female reproductive system and frequently in breast and ovarian cancers, while the inactivation of PTEN is the most observed in endometrial cancer at 32%[58].

Drug development research has been targeting PI3K/AKT pathways for cancer treatment. ARQ 092 and ARQ 087 drugs target AKT and FGFR, respectively, and these have been found to be effective both *in vitro* and *in vivo*. In the in vitro experiment, a combination of ARQ 092 and ARQ 087 resulted in inhibition of AKT levels and its downstream targets of a 45 cancer cell lines, whereas ARQ 087 suppressed the phosphorylation levels of FGFR and ERK. This would lead to the enhanced exertion of antiproliferative ability on the cancer cells. The in vivo study showed that the combination of those compounds resulted in the inhibition of AKT phosphorylation and its downstream targets, and the suppression of FGFR phosphorylation. Therefore, these studies suggest that combination of ARQ 092 and ARQ 087 targeted PI3K/AKT pathway with high efficiency for cancer treatment[59].

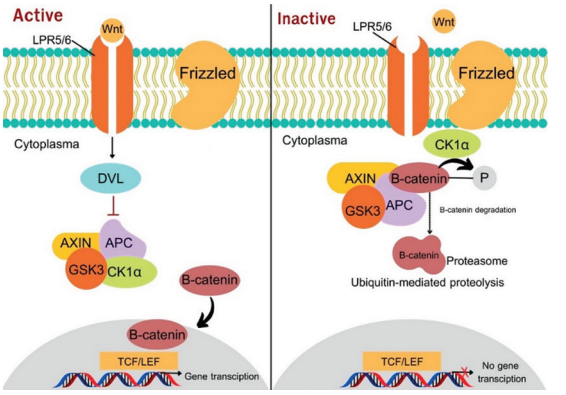

Figure 4. Mechanism of Wnt signaling pathways.

Wnt signaling pathways

The Wnt/β-catenin signaling pathway, also called the canonical Wnt signaling pathway, is a family of proteins that is implicated in many vital cellular functions. It played an important role as a key regulator of cell proliferation, differentiation, apoptosis, migration, invasion, and maintaining homeostasis[60,61]. Increasing evidence indicates that dysregulation of the Wnt/β-catenin contributes to cancer development and progression[60,62]. Normally, the Wnt/β-catenin signaling pathway is inactive because Wnt ligand does not binding to Frizzled (FZD) receptor and LRP-5/6 receptors or low-density lipoprotein receptor. These pathways are activated by the binding of Wnt ligand to the LRP-5/6 receptors and FZD receptor, which in turn induces Disheveled (DVL), causing the aggregation of the complex as AXIN, GSK3β, CK1, and APC. In the presence of these complex, β-catenin is incapable of phosphorylating and hence unphosphorylated β-catenin translocates into the nucleus leading to the activation of Wnt target genes such as c-Myc, Cyclin D1, and Cdkn1a. However, without Wnt, the β-catenin will undergo phosphorylation by CK1 and GSK3 kinases. Then, the phosphorylated β-catenin can be removed through the ubiquitin-proteasome system. Therefore, this signaling is implicated in cancer[62-65] (Figure 4).

One recent study has shown that artemisinin, an antimalarial drug, showed anticancer potential. The authors found that artemisinin suppressed cell proliferation and promoted cell apoptosis in EC109 cells. Furthermore, artemisinin inhibited migration and invasion and induced arrest at the G0/G1 phase of the cell cycle. Treatment of artemisinin has to be targeted for the Wnt/β-catenin pathway to decrease the level of β-catenin, c-myc, and surviving in EC109

cells. The authors strongly suggested that the anti-cancer efficacy was possibly due to the inhibition of the Wnt/β-catenin signaling pathway[66]. Another study found that anti-tumor activity targeted the Wnt/β-catenin signaling pathway through the use of Rutaecarpine, a natural product derived from alkaloid, potentially promoted antiproliferative activity and induced G0/G1 cell cycle arrest and apoptotic cell death in human CRC cells[67].

Cannabis plant

The biology of cannabis

Over the past few years, scientists have begun paying attention to the cannabis plant. Cannabis plants are a member of *Cannabis sativa* L. genus, which belong to the Cannabaceae family[68]. Nowadays, cannabis strains such as hemp and marijuana are legally grown for industrial fiber and medicinal purposes. Previous studies have shown that cannabis-based drugs are used in patients with neuropathic pain and psychiatric symptoms including depression and anxiety because of the variety of beneficial chemical constituents contained in cannabis[69-71]. Among these, the most important compounds, also known as cannabinoids, exist in the *Cannabis sativa* L. plant. The term cannabinoids refers to the chemicals found in cannabis that are linked to the endocannabinoids system[72]. This system produces diversified effects and is now known to maintain homeostasis such as energy balance, appetite stimulation, blood pressure, pain modulation, and immune response[73].

There are several types of cannabinoids. However, the most abundant is THC. THC have raised interest in the scientific community regarding its pharmacological activity as well as its potential in cancer research[22-24]. THC has been used for treating chronic pain, nausea, and vomiting, which are consequences from chemotherapy, as well as for managing other diseases such as reducing spasms in cases of multiple sclerosis[74]. Moreover, it has been reported that THC can inhibit the growth and proliferation of cancerous cells through integration with cannabinoid receptors as CB1R and CB2R[74]. However, the clinical use of THC compounds is limited due to their psychoactive side effect because THC binds with the cannabinoid 1 (CB1) receptors in the brain[27]. This binding produces a "high" or sense of euphoria, along with increased risks of developing chronic psychosis or drug addiction[75,76]. In contrast to the THC, CBD is the second most prevalent bioactive constituents of the cannabis plant, but it binds only very weakly to CB1 receptors and this weak binding does not produce a psychoactive property[77]. Generally, CBD is non-toxic to normal cell. Study has shown that CBD appeared to be more toxic to polyp cells than to adjacent colonic cells, at a concentration of 15 μM[78]. Hence, CBD has become a multi-purpose medicine, such as antipsychotic, anxiolytic, and anticonvulsant[79,80]. Additionally, CBD also has anti-cancer potential for various type of cancers. In the following sections its anti-cancer effects will be discussed in more detail and an in-depth understanding of how CBD modulates cancer signaling pathways in various cancer types will be explored.

Anti-cancer properties of CBD

Breast cancer

Breast cancer is the second biggest killer of women worldwide[81]. Understanding breast cancer treatment can improve patient survival. To this end, research has been conducted on the effect of CBD on breast cancer cells, animal, and human models[82,83]. One recent study has shown that treatment with different doses of CBD led to morphological changes to estrogen receptor (ER)-positive, well-differentiated T-47D and the triple-negative, poor differentiated MDA-MB-231 as well as MCF-7 breast cancer cells[84]. The cells were found to be rounded up and more easily detached. The investigation of cell viability revealed the viability of both cell lines decreased in a dose dependent manner from 1 to 7 μM. Moreover, inhibition of cell viability after CBD treatment was due to apoptosis. Nuclear and cytoplasmic localization of PPARγ were also investigated using immunocytochemistry. The results showed that CBD treatment enhanced PPARγ expression and localization in the nuclei of the treated cells. This would lead to inhibits of the protein expression and activity of mTORC and cyclin D1 as the mechanism underlying CBD-induced apoptosis. Ligresti et al. also demonstrated the ability of CBD to inhibit breast cancer cell viability through the generation of reactive oxygen species (ROS)[85]. Another study by Shrivastava et al. provided evidence targeting the human breast cancer cell line, MDA-MB231, with CBD triggered endoplasmic reticulum stress, inhibition of the AKT/mTOR pathway, and up-regulation of autophagy-mediated cell death[86]. Using the animal models, treatment with CBD has been shown to inhibit breast cancer primary tumor growth and metastasis through direct inhibition of EGF/EGFR signaling and the tumor microenvironment[87] (Figure 5).

Lung cancer

The antitumor activity of CBD has been studied in lung cancer cells. CBD exerts cytotoxic effect and inhibits cell proliferation of lung cancer cells. Milian et al. also demonstrated that CBD inhibited the proliferation and expression of EGFR in the lung cancer cells, which resulted in the epithelial phenotype being restored in vitro[88]. Furthermore, a significant finding from previous research has been the identification of the possible mechanism responsible for halting the proliferation. These effects rely on process such as programmed cell death or apoptosis. Some studies have analyzed the expression and localization of the Cas3/7 apoptotic marker in A549 and H1299 cell lines. They found that subcellular localization in both cell lines was increased as detected by increasing the immunofluorescence signal intensity of the active caspase-3/7 compared to control[89]. More evidence was provided by Hamad et al. as they investigated the ability of CBD to decrease the viability and induce cell death in both lung cancer stem cells and adherent lung cancer cells. They also found that CBD activated the effector caspases 3/7, increased the expression of pro-apoptotic proteins, increased the levels of ROS, and caused a loss of mitochondrial membrane potential[90] (Figure 6).

Gastric cancer

Gastric cancer is a common malignant tumor that originates in the gastric mucosal epithelium. Based on in vitro assay, CBD was shown to inhibit the proliferative of gastric cancer SCG-790171, AGS, MKN45, SNU638, and NCI-N87 cells by promoting apoptosis and cell cycle arrest at the G0-G1 phase[91,92]. The authors further investigated the mechanism by which cell cycle was arrested. The results showed that CBD increased the expression level of both ataxia telangiectasia-mutated gene (ATM) and p21, whereas that of p53 protein decreased, which subsequently inhibited the levels of CDK2 and cyclin E, thereby resulting in cell cycle arrest at the G0-G1 phase. In addition, increasing intracellular ROS level was found to be associated with the release of cytochrome C into the cytoplasm, leading to apoptosis[92]. More recently, Jeong et al. reported for the first time that CBD promotes apoptosis by suppressing X-linked inhibitor apoptosis (XIAP), a member of the IAP protein family. Treatment with CBD led to reduced XIAP protein levels while increasing ubiquitination of XIAP. They also found that the expression of Smac, a known inhibitor of XIAP, was elevated during CBD treatment, contributing mitochondrial dysfunction in gastric cancer (Figure 7) (Jeong et al., 2019)[91].

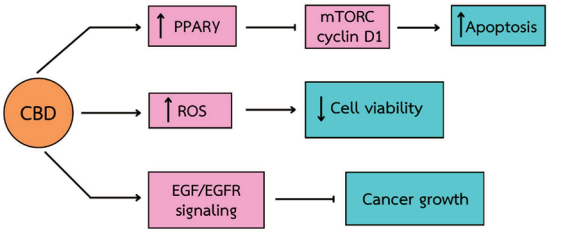

Figure 5. Possible mechanism in the anti-cancer activity of CBD.

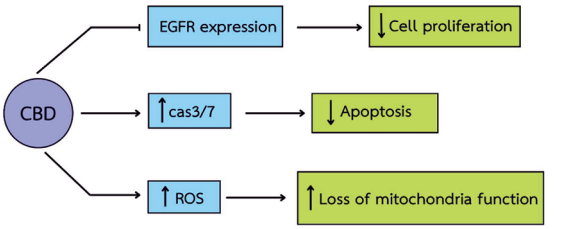

Figure 6. Possible mechanism in the anti-cancer activity of CBD.

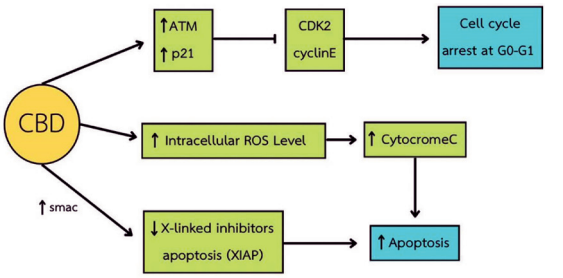

Figure 7. Possible mechanism in the anti-cancer activity of CBD.

Colorectal cancer

Colon cancer is a severe health problem malignancy and a main cause of death worldwide[93]. Several studies have reported that CBD induces anti-proliferative effect in a CB1-, TRPV1-, and PPARγ-antagonists sensitive manner in Caco-2 and HCT116 cells, indicating that CBD can exert antiproliferative effects through multiple mechanisms[94]. In the genotoxicity assay, pre-treatment with CBD for 24 hours significantly reduced the H_2O_2, induced DNA damage, suggesting that CBD protects DNA damage caused by an oxidative insult[94]. In a drug resistant study, CBD decreased the viability of oxaliplatin-resistant cells (DLD-1 R, colo205 R) in a dose-dependent manner from 1 to 7 μm. The study

found that CBD overcomes oxaliplatin-resistant by inducing autophagic cell death[95]. Moreover, the in vivo evidence showed that using CBD at dose of 5 mg/kg decreases the growth rates and tumor sizes in CT26 colon cancer cell induced mice cancer. On histopathological examination revealed that treatment with CBD was found to decrease the mitotic figures and pleomorphism in comparison with the vehicle control group. Furthermore, the study observed the beneficial effect of CBD on inhibition of angiogenesis by suppression of VEGF expression, the important role in tumor growth marker, suggesting that CBD has anti-angiogenesis effects[96] (Figure 8).

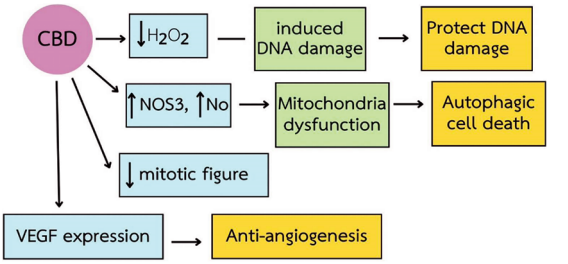

Figure 8. Possible mechanism in the anti-cancer activity of CBD.

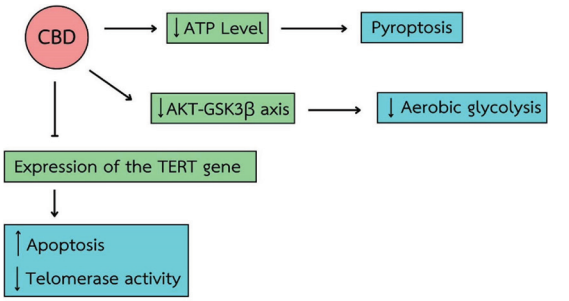

Figure 9. Possible mechanism in the anti-cancer activity of CBD.

Liver cancer

Liver cancer has the third highest mortality rate of human cancers worldwide[32]. A 5-year survival rate is only 3% and the rate of recurrence is high[3]. Therefore, there is a strong need to find precise treatment strategies that can lead to a better prognosis and increase survival rates for patients. In this regard, CBD is one of the high potential compounds in the fight against liver cancer. The current study has demonstrated that CBD suppresses hepatocellular carcinoma (HCC) cell growth, both *in vitro* and *in vivo*, and promotes pyroptosis, a kind of programmed necrosis, in a caspase-3/GSDME-dependent manner. Indeed, CBD can mediate the metabolic mechanism of HCC cells through the depletion of ATP and crucial intermediated metabolites as AKT-GSK3β axis is a regulator of cell glycolysis, leading to decrease aerobic glycolysis[97]. In another study where mice were pretreated orally with cannabis extract at 0.5 mL/kg body weight, every other day for two weeks before the injection of dimethylnitrosamine (DMNA)-induced hepatocarcinogenicity, the results revealed that the protective effect of cannabis extract has higher potential in groups taking cannabis due to its anti-tumor effects causing the direct induction of apoptosis and decreasing telomerase activity by inhibiting the expression of the TERT gene[98] (Figure 9).

Conclusion

Cancer remains one of the leading causes of death around the world. The activation of oncogenes or the inactivation of tumor suppressor genes are associated with cancer formation and progression. Currently, the most common approaches for treating cancer, including chemotherapy, surgery, and radiotherapy, have unexpected outcome and there is a need to improve their efficacy with lower toxicity and lower treatment. Thus, finding new drugs to treat cancer remains global challenge.

Natural plants have a long history of use in the treatment of various diseases. Plants are excellent sources of bioactive components with health benefit effects. From this inception, the consumption of food that does more than simply provide nutrients may be associated with maintaining health as well as reducing the risk of disease. As presented in the present review, plant-derived cannabinoids contain a molecule that is efficient at activating cannabinoid receptors of CBD and CBD itself is low toxicity. The functional therapeutic properties of CBD described include the relief of neuropathic pain and psychiatric symptoms including depression and anxiety. The authors had demonstrated that CBD has targeted a key molecular against cancer including the inhibition of mTOR/cyclin D1, EGF/EGFR, G-protein-coupled protein receptors/mitogen-activated protein kinase pathway, CDK2, cyclin E, TERT, VEGF expression, and increased the expression level of ATM, p21, and Smac in various cancers. Thus, CBD exhibits the suppression of cell proliferation, induces both apoptosis and necrosis, and triggers cell cycle arrest. Moreover, CBD inhibits angiogenesis, which would lead to an interruption of the invasion and metastasis of cancer. CBD can prevent DNA damage caused

by oxidative stress. This paper showed that based on *in vitro* and *in vivo* studies, CBD can be useful in fighting cancer and its cancer preventive properties give it high potential as natural plant source that could be attractive to consumers.

What is already known on this topic?

CBD is one of the bioactive compounds against various cancers giving it high potential as a natural anticancer plant that could be attractive to consumers.

What this study adds?

Based on the *in vitro* and *in vivo* evidence analyzed, CBD exerts modulation of various cancer signaling and contribution to cancer killing effect.

Conflicts of interest

The authors declare no conflict of interest.

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