Anticancer Activity of Cannabidiol (CBD)

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As the major nonpsychotropic constituent of Cannabis sativa, cannabidiol (CBD) is regarded as one of the most promising therapeutic agents due to its proven effectiveness in clinical trials for many human diseases. Due to the urgent need for more efficient pharmacological treatments for several chronic diseases, in this review, we discuss the potential beneficial effects of CBD for Alzheimer's disease, epilepsy, multiple sclerosis, and neurological cancers. Due to its wide range of pharmacological activities (e.g., antioxidant, anti-inflammatory, and neuroprotective properties), CBD is considered a multimodal drug for the treatment of a range of neurodegenerative disorders, and various cancer types, including neoplasms of the neural system.

Keywords: Cannabis sativa ; cannabidiol ; CBD

1. Mechanisms of Action of CBD in Cancer

CBD was shown to have effects on many types of cancer. Some neural system cancers are presented in Table 1. CBD inhibits cancer cell growth and migration and affects the disruption of F-actin integrity [1][2][3][4][5][6]. Moreover, CBD inhibits migration and invasion of endothelial cells and angiogenesis. Additionally, it downregulates proangiogenic factors [7]. The mechanism of action of CBD against cancer cells may be based on several pathways.

Table 1. The activity of cannabidiol (CBD) against selected types of neural system cancers.

Biological Target: Cancer Cells	Dose	Activity	References
Glioma stem-like cell lines	10–25 μM	*in vitro*: Decrease in cell viability, induction of autophagy	[8]
Glioma cell line U87	0.01–9 μM	*in vitro*: Inhibition of migration, no effect on cell viability	[4]
Glioma cell line U87 and U373	20–40 μM	*in vitro*: Induction of apoptosis	[9]
Glioma cell line U87 and primary glioblastoma cells MZC	>25 μM	*in vitro*: Increase in calcium influx, reduction of viability, induction of apoptosis	[10]
Glioma cell line U87-MG	0.5–12 μM	*in vitro*: Decrease in cell invasion	[11]
Neuroblastoma cell lines SK-N-SH25, IMR-3226, NUB-627 and LAN-1	5–50 μg/mL	*in vitro*: Reduction of cell viability, induction of apoptosis	[3]
SK-N-SH cells xenograft mouse model	20 mg/kg	*in vivo*: Suppression of tumor growth	[3]
Neuroblastoma celllines SH SY5Y and IMR-32	5–10 μM	*in vitro*: Induction of apoptosis, reduction of cell migration and invasion, inhibition of mitochondrial respiration	[12]
Medulloblastoma cell lines D283, D425, and PER547	EC_{50} 3.2–4.1 μM	*in vitro*: Elevation of ROS production, induction of apoptosis and autophagy	[13]
Ependymoma cell lines IC-1425EPN and DKFZ-EP1NS	EC_{50} 7.5–10.1 μM	*in vitro*: Elevation of ROS production, induction of apoptosis and autophagy	[13]

EC_{50}—Half maximal effective concentration.

CBD can promote CDKN1A (p21) expression in cells. Increased p21 protein expression evokes cell cycle arrest via cyclin D inhibition and the stimulation of GADD45A/B expression [2]. CBD can also induce endoplasmic reticulum (ER) stress [6][14], inhibiting AKT and mTOR signaling and subsequently decreasing the levels of phosphorylated mTOR and cyclin D1. CBD can inhibit the interaction between beclin-1 and Bcl-2, leading to reduction of mitochondrial membrane potential,

mitochondrial Ca^{2+} overload, the release of cytochrome c to the cytosol, and activation of the intrinsic apoptotic pathway [14]. CBD also increases the generation of reactive oxygen species (ROS) [15][16][17]. Finally, during CBD-treatment, cancer cells can be destroyed by the induction of apoptosis and/or autophagy (Figure 5) [2][3][14][8].

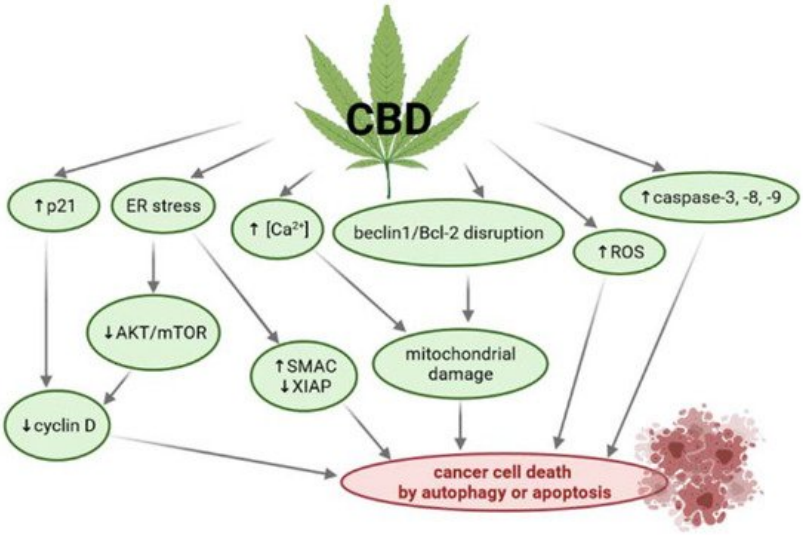

Figure 5. Pathways of anticancer activity of cannabidiol (CBD). Legends: AKT—Protein kinase B; Bcl-2—B-cell lymphoma 2; ER—endoplasmic reticulum; mTOR—the mechanistic target of rapamycin; p21—cyclin-dependent kinase inhibitor 1; ROS—reactive oxygen species; SMAC—second mitochondrial-derived activator of caspase; XIAP—X-linked inhibitor of apoptosis protein [own drawing].

2. Anticancer Effect of CBD

In the *in vitro* studies, CBD induced the decrease in glioma stemlike cell viability. The half-maximal inhibitory concentration (IC_{50}) was between 14.6 µM and 19.4 µM at 24 h post-treatment. CBD in the lowest effective dose (10 µM) reduced AKT activity in glioma stemlike cells, leading to autophagy [8]. In U87 human glioma cells, the CBD treatment for 6 h resulted in a concentration-dependent migration inhibition. The IC_{50} was 5.05 ± 1.1 µM. Simultaneously, in concentrations 0.01–9 µM of CBD, no effect on cell viability was observed [4]. In other studies, CBD induced apoptosis in the U87 and U373 human glioma cell lines. In the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) test, CBD inhibited the mitochondrial oxidative metabolism in concentrations from 5 µM to 40 µM. The IC_{50} values were 26.2 ± 2.8 µM for U87 and 24.1 ± 2.16 µM for U373 cells [9]. In athymic nude mice with inoculated U87 cells, CBD-treated animals at day 18 had about 70% smaller and at day 23 about 50% smaller tumors than in control mice [9]. Additionally, CBD induced an increase in calcium influx in U87MG cells, with an EC_{50} value of 22.2 µM. In the U87MG glioma cell line and MZC primary glioblastoma cells, CBD affected the viability of both cells at doses > 25 µM, inducing apoptosis [10]. CBD in concentrations of 0.5–12 µM caused also decrease in U87-MG cell invasion from 10% to 90% [11]. Single studies showed an excellent therapeutic interaction of cannabidiol and γ-irradiation or chemoradiation [18][19].

In acute lymphoblastic leukemia of T lineage (T-ALL), CBD at 10 µM inhibited proliferation and at 30–100 µM induced cell death. CBD at lethal concentrations caused mitochondrial Ca^{2+} overload and mitochondrial pore formation. In Jurkat cells, one of the leukemic cell lines, 10 µM concentration of CBD induced autophagy, and 30 µM CBD caused mitochondrial damage and induced cytochrome C release from mitochondria. CBD also increased caspase-3 and -9 activity, which confirms the impact on intrinsic apoptosis [15]. Another study showed that CBD was highly cytotoxic, with an IC_{50} of 12.1 µM. CBD also triggered an increase in ROS production, when compared to untreated Jurkat cells [15][16].

CBD at concentrations of 5–50 µg/mL effectively reduced the viability of neuroblastoma cell lines (SK-N-SH25, IMR-3226, NUB-627, and LAN-1) in a dose- and time-dependent manner. Moreover, CBD led to cell arrest in the G1 phase and affected cell morphology. The cells became rounded and swollen, which confirmed that CBD induces apoptosis. In SK-N-SH cells xenograft mice treatment with 20 mg/kg of CBD suppressed tumor growth [3].

CBD induces apoptosis also in SH SY5Y and IMR-32 neuroblastoma cell lines. This activity was observed in concentrations of 5–10 µM. Apoptosis was related to the induction of caspase-2 and -3 and inhibition of mitochondrial respiration. Moreover, CBD significantly reduced migration and invasion of neuroblastoma cells [12].

The next research studied three medulloblastoma cell lines (D283, D425, and PER547) and two ependymoma cell lines (IC-1425EPN and DKFZ-EP1NS). CBD had cytotoxic activity in all cancer cell lines with EC_{50} of 3.2–4.1 µM for medulloblastomas and 7.5–10.1 µM for ependymomas. The authors observed that CBD increases ROS production.

Finally, cannabidiol leads to induction of autophagy and apoptosis by MAPK and AKT/mTOR signaling [13].

Thus far, CBD is not accepted by European Medicines Agency (EMA) or U.S. Food and Drug Administration (FDA) for cancer treatment. The FDA only approved Marinol and Syndros for therapeutic uses in nausea associated with cancer chemotherapy [20].

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