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Review Article

Potential Use of Cannabinoids in Cancer Management: Narrative Review

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Abstract

Cannabidiol (CBD) is a non-psychoactive phytocannabinoid that has shown favorable activity in several non-oncologic indications. However, its use in cancer management has been at best, controversial. Desbite the enormous preclinical studies that showed significant opportunities, mature data that support the clinical utility of CBD among cancer patients remain limited. In this review we examined the most relevant evidence of the antitumor effects of CBD, besides, its potential role in alleviating cancer-associated symptoms, and we also reviewed the most common adverse events that are associated with its use. We finally highlighted some of the ongoing clinical trials.

Keywords: Cannabidiols; Cancer; Patients

Abbreviations

CBD: Cannabidiol; CINV: Chemotherapy-Induced Nausea and Vomiting; FDA: Food and Drug Administration; GPCR: G-Protein Coupled Receptor; RCT: Randomized Controlled Trials; THC: Tetra Hydro Cannabinol

Introduction

The endocannabinoid system is a recently identified signaling system encompassing the cannabinoid CB-1 and CB-2 receptors, and their intrinsic lipid ligands, endocannabinoids. Currently, the term 'cannabinoid' denotes more than 100 terpenophenols derivatives from Cannabis sativa [1].

Cannabis or marijuana is the most commonly used illegal substance worldwide. Most of the cannabis use is recreational but there is increasing use of cannabis and cannabis-derived substances for medical purposes. However, the clinical use of D9-tetrahydrocannabinol and additional synthetic agonists are often limited by their unwanted psychoactive side effects. For the latter property, interest in non-psychoactive phytocannabinoids, such as Cannabidiol (CBD), has substantially increased in recent years.

The discovery of CBD was made in 1940, which is more than two decades earlier than THC [2]. It is non-psychoactive with low affinity for CB receptors and widely used to treat diseases, such as neurological diseases and cancer [3,4]. CBD is known to exert its antitumor effects through nitric oxide synthases activation, downregulation of protein kinase B (AKT)/mTOR, and mitogen-activated protein kinase signaling [4]. However, clinicians have concerns about whether these treatment options are legal, safe, and effective and they are largely unacquainted with these products [5,6].

Therapeutic value of CBD in non-cancer patients

CBD has been used in the management of several non-oncological conditions [7]. At present the only Food and Drug (FDA)-approved indication for the medical use of CBD is to treat intractable seizures in patients with the Lennox–Gastaut syndrome or the Dravet syndrome [8]. CBD has also been shown to express therapeutic value in other non-oncologic indications. In a recently published meta-analysis, CBD treatment was found beneficial in the treatment of psychotic disorders and substance abuse addiction [9]. Currently, only epilepsy, cancer-related pain, and multiple sclerosis are recognized indications for CBD by international federal agencies.

Therapeutic value of CBD in cancer patients

Currently, there are no data from large, multicenter, double-blinded, placebo-controlled trials available concerning the systemic anticancer effect of cannabinoids. Although some authors attempted to provide guidelines to clinicians about the use of CBD, the guidelines did not address the specific utilization of those compounds among cancer patients [10]. CBD has been shown to have anti-neoplastic effects in vitro and/or in vivo in some malignancies [11-13]. Moreover, it was also shown that CBD could supplement the efficacy of several chemotherapeutic agents [14,15], and could overcome resistance to other drugs such as oxaliplatin [16].

CBD and breast cancer

CBD inhibited the growth of different breast tumor cell lines [17], and decreased breast cancer cell progression, invasion, and metastatic spread [18]. CBD was also found to induce apoptosis in estrogen receptor-positive and estrogen receptor-negative breast cancer cells [19]. A strong association between HER-2 expression and CB-1 and CB-2 receptors was discovered where 91% of the CB-positive tumors were also positive for HER-2 [20]. That association could be exploited in the management of those tumors. In an experimental mice model of HER2-posititive cancer, treatment with THC delayed the onset and progression of the tumors [17].

CBD also subdued the growth of triple negative breast tumors in a mouse model and reduced tumor volume and tumor vascularization [21]. The progression of estrogen-related cancer is promoted by G-protein coupled receptor (GPCR) affinity for estrogen, a pathway that is affected by CB receptors signaling suggesting that an interaction may be clinically useful [22].

CBD and lung cancer

In several lung cancer cell lines, it was shown that CBD induced

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apoptosis and impaired invasion of those tumor cell lines [11]. Haustein et al. have also shown that cannabinoids increased lung cancer cell lysis by lymphokine-activated killer cells [23]. At present, there are no mature data that supported the clinical benefit of CBD in lung cancer patients.

CBD and leukemia, lymphoma, and myeloma

It was shown that CBD treatment induced apoptosis in human acute myeloid leukemia HL-60 cell line [24]. It was also shown that human leukemias and lymphomas expressed significantly higher levels of CB-2 receptors compared with other tumor cell lines, suggesting that tumors of immune origin may be sensitive to the CB-2-mediated effects of CBD [25]. An interesting data were reported by Morelli et al. where they have shown that chemoresistance of myeloma cells towards bortezomib was reduced when bortezomib was combined with CBD [26].

CBD and pancreatic cancer

Multiple in vitro and in vivo studies have shown an inhibitory effect of CBD and THC on pancreatic cancer cells [27,28], an effect that was predominately mediated through CB-1, CB-2, and GPCR pathways. It was also shown that the CB-1 inverse agonist AM251 demonstrates a synergistic anticancer effect with 5-fluorouracil on pancreatic cells [29]. Moreover, cannabinoids have been shown to reduce chemotherapy-induced neuropathy in animal models exposed to paclitaxel or cisplatin that are used in the management of advanced pancreatic cancer [30]. Yet, there are no clinical studies to date that showed treatment benefits of CBD in patients with pancreatic cancer.

CBD and glioma

Several animal models have shown that CBD exhibited anti-proliferative activity against glioma cells [31,32], and an ability to induce an oxidative stress on such cells [33]. It was also shown that CBD possess an inhibitory effect on the growth of multiple glioblastoma cell lines [34]. Guzmán et al. have conducted a pilot phase I trial on nine patients with glioblastoma multiforme who had previously failed standard therapy and had clear evidence of tumor progression [35]. In the latter study, THC was administered intratumoraly and a median survival of 24 weeks was reported. The same group are currently concluding a phase II clinical trial among patients with glioblastoma multiforme randomized to receive temozolomide in combination with CBD and THC versus temozolomide and placebo. The results of the latter study are not yet available.

CBD and angiogenesis

A significant potential mechanism for the anti-tumor effect of CBD its ability to promote angiogenesis [36]. Cannabinoids have been demonstrated to act as anti-angiogenic factors by inhibiting the ability of tumor cells to produce pro-angiogenic factors [37].

Cannabinoids and Symptoms Control in Cancer Patients

Chemotherapy-Induced Nausea and Vomiting (CINV)

Cannabinoids exert their anti-emetic properties through interactions with the centrally located CB-1 receptors and 5-HT3 receptors, which mediate emesis. Dronabinol (also known as Marinol and Syndros), and Nabilone (Cesamet is the brand name), are both synthetic THC and were granted an FDA approved for treatment of CINV after the failure of a trial of first-line standard anti-emetics [38]. Moreover, in a recently reported study that included more than 3,000 cancer patients, cannabis was shown to control emesis in 57% of patients [39]. Nevertheless, at present, CINV is not an FDA-approved indication for the use of CBD.

Anorexia-cachexia syndrome

Dronabinol proved to be effective in improving anorexia in patients with AIDS and may also benefit patients with advanced stage of cancer and was granted an FDA-approval for such indication [40]. In a recent survey of 237 oncologists in the USA, 65% thought that cannabinoids were equally or more effective than standard treatments for anorexia and cachexia [41].

On the contrary, Jatoti et al. reported on 469 patients with advanced cancer were randomized into three arms: oral dronabinol plus placebo, oral megestrol acetate plus placebo, or both agents [42]. In the latter study, megestrol acetate-treated patients reported significant appetite improvement and weight gain compared with dronabinol-treated patients: 75% versus 49% for appetite and 11% versus 3% for ≥ 10% baseline weight gain. Combination treatment resulted in no significant differences compared with megestrol acetate alone. Moreover, in a more recent phase III study, 289 cachectic patients were randomized to receive cannabis extract, THC, or placebo, and high rates of appetite improvement were observed in all groups (73%, 58%, and 69%, respectively) with comparison showing no significant difference between the three interventions [43].

Cancer-related pain

According to the College of Family Physicians of Canada (CFPC), the use of cannabinoids as first- or second-line treatment to palliate cancer pain was not recommended. However, the CFPC recommended that cannabinoids could be considered as adjuncts to other prescribed analgesics [44]. On the other hand, the CFPC recommended the approved Nabilone or Nabiximols - a cannabis extract that contains THC and CBD (known as Sativex) - , as the initial agents.

In a study conducted among adults with moderate to severe cancer pain who were currently using opioids, nabiximols was compared versus placebo versus THC extract. The study showed that there was a statistically significant difference favoring nabiximols versus placebo, with no difference versus THC extract [45]. In another study, different doses of nabiximols were compared to placebo in patients treated with opioids. The effectiveness of low and medium nabiximols doses, but not at a high dose was demonstrated [46]. In a systematic review of cannabinoids in the management of cancer pain, eight randomized controlled clinical (RCTs) trials met the inclusion criteria. Low-quality evidence supported that cannabinoids as active analgesics for cancer pain. The systematic review also showed that THC is an effective analgesic for cancer pain, albeit, pain relief was achieved only at high doses [47].

At present, Nabiximols is approved in the United Kingdom as a botanical drug. In the year 2011, GW Pharmaceuticals granted Novartis the rights to commercialize nabiximols in Asia, excluding China and Japan, and in Africa and the Middle East.

Neuropathic pain

This synergetic effect of cannabinoids in combination with

opioids in relief of Chemotherapy-Induced Peripheral Neuropathy (CIPN) was demonstrated in animal models [48]. In another study on mice, Ward et al. showed that CBD inhibited paclitaxel-induced neuropathic pain through 5-HT1A receptors [49]. In a systematic review and a meta-analysis of eleven RCTs including 1,219 patients, the authors showed that selective cannabinoids provided a small analgesic benefit in patients with chronic neuropathic pain, however, there was a significant heterogeneity among the included studies [50]. In another meta-analysis of 6 RCTs on neuropathic pain, cannabinoids were more effective than placebo [51]. Despite that moderate evidence, the International Association for Study of Pain guidelines recommend against cannabinoids for the treatment of the neuropathic pain due to inconclusive data [52].

Stress and anxiety

For alleviating the stress and anxiety symptoms among cancer patients, only THC has shown significant benefit [53]. However, there are no data to support the use CBD for such indication.

Adverse events associated with CBD

The use of CBD is not entirely safe. The FDA has raised concerns regarding the long-term safety of CBD. There are several reported adverse events that appear to be dose dependent though not proportional in all reported cases [53].

Hepatic toxicity

In an animal model, Ewing et. al. experimented on 8-week-old male B6C3F1 mice with either 0, 246, 738, or 2460 mg/kg of CBD (acute toxicity, 24 h) or with daily doses of 0, 61.5, 184.5, or 615 mg/kg for 10 days (sub-acute toxicity) [54]. The authors reported significant elevation of the transaminases and the total bilirubin among animals in the acute and the sub-acute models, besides; it regulated more than 50 hepatotoxicity genes. In recent clinical trials, elevated liver enzymes were observed in 5–20% of patients treated with CBD, and a few patients were withdrawn due to the threat of fulminant liver failure [55,56]. Therefore, caution should be taken when CBD is used with medications with potential to cause hepatic injury or in people with pre-existing hepatic impairment.

Somnolence, and sleep disorders

In clinical trials, somnolence occurred in 23% and 25% of patients treated with CBD (10 and 20 mg/kg/day), followed by fatigue (11% and 12%), lethargy (4% and 8%), and sedation (3% and 6%) [53]. In a small randomized study of 34 children with Dravet syndrome (27 vs. 7, CBD vs. placebo, respectively), somnolence was experienced by 27% of patients who received CBD at 10 mg/kg or less per day compared to 14% among controls [57]. On the other hand, none of the patients who received a higher CBD dose (20 mg/kg per day) experienced somnolence.

Although one clinical trial showed that CBD improved sleep scores in 67% of 103 studied patients [58], other studies have shown that CBD use may be associated with insomnia and other sleep disorders [53]. Such conflicting data may be explained by the confounding effects of associated use of dopamine agonists, stimulants, antiepileptics, steroids, etc. Moreover, some of the CBD users may also suffer from overlapping anxiety or mood changes that may affect the quality of their sleep.

Viral infections

Infection risk was 10% higher in CBD treated persons, particularly viral infections and pneumonia [59]. Several in vitro and in vivo studies have reported on increased or progression of viral infections among CBD users. There were several pertinent mechanisms that could explain the determinant effect of CBD in viral infections. Inflammation is essential for recruitment of immune cells to the site of infection to control virus production and limit spread [60]. CBD has been shown to have significant anti-inflammatory and impairment of many Ca2+-dependent enzyme systems which are central to inflammatory and cell-autonomous antiviral responses [59].

Impairment of the immune system

There is a concern about the impact of CBD and other cannabinoids on the immune system that may lead to cancer development, or stimulation of cancer cells' proliferation. Moreover, it was shown that that cannabinoids could impair polymorphonuclear leukocyte functions [61], and decrease immune response, particular of T-cell lymphocytes [62]. Moreover, Rieder et al. have shown that CBD induces apoptosis in immune cells leading to significant immunosuppression [63].

Dermatologic toxicity

Although uncommon, some rare phenomenon such as acute generalized exanthematous pustulosis has been reported [64]. Nevertheless, topical CBD was found to be safe and exhibits an anti-inflammatory response on several skin conditions including psoriasis and atopic dermatitis [65].

Regulations in USA for the Medical Use of CBD

At present, the annual CBD sales in the USA is exceeding $200 million [66]. On the other hand, other estimates suggested that the consumer CBD market alone may have reached sales of $600 million to $2 billion in 2018 and may approach $16 billion by 2025 [Available online: https://www.cowen.com/reports/cowen-collective-view-of-cbd/ (accessed on 9 June 2019)].

The FDA has clearly stated that products that are specifically marketed with claims of a therapeutic benefit remain under the purview of the FDA and require approval – including cannabis- or hemp-derived CBD [Gottlieb, S. Statement from FDA Commissioner Scott Gottlieb, M.D., on Signing of the Agriculture Improvement Act and the Agency's Regulation of Products Containing Cannabis and Cannabis-Derived Compounds. U.S. Food and Drug Administration. Available online: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-mdsigning-agriculture-improvement-act-and-agencys (accessed on 20 September 2019).

Currently, CBD is increasingly used in state-approved medical cannabis programs. These programs range from what is deemed a "comprehensive" program that allows CBD and THC use (N = 23 states) or a restrictive program based on CBD with restrictions on the THC allowed (N = 13 states) while four states have no program in place [State Medical Marijuana Laws. National Conference of State Legislatures (NCSL). Available online: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx]. Currently, 11 states also

have adult recreational use cannabis programs. With much inter-state variation, practically all state programs have specified conditions for which medical cannabis can be legally used including, among others, epilepsy/seizures, chronic pain, nausea/vomiting, muscle spasms, inflammatory conditions (e.g., Cohn's), Alzheimer's and Parkinson's disease, HIV/AIDS, and cancer.

Ongoing Clinical Trials

Several ongoing clinical trials would be able to shed some lights on the potential anti-cancer effects of CBD and other cannabidiols and their safety among cancer patients. For example, one of those trials is examining the effect of THC: CBD oromucosal spray in combination with temozolomide in patients with recurrent glioblastoma (https://clinicaltrials.gov/ct2/show/NCT01812616). Another ongoing trial is examining the effect of CBD used as monotherapy in patients with solid tumors (https://clinicaltrials.gov/ct2/show/record/NCT02255292?term=cannabinoid+AND+cancer). The following link lists the currently ongoing studies on the medical use of CBD and other cannabinoids (https://www.cannabis-med.org/studies/study.php).

Conclusion

There are large and promising preclinical data suggesting that CBD and other cannabinoids possess anticancer properties and have the potential to alleviate some of the cancer-associated symptoms. Nevertheless, there is lack of good quality clinical evidence to confirm or redefine their role for cancer patients. Interestingly, the efficacy of cannabinoids is linked to its ability to target multiple cellular pathways that could be exploited in the ongoing clinical trials. We believe that in the very near future, the oncology community would be fully informed about the potential efficacy and the safety of cannabinoids.

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