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Review

Medicinal Cannabis in Cancer Treatment

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Abstract: Cannabis has been used as an herbal remedy for thousands of years and recent research indicates promising new uses in medicine. Researchers have been particularly interested in the potential uses of cannabinoids in treating cancer due their ability to regulate cancer-related cell cycle pathways, leading to many beneficial effects such as tumor growth prevention, cell cycle obstruction, and cell death. The aim of this review is to summarize current knowledge on mechanisms of cannabinoids and their role in treating chemotherapy-induced nausea and vomiting, relieving cancer-associated pain, and obstructing tumor cell growth.

Keywords: cannabidiol; Δ-9-tetrahydrocannabinol; cancer; nausea; vomiting; pain management; antitumor

1. Introduction

Marijuana, also known as hashish, ganja, bud, hemp, weed, or, more commonly, cannabis, is produced by female plants from three cannabinoid-containing species (indica, sativa, ruderalis) of the genus Cannabis [1]. It is the most commonly used illegal drug among Americans [1]. Marijuana is used recreationally to produce a pleasant feeling; however, it can be habit forming and causes various side effects. The use of cannabis for medicinal purposes is gaining prominence. Cannabis possession is prohibited in the US unless it is done so for authorized research purposes. However, many states now allow its medical and/or recreational use as efforts have been made to loosen regulations on the drug [2].

Though it was only introduced into western medicine around 180 years ago, Cannabis has been used for medicinal purposes for at least 3,000 years [3]. Cannabis was marketed for its analgesic, sedative, anti-inflammatory, antispasmodic, and anticonvulsant effects [3]. The U.S. Treasury Department implemented the Marijuana Tax Act in 1937, which enforced a specific tax of $1 an ounce when cannabis was used for medical purposes and $100 an ounce when used for non-medical purposes [3]. This led to the drug being prescribed only in critical cases and was thought this would help prevent addiction. Then, the Controlled Substances Act was passed by Congress in 1970, designating marijuana as a Schedule I drug with a high potential for abuse or addiction and no FDA-approved medicinal use [3]. However, when the Compassionate Use Investigational New Drug program was put in place in 1978, patients were given cannabis in critical cases, depending on the necessity [3].

The main psychoactive chemical in marijuana that causes many of the potent effects that users desire is delta-9-tetrahydrocannabinol (THC) [4]. THC comes from the resin produced by the leaves and buds of the flowers of the female cannabis plant [4]. Cannabidiol (CBD) is another common cannabinoid, but it produces mild to no psychoactive effects compared to THC [1]. THC affects the body variously, depending on how it is consumed. When inhaled, THC is released into the bloodstream from the lungs and quickly travels to other areas of the body, including the brain [4]. This leads to a sense of ecstasy, relaxation, amplified sensory perception (such as seeing vivid colors), laughter, altered perception of time, and boosted appetite. When consumed in foods or beverages, the

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effects are delayed from 30 minutes to 1 hour as the drug passes through the digestive system into the blood [4]. A considerably lower amount of THC enters the bloodstream when eaten or drank rather than smoked. This can lead to people unknowingly consuming a greater quantity of the chemical, causing some individuals unwanted effects of anxiety, fear, distrust, or panic [4].

The body easily recognizes THC because its chemical structure is similar to anandamide, a natural brain chemical. This allows it to alter brain communication [4]. Endogenous cannabinoids, compounds that are similar to cannabinoids but made by our own body, have been found to help in the response to pain, mood, inflammation, memory, and movement [3]. Only two key endogenous cannabinoids have been identified: anandamide (AEA or arachidonoyl ethanolamide) & 2-arachidonoyl glycerol (2-AG) [4]. These send chemical messages between neurons, serving as neurotransmitters [4]. Endogenous cannabinoids affect the areas of the brain that control happiness, memory, reasoning, coordination, attentiveness, movement, and sensory and time perception [4]. THC acts on cannabinoid receptors on neurons in several brain regions and modulates numerous essential tasks in the body, leading to many of the effects previously mentioned[4].

Researchers have been interested in the therapeutic uses of cannabinoids in cancer treatment due to several beneficial properties [5]. Cannabinoid agonists can regulate cancer-related cell cycle pathways by binding to CB1 or CB2 receptors [6]. This produces many desirable effects in cancer therapy including tumor growth prevention, cell cycle obstruction, and cell death [6]. Cannabinoids have been found to work independent of some receptors but dependent on other receptors, like TRPV1 [6]. They may cause apoptosis by activating the MAPK pathways (which promote cellular proliferation, differentiation, development, inflammatory responses, and apoptosis) and inhibiting the PI3K-Akt pathway (which promotes metabolism, proliferation, cell survival, growth, and angiogenesis) [6]. Cannabinoids also appear to affect the MEK-extracellular signal-regulated kinase signaling cascade and the cyclic AMP-protein kinase-A pathway [5].

Multiple studies have shown that treatment with THC and CBD inhibits metastasis [6].

2. Use of Cannabis in Cancer Treatment

Researchers had begun studying the possible therapeutic uses of cannabinoids in treating the side effects of therapy and tumor-related symptoms in the 1970s [6]. The known beneficial effects of CBD on cancer include tumor cell suppression, the relief of cancer-related pain, and the reduction of chemotherapy effects, such as nausea and vomiting [7]. However, patient interest is also to be considered. In a retrospective study with 163 patients, Raghunathan et al. found that although they are aware of the side effects and the need for solid evidence, cancer patients turn towards medical cannabis for treatment [8]. Survey results showed that medical cannabis was usually used to promote sleep (53%), relieve pain (47%) and anxiety (46%), and improve appetite (46%) [8]. Surprisingly, 29% were interested in trying cannabinoid therapy as a treatment for cancer [8]. To learn more about cannabinoids and their possible uses in cancer treatment, clinical trials and studies have been conducted and more are planned.

Anecdotal success stories of cannabinoids are primarily to blame for the rise in the medical prescription of cannabis-derived oils and herbal cannabis [9]. Oelen et al. surveyed 152 people who were aged 18 years or older and receiving intravenous systemic treatment at an outpatient facility in the Netherlands for solid cancer, in order to gauge patient views towards the use of cannabinoids in medical treatment [9]. The questionnaire included questions on cannabis consumption, sociodemographic factors, and clinical characteristics [9]. Depending on their responses, patients were divided into one of the following categories: (1) never used cannabinoids, (2) recreative use of cannabinoids in the past, (3) medical use of cannabinoids in the past (4) current recreative use of cannabinoids, and (5) current medical use of cannabinoids [9]. Then, the frequency of cannabinoid consumption was calculated for each group [9]. According to the report, nearly

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25% of participants have used cannabinoids for medicinal purposes [9]. About 23% of current non-users reported having possible future medical use [9]. About 50% of users reported the potential of cannabinoids in cancer treatment as their primary reason for using these drugs [9]. Overall, when compared to the general population, cancer patients consume a substantial amount of cannabinoids [9].

However, in a systematic meta-analysis reviewing 17 research articles, Belgers et al. discovered that cannabinoids had no effect on health-related quality of life (HRQoL) or mental wellbeing [10]. However, just two studies have looked into how cannabis affects the HRQoL in patients with brain tumors [10]. One study found no improvement in HRQoL when THC was used to treat chemotherapy-induced nausea and vomiting in 32 patients with primary brain tumors [10]. The second study reported that there was no difference in HRQoL between different CBD:THC ratios when it looked at two different CBD:THC ratios (1:1 and 1:4) and their impact on HRQoL in 88 patients with primary malignant brain tumors [10], but both investigators did not report a definitive effect [10].

Though there have been various studies in adult oncology, there are only a few studies on the role of cannabinoids in childhood cancers. Schab et. al mentioned studies have shown that cannabinoids have hindered the growth of rhabdomyosarcoma and neuroblastoma cells and stopped cell cycle progression in osteosarcoma cells in children [11]. Moreover, it was found that CB1 expression may help foreshadow the shrinking of low-grade gliomas in children [11]. Another review on the role of cannabinoids in pediatric oncology indicated that a majority of previous studies were based on acute lymphoblastic leukemia, suggesting that cannabinoids have the ability to eliminate cancer cells in vivo and in vitro [12].

So far, cannabinoids have been proven to be safe in treating cancer, but not useful in controlling or curing the disease [13]. Cannabinoids have been found to have an effect on tumors of the brain, prostate, colon and rectum, breast, uterus, cervix, thyroid gland, skin, pancreas, and lymph [6]. THC has been found to help in mitigating pain, decrease inflammation, and act as an antioxidant [13]. However, the full potential of cannabinoids is yet to be understood. Few drugs, including Dronabinol (Marinol®), Nabilone (Cesamet®), and Nabiximols, which contain a mix of CBD and THC, have already been approved for use [13]. Dronabinol, which is usually in the form of a capsule, is used to help relieve chemotherapy-induced nausea and vomiting, but it appears to be about equally as effective as megestrol acetate, a progestin medication [13]. Nabilone, usually taken by mouth, is a synthetic cannabinoid similar to THC and is also used to help relieve chemotherapy-induced nausea and vomiting [13]. Nabiximols, usually taken in the form of a mouth spray containing Δ9-THC and CBD in a 1:1 ratio, are still under study in the United States but have promising potential for relieving cancer-associated pain, though some studies have shown no positive results from it [13]. According to the American Cancer Society, further scientific research on cannabinoids for cancer patients is necessary. Additionally, more advanced, and efficient medicines are required to combat the side effects of cancer and its treatments [13].

3. Use of Cannabinoids in Chemotherapy-Induced Nausea and Vomiting

The anti-emetic effects of cannabinoids have been demonstrated in numerous studies. Cisplatin is a chemotherapy drug used to treat various cancers, including those of the ovaries, cervix, bladder, head, neck, testes, and lungs. However, it is known to cause a severe emetic response. In a study, Costall et al. found that intravenously administering 10mg/kg of the drug to ferrets induced a severe emetic response which was hindered by the 5-HT3 receptor antagonist, tropisetron (0.1 and 1.0 mg/kg i.v.), and dopamine receptor antagonist, metoclopramide (4.0 mg/kg i.v.) [14]. It was also noted that lower doses of tropisetron (0.01 mg/kg i.v.) and metoclopramide (2.0 mg/kg i.v.) did help reduce the emetic response, but did not completely prevent it [14]. The results of the study suggested that 5-hydroxytryptamine M-receptor antagonism is the cause of the anti-emetic response of tropisetron and metoclopramide against cisplatin-induced emesis [14].

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Likewise, Miner and Sanger observed that dopamine receptors at the chemoreceptor trigger zone (CTZ) in the area postrema were antagonized by traditional doses of 10 to 30 mg of metoclopramide [15]. They suggested that this may account for the antiemetic action of the drug [15]. As Costall et al mentioned, Miner and Sanger also noted that emesis was only reduced when high doses of metoclopramide were administered intravenously and this was due to the 5-HT M receptors being antagonized [15]. They also stated that animals that were treated with cisplatin, but not metoclopramide regularly vomited after 84.1 ± 11.5 min [15]. Metoclopramide prevented vomiting in 75% of the animals when given at a dosage of 2 x 0.5 mg/kg [15]. When given at a lower dosage of 2 x 0.05 mg/kg, the drug was able to reduce the severity, but not completely prevent the effects [15]. Though Miner and Sanger concluded that metoclopramide, a 5-HT M-receptor antagonist, prevented cisplatin-induced emesis in ferrets, they weren't sure how exactly cisplatin affected 5-HT M-receptors [15]. However, they mentioned that Harris suggested that cytotoxic drugs may produce emetic effects by interfering with enzymes that degrade neurotransmitters such as enkephalins, which are involved in the emetic response [15].

In another study, Abrahamov et al. administered delta-8-THC, a cannabinoid that has a decreased psychoactive potency when compared to delta-9-THC, to eight children [16]. These subjects were between 3 to 13 years of age and treated with various chemotherapy drugs for up to 8 months for a variety of blood cancers [16]. The researchers administered the THC treatment two hours before the subjects' cancer treatment and then continued to administer it every 6 hours over the next 24 hours [16]. They found that the emetic response was entirely prevented and side effects were minor [16].

Moreover, Jhangiani and coworkers conducted a double-blind, five-day study on the effectiveness of the cannabinoid, dronabinol, a steroid, ondansetron, or a combination of both in treating nausea and vomiting resulting from chemotherapy, and the body's tolerability towards the drugs [17]. Patients who were currently undergoing chemotherapy that caused a moderate to high emetic response were given ondansetron (16 mg IV), dexamethasone (20 mg PO), and either placebo or dronabinol (2.5 mg) before receiving chemotherapy on the first day [17]. Those receiving active treatment (dronabinol, ondansetron, or combination therapy) were also given 2.5 mg of dronabinol after chemotherapy on the first day [17]. Patients received predetermined doses of either placebo, 10 mg dronabinol, 16 mg ondansetron, or combination therapy on the second day, and either placebo, flexible doses of dronabinol (10–20 mg), ondansetron (8–16 mg), or dronabinol and ondansetron (10–20 mg dronabinol, 8–16 mg ondansetron) on the third to fifth days [17]. The researchers concluded that both dronabinol and ondansetron were similarly effective in treating nausea and vomiting [17]. They also noted that active treatment groups led to a considerably higher incidence of nausea absence [17]. Results showed that 71% of patients receiving dronabinol did not exhibit nausea, 64% receiving ondansetron did not, and 53% receiving combination therapy did not when compared to 15% of those receiving placebo [17]. As illustrated by the data, the intensity of nausea and vomiting was lowest in those that received dronabinol [17].

4. Use of Cannabinoids in Cancer-Associated Pain

Many cancer patients rely on opioids for pain relief but face a multitude of dangerous side effects as a result [6]. The earliest uses of cannabinoids in oncology were to treat pain resulting from treatment and the disease itself [6]. This led to cannabinoids replacing opioids in treatment [6]. For example, an oromucosal spray containing THC and CBD is being clinically used in cancer treatment if opioid treatment is not effective [7]. Studies have shown that it is effective for prolonged use and does not produce drug resistance [7].

To assess the extent and duration of the anesthetic effects of smoked marijuana and dronabinol, Cooper et al. conducted a randomized, double-blind trial, with 15 healthy male and 15 healthy female daily marijuana smokers under a controlled environment using a validated experimental model of pain [18]. The cold-pressor test was used to measure the pain response. Subjects submerged their left hand in 4°C cold water. Then, pain

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sensitivity was determined by how long it took to report pain, and pain tolerance was determined by how long it took to remove the hand from the water [18]. When compared to placebo, the results showed that marijuana and dronabinol decreased pain sensitivity by 3.56%, increased pain tolerance by 1.98%, and decreased subjective ratings of pain intensity by 3.56% [18]. This suggests that marijuana and dronabinol both decrease pain under controlled conditions, with dronabinol being more effective [18].

Furthermore, Ling et al. found that, on average, patients already receiving opioids for advanced cancer pain exhibited lower pain scores when treated with nabiximols [19]. The patients were followed over the next 6 months and data showed that more patients reported increased quality of life and decreased opioid use [19]. Fewer patients reported severe pain, however, more extensive clinical trials are necessary to accurately evaluate the effectiveness and safety of cannabis for treating cancer pain. [19].

5. Antitumor Properties of Cannabinoids

Cannabinoids have also been shown to exert anti-tumor effects on cells. Kiskova et al. found that THC and CBD obstructed the growth of the disease in breast cancer models, suggesting that cannabinoids may slow down tumor growth in breast cancer patients [20]. Cannabinoids used G-protein coupled CB-receptors (CB-Rs), CB1-R, and CB2-R, and various other receptors to affect the signaling pathways of cells [20]. They block critical active pro-oncogenic signaling pathways (for example extracellular-signal-regulated kinase pathway) to inhibit cell cycle progression and cell growth and induce cancer cell apoptosis [20]. The cannabinoids were found to be active in both estrogen receptor-positive and estrogen receptor-negative breast cancer cells [20]. Cannabinoids were previously administered to patients with advanced stages of breast cancer, but Kiskova et al. suggested that they might be more beneficial if given at earlier stages [20].

Gómez del Pulgar et al. also found THC and other cannabinoids to induce apoptosis of cancer cells, specifically glioma cells by producing ceramide [21]. They suggested that malignant gliomas can be treated with cannabinoid therapy because they selectively induce ceramide synthesis and apoptosis in transformed glial cells, but not in non-transformed neural cells [21]. Primary neurons and astrocytes are not affected by cannabinoids as they do not lead to apoptosis or ceramide accumulation [21].

6. Conclusions

Many medicinal uses of marijuana have been proposed, but can we use it as medicine? The possible therapeutic properties of marijuana have been up for debate and research for a long time. Some THC-based medications, including dronabinol (Marinol®) and nabilone (Cesamet®), have already been approved for use in pill form by the FDA for treating chemotherapy-induced nausea [4]. Various other cannabinoid medications are currently being studied or approved for use in treating cancer or related symptoms [4]. However, the impact of long-term use on those with health- and/or age-related vulnerabilities is not well understood [4]. Clearly it will be necessary to conduct more research to advance our understanding of the various uses of medical marijuana [4].

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