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Review article

Ligands for cannabinoid receptors, promising anticancer agents

Marjan Nikan [a], Seyed Mohammad Nabavi [b], Azadeh Manayi [a,*]

[a] Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

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ABSTRACT

Cannabinoid compounds are unique to cannabis and provide some interesting biological properties. These compounds along with endocannabinoids, a group of neuromodulator compounds in the body especially in brain, express their effects by activation of G-protein-coupled cannabinoid receptors, CB1 and CB2. There are several physiological properties attributed to the endocannabinoids including pain relief, enhancement of appetite, blood pressure lowering during shock, embryonic development, and blocking of working memory. On the other hand, activation of endocannabinoid system may be suppresses evolution and progression of several types of cancer. According to the results of recent studies, CB receptors are over-expressed in cancer cell lines and application of multiple cannabinoid or cannabis-derived compounds reduce tumor size through decrease of cell proliferation or induction of cell cycle arrest and apoptosis along with desirable effect on decrease of tumor-evoked pain. Therefore, modulation of endocannabinoid system by inhibition of fatty acid amide hydrolase (FAAH), the enzyme, which metabolized endocannabinoids, or application of multiple cannabinoid or cannabis-derived compounds, may be appropriate for the treatment of several cancer subtypes. This review focuses on how cannabinoid affect different types of cancers.

Contents

* Corresponding author.
E-mail address: Manayi@sina.tums.ac.ir (A. Manayi).

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1. Introduction

Cannabinoids are a chemical class of C_{21} terpenophenolic compounds that represent a group of compounds found in *Cannabis sativa* L. (family: Cannabaceae) [1]. Two types of cannabinoid receptors, CB1 and CB2, have been reported and cloned [2–4], both of which coupled to G-proteins. There is strong evidence that other additional CB receptors may present [5–7], G-protein coupled receptor 55 (GPR55), is also widely expressed in the brain, jejunum, ileum, osteoclast, and osteoblast. Although, the physiological role of the GPR55 is not clearly specified, it regulates cell bone functions [8]. CB1 receptor is responsible for marijuana's psychoactive effects. This receptor is present in many areas of the brain and plays a role in memory, mood, sleep, and appetite and pain sensation. The release of several neurotransmitters such as dopamine, noradrenaline, serotonin (5-HT), gamma-aminobutyric acid (GABA), and glutamate are modulated with activation of CB1 receptors, which usually located pre-synaptically [9]. CB1 receptors are also found on organs including muscle [10,11], liver [12], pancreas [13], adipose tissue [14,15], and many other tissues [16]. While, CB2 receptors are responsible for marijuana's anti-inflammatory effects as they are found in immune cells. Inflammation is an immune response that is believed to be a factor in many diseases and conditions [17–19]. However, CB2 receptors have also been recently reported in some regions of the brain and brainstem [20,21].

Δ^9-tetrahydrocannabinol (THC) is the most well-known member of phytocannabinoids, plant substances that stimulate CBs. The compound is the principal active component of *C. sativa*. THC acts on both CB1 and CB2 receptors, but the euphoria and psychoactivity result from stimulation of CB1. Numerous other non-Δ^9-THC, phytocannabinoids exist, including the non-psychoactive cannabidiol (CBD), cannabidiolicacid CBDA, cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), Δ^9-tetrahydrocannabivarin (THCV), β-caryophyllene, and tetrahydrocannibinolic acid (THCA). Intriguingly, compounds from *Echinacea*, *Brassica*, as well as certain flavonoids and catechins also appear to modulate endocannabinoid tone [22]. Endocannabinoids are lipid mediators that activate cannabinoid receptors. The endocannabinoid system (ECS) as a whole refers to endocannabinoids, the proteins that regulate their production and degradation, and the receptors through which they signal. The ECS is involved in the direct regulation of appetite, pain and inflammation, thermoregulation, intra-ocular pressure, sensation, muscle control, motivation/reward, mood, and memory [23]. It has been suggested that modulation of the ECS may have therapeutic potential in a wide array of disease processes, including obesity/metabolic syndrome, diabetes, neurodegeneration, cardiovascular, liver, gastrointestinal (GI), skin, pain, psychiatric disorders, cachexia, cancer, and chemotherapy which induced nausea and vomiting [24]. Some of the both natural and synthetic cannabinoids were used clinically in multiple sclerosis for muscle spasm and pain, recurrent glioblastoma multiform, neuropathic pain, and protective agents in brain trauma [8]. For instance, 1′,1′-dimethylheptyl-Δ^8-tetrahydrocannabinol-11-oic acid was effectively reduced chronic neuropathic pain with dose of 10 mg capsule per day comparing to the placebo [8]. In addition, there are evidences that cannabis showed significant analgesic property in neuropathy of patient with HIV [25,26].

2. The endocannabinoid system

Endocannabinoids are widely distributed in the brain and throughout the body. The two well-studied endocannabinoids identified to date are 2-arachidonoylglycerol (2-AG) and anandamide (AEA) that bind with high and similar affinity to CB1 receptors [2,27]. 2-AG has been shown to act as full agonist at both CB receptors with higher efficacy at the CB2 receptor [28], while anandamide is only a partial agonist [29,30]. Other endocannabinoids include N-arachidonoyl dopamine [13], homo linoleoyl ethanolamide (HEA), docosa tetraenyl ethanolamide (DEA), virodhamine, noladin ether and other cognate compounds such as palmitoyl ethanolamide (PEA) and oleoylethanolamide (OEA) (Fig. 1) [31,32]. Activation of CB1 causes psychomodulatory effects, while CB2 is responsible for treatment of inflammation, pain, atherosclerosis, and osteoporosis [33].

Evolution and progression of prostate, breast, and bone cancer as well as their accompanying pain syndromes may be targeted to suppress trough endocannabinoid system (ECS). Other than these three types of cancer, activation of the endocannabinoid signaling system produces anti-cancer effects in other several types of cancer including lung, brain, and skin [24,34,35].

Studies revealed that ECS plays a role in the central regulation of energy balance. The body's energy status modulates endocannabinoid levels (specifically 2-AG), which increase after acute food deprivation and decrease during feeding [36]. Besides, human studies also revealed that dysregulation of the ECS contribute to obesity with significant correlation between visceral fat mass and circulating 2-AG levels [37]. Previous reports have also revealed significantly higher 2-AG levels in visceral fat of obese subjects than subcutaneous fat [38] and patients characterized by abdominal obesity have higher circulating 2-AG levels [37,39]. Previous studies also suggested that endocannabinoids may aid in pain relief, enhancement of appetite, blood pressure lowering during shock, embryonic development, and blocking of working memory as well [40].

3. Phytocannabinoids

Phytocannabinoids are plant substances that stimulate cannabinoid receptors. More specifically, they are any plant-derived natural products capable of either directly interacting with cannabinoid receptors or sharing chemical similarity with cannabinoids. Based on their chemical structures, cannabinoid agonists can be classified into at least four groups including classical cannabinoids from *Cannabis* spp., bicyclic or non-classical cannabinoids, fatty acid amides and esters, and aminoalkylindoles (AAIs) (Fig. 1) [41–43].

Beside cannabis constituents, other plant-derived natural products have been reported to interact with the endocannabinoid system, including the terpene beta-caryophyllene, fatty acid derivatives, such as N-linoleoylethanolamide, and various N-alkylamides from *Echinacea* spp. [33,44]. THC is pharmacologically and toxicologically the best studied constituent of *Cannabis*, responsible for most of the psychoactive effects of natural *Cannabis* preparations. The second major constituent of *Cannabis*, cannabidiol (CBD) was first isolated in 1940 [45]. THC and CBD are the two most common naturally occurring cannabinoids [46]. Another phytocannabinoid, the cannabidivarin (CBDV), is effective anticonvulsant in a broad range of seizure models and shows potential therapeutic effect in preclinical models of CNS disease [47,48]. Also, it was represented that cannabidivarin is effective in the treatment of epilepsy [49].

The numbers of bioactive phytochemicals, which interact with CBs are increasing. Previous studies have clearly shown that a bark extract of *Magnolia officinalis*, which has been used in traditional Chinese Medicine for the treatment of anxiety, insomnia disorders and allergic diseases, exhibits CB-agonistic effects [50,51]. Bark *M. officinalis* contain biphenylic compounds that these main active constituents interact with CB receptors [50,51].

Sesquiterpene, (*E*)-caryophyllene, is a part of plants essential oils like *Origanum vulgare*, *Cinnamomum* spp., *Piper nigrum*, and even *C. sativa*. This compound like other CB2 receptor agonist lead to anti-inflammatory effect both *in vitro* and *in vivo* may be trough down-regulation of interleukin 1 (IL-1) and expression tumor necrosis factor (TNF-α) [33].