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Review

A focused review on CB2 receptor-selective pharmacological properties and therapeutic potential of β-caryophyllene, a dietary cannabinoid

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ABSTRACT

The endocannabinoid system (ECS), a conserved physiological system emerged as a novel pharmacological target for its significant role and potential therapeutic benefits ranging from neurological diseases to cancer. Among both, CB1 and CB2R types, CB2R have received attention for its pharmacological effects as antioxidant, anti-inflammatory, immunomodulatory and antiapoptotic that can be achieved without causing psychotropic adverse effects through CB1R. The ligands activate CB2R are of endogenous, synthetic and plant origin. In recent years, β-caryophyllene (BCP), a natural bicyclic sesquiterpene in cannabis as well as non-cannabis plants, has received attention due to its selective agonist property on CB2R. BCP has been well studied in a variety of pathological conditions mediating CB2R selective agonist property. The focus of the present manuscript is to represent the CB2R selective agonist mediated pharmacological mechanisms and therapeutic potential of BCP. The present narrative review summarizes insights into the CB2R-selective pharmacological properties and therapeutic potential of BCP such as cardioprotective, hepatoprotective, neuroprotective, nephroprotective, gastroprotective, chemopreventive, antioxidant, anti-inflammatory, and immunomodulator. The available evidences suggest that BCP, can be an important candidate of plant origin endowed with CB2R selective properties that may provide a pharmacological rationale for its pharmacotherapeutic application and pharmaceutical development like a drug. Additionally, given the wide availability in edible plants and dietary use, with safety, and no toxicity, BCP can be promoted as a nutraceutical and functional food for general health and well-being. Further, studies are needed to explore pharmacological and pharmaceutical opportunities for therapeutic and preventive applications of use of BCP in human diseases.

1. Introduction

The endocannabinoid system (ECS) has a myriad of physiological functions and contributes to the pathogenesis of many diseases, signifying broad therapeutic potential of targeted ECS modulators [1]. ECS consists of endogenous endocannabinoids, cannabinoid (CB) (mainly CB1 and CB2) receptors, and enzymes required for synthesizing and degrading endogenous CBs [2]. Each of these components is considered a potential target for drug discovery and development. Among both, CB1 and CB2 receptor types, pharmacological activation of CB2 receptors (CB2Rs) have received attention for its pharmacological effects as antioxidant, anti-inflammatory, immunomodulatory and antiapoptotic that can be achieved without causing psychotropic adverse effects through CB1 receptors (CB1Rs) [3]. The clinical development of ligands that directly stimulate CB1R has been limited by undesired psychotropic effects [4]. However, the activation of CB2R produces therapeutic responses devoid of psychotropic side effects [5]. Therefore, CB2R activation by pharmacological agonists has received increased attention in both academia and the pharmaceutical industries [6,7].

Substantial efforts have been made for developing ligands for CB1

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and CB2Rs, leading to hundreds of synthetic cannabinoids and recognition of phytocannabinoids which have displayed different affinities for treating numerous disorders. Nevertheless, only limited numbers of ligand are clinically applicable. Lately, more comprehensive structural information for cannabinoid receptors and its mode of actions was investigated appreciated to the cryo-electron microscopy, which can hasten structure-related cannabinoids discovery [8]. Simultaneously, novel cannabinoids-based peptides obtained from animal sources have received attention for their therapeutic potential *in vivo* targeting cannabinoid CB1/CB2Rs. Taken together, it is anticipated that more novel cannabinoids will be discovered and examined as promising ligands from various natural sources and species [8].

Munro et al. cloned CB2R from the human leukemia cell line HL-60 [9]. The expression of CB2R has been found to be high in immune cells and lymphoid organs and low in various peripheral tissues under normal biological conditions [10]. Furthermore, CB2Rs are involved in multiple pathological conditions, such as spinal and brain injuries, anxiety, depression, colitis, hepatic, vascular, cardiometabolic, neuroinflammatory, and neurodegenerative diseases, and cancer [11–13]. CB2R is a G-protein-coupled receptor (GPCR) that regulates many intracellular signaling pathways following interaction with Gi/o proteins [14]. GPCRs represent important therapeutic targets, and approximately 60% of clinically available drugs are derived from natural sources targeting GPCRs. The effects of GPCR modulators including CB2R agonists and antagonists have revealed novel physiological and pathogenic mechanisms applicable to drug development. Among potential therapeutics, plant-derived chemicals also known as phytochemicals offer considerable structural diversity and have been the single most prolific source of leads for the development of new drug entities from the dawn of the drug discovery. Phytochemicals are considered rich sources of bioactive ligands and serve as agonists, antagonists, or inhibitors/blockers of specific receptors with strong focus in drug discovery and development [15].

Among numerous plant-derived compounds investigated for bioactivities, β-caryophyllene (BCP) has garnered increasing interest for its pharmacological properties and therapeutic potential owing to its agonist activity on human CB2R (pKi value = 155 nM) and lack of substantial affinity for CB1R [12,16]. Upon binding to the CB2R, BCP activates $G_{i/o}$ α-subunit favoring a variety of receptor conformations that can influence numerous signaling pathways in the following ways: 1) suppression of adenylate cyclase, reduced cyclic AMP production, and less stimulation of cyclic AMP-dependent protein kinase (PKA), ending in prevention of A-type K^+ channels and inhibition of some gene expression; 2) activation of Akt/PKB, promoting cell survival, migration, and growth; 3) activation of de novo synthesis of ceramide and inhibition of the MAPK cascade, favoring apoptosis; 4) recruitment of β-arrestin to the activated CB2R, leading to desensitization and/or internalization of the receptor and potential stimulation of arrestin signaling. In addition, activation of $G_{i/o}$ α-subunit allows the release of the Gβγ subunit, which inhibits voltage-dependent calcium channels (ICa) and activates opening of G-protein gated inwardly rectifying potassium (GIRK) channels, and activates phosphatidylinositol-3-kinase (PI3K) leading to tyrosine phosphorylation and activation of Raf-1, and subsequently phosphorylates and activates MAP kinase signaling, stimulating cell survival and regulating gene expression [17–19]. The stimulation of CB2Rs represents a clinical therapeutic target in various disorders diseases [12,20].

BCP is a naturally occurring bicyclic sesquiterpene, which is the most diverse group of naturally occurring specialized secondary metabolites [21]. It is a primary ingredient in essential oils extracted from edible plants such as cloves, hops, pepper, oregano, and rosemary and contributes to the aroma of many of them [22]. Caryophyllane sesquiterpenes are usually occurred in plants as mixtures of distinct sesquiterpenes, mainly β-caryophyllene, β-caryophyllene oxide, α-humulene, and isocaryophyllene with minor metabolites, which marked by a unique bicycle [7.2.0] undecane ring system, namely caryophyllane skeleton, in which a dimethylcyclobutane and nine-membered rings are fused. Involving a trans-endocyclic (4–5) double bond in the nine-membered ring of caryophyllane structure results in generating the caryophyllene skeleton [23].

β-caryophyllene is featured by conformational mobility, due to the flexibility of the nine-membered ring, and by a greater reactivity of the trans-endocyclic 4,5-double bond (E configuration). Four possible conformations (i.e., βα-, αα-, ββ-, and αβ-conformers) differentiated by the relative arrangement of the exocyclic methylene and olefinic methyl groups are recognized [24]. Besides β-caryophyllene, its cis-isomer isocaryophyllene or γ-caryophyllene having an endocyclic Z double bond, has been also recognized [24]. Both trans-caryophyllene and isocaryophyllene can be epoxidized to produce the epimeric endocyclic epoxides, between which β-caryophyllene oxide, is the most ample naturally occurring one [24]. α-humulene or α-caryophyllene is the ring-opened isomer of β-caryophyllene, which is marked by an eleven-membered ring with three trans-endocyclic (1–2, 4-5, 8–9) double bonds, whose planes should be almost perpendicular to the plane of the ring [25].

Comparing their pharmacological targets and effects, it has been found that β-caryophyllene oxide and α-humulene do not displace [3H] CP-55,940 from the *h*CB2 receptor (pKi > 20 μM) [12]. β-caryophyllene oxide has been also showed to induce a significant $[Ca2+]_i$ release in CB2R positive, but stimulate them more intensely in CB2R deficient HL60 cells, demonstrated CB2R-independent mechanism, so its mechanism of action is not linked to ECS, whereas (*Z*)-BCP (isocaryophyllene) results in a dose-dependent displacement of [3H]-CP55,940 from *h*CB2 receptor in HEK293 cells with pKi value of 485 nM [12]. It has been reported that β-caryophyllene oxide exhibit analgesic, antifungal, genoprotective, antioxidant, anti-inflammatory, and antiproliferative properties [13,26–28], whereas antibacterial, antifungal, antiproliferative, and chemosensitizing effects are related to α-humulene biological activities [29–32]. In contrast, the pharmacological effects of isocaryophyllene have been scarcely identified, and limited preliminary studies are available on antifungal and antiproliferative effects [32–34]. β-caryophyllene oxide has a strong anticancer effect because of its chemical structure. Thus, β-caryophyllene oxide contains methylene and epoxide exocyclic functional groups, so it covalently binds to proteins and DNA bases by sulfhydryl and amino groups [13]. The cis-configuration of caryophyllane scaffold and the exocyclic double bond, as occurred in α-humulene and isocaryophyllene respectively, seem to be linked with a higher cytotoxic power [35]. It has been emphasized that any plant containing terpenoid concentrations more than 0.05% are considered important for their pharmacological properties and therapeutic potential [36]. Therefore, plants containing BCP could be important for their pharmacological and therapeutic properties. The list of plants wherein BCP has been quantified or characterized is provided in supplementary file Table 1. Additionally, anti-oxidant, anti-inflammatory, immunomodulatory and anti-apoptotic activities have been demonstrated mediating CB2R dependent and independent pathways (Fig. 1).

In 2008, Gertsch and colleagues [12] have reported that BCP elicits its effects by acting as a full functional selective agonist of the CB2R. Remarkably, BCP selectively binds to CB2R, because it has insufficient binding activity to the human CB1 (hCB1) receptor, and it is not able to replace high affinity agonizts from hCB1. BCP is found to bind hCB2R with an inhibitory constant pKi of 155 nM, with a receptor binding affinity about 150 times less than the potent high affinity cannabinoid ligand WIN55,212-2 (pKi hCB2R is 1.2 nM). Molecular docking analysis revealed that (*E*)-BCP has unusual cyclobutane-containing scaffold, and the interaction of (*E*)-BCP with hCB2R is on the binding site of CP55,940 (THC binding site) exactly in a hydrophobic region of hCB2 binding pocket, being the putative binding site located adjacent to helices III, V, VI, and VII at the near extracellular site of the seven transmembrane domain, which interacts with hydrophobic amino acid residues, such as valine-113, phenylalanine-117, isoleucine-198, tryptophan-258 and

Table 1
The *in vivo* studies demonstrating cannabinoid type 2 receptor (CB2R)-mediated therapeutic potential of β-caryophyllene (BCP).

Experimental model	Con. of BCP	Effects	CB2R-mediated mechanisms	Ref.
Alcohol-induced conditioned place preference and sensitivity in C57B6 mice	25, 50 and 100 mg/kg, i.p.	Alcohol addiction	▪ Reduces voluntary alcohol intake and CPP activation of CB2R	[53]
Formalin-induced inflammation model and partial ligation of sciatic nerve-induced neuropathic pain in $CB2^{-/-}$ mice	1, 5 and 10 mg/kg, p.o., 30 min before formalin/14 days of ligation	Neuropathic pain	▪ Reduces inflammation and mechanical allodynia and thermal hyperalgesia ▪ Attenuates glial activation	[121]
Hot plate and formalin-induced acute pain and constriction chronic injury of the sciatic nerve (CCI)-induced hypernociception in C57BL/6J mice	1, 5 or 10 mg/kg, p.o. for 14 days after CCI	Neuropathic pain	▪ Attenuates acute and chronic pain mediated through both opioid and CB2R activation	[75]
Partial sciatic nerve ligation induced neuropathic pain in ddY mice	4.5, 9.0 and 18.0 μg/paw, i.pl.	Neuropathic pain	▪ Exhibits anti-allodynic effects	[124]
Capsaicin-induced acute pain model in ddY mice	9, 18 μg/paw, i.pl., 10 min before capsaicin	Nociception	▪ Activates μ-opioid receptors leading to anti-nociception by releasing β-endorphin	[127]
2′-3′-dideoxycytidine (ddC, zalcitabine)-induced neuropathic pain and inflammation in BALB/c mice	50 mg/kg, p.o. 16 h before first dose of ddC followed by a dose of 25 mg/kg/day, BD for 5 days	Neuropathic pain	▪ Attenuates inflammation and mechanical allodynia ▪ Suppresses phosphorylated ERK1/2 levels	[131]
High-fat diet and fructose (10%) fed for 12 weeks induced insulin resistance in Wistar rats	30 mg/kg, p.o. for 4 weeks	Insulin resistance and dyslipidemia	▪ Improves oxidative stress, inflammation, glycemia and dyslipidemia by CB2R/PPAR-γ ▪ Inhibits vascular inflammation, adhesion molecules and restores vascular eNOS/iNOS	[103]
High-fat diet and fructose (10%) fed for 12 weeks induced insulin resistance in Wistar rats	30 mg/kg, p.o. for 4 weeks	Insulin resistance and associated neurobehavioral changes	▪ Mitigates anxiety, depression and memory deficit by upregulating PGC-1α/BDNF pathway ▪ Inhibits oxidative stress and inflammation activating CB2R/PPAR-γ	[62]
High fat diet-induced atherogenesis in C57BL/6 mice for 12 weeks	10 mg/kg twice weekly for 12 weeks, i.p.	Atherosclerosis	▪ Modulates endothelial dysfunction via inhibition of IRF-1 and VCAM-1	[139]
Dextran sulfate sodium-induced colitis in CD1 mice	12.5, 25, or 50 mg/kg	Ulcerative colitis	▪ Inhibits inflammation through activation of CB2R/PPAR-γ	[52]
Autoimmune Encephalomyelitis-induction in C57BL/6 mice	50 mg/kg twice a day, p.o.	Immunomodulation	▪ Inhibits oxidative stress and inflammation ▪ Attenuates glial activation and modulates Treg/Th1 balance	[197]
Paclitaxel-induced peripheral neuropathy in Swiss mice	25 mg/kg twice a day, p.o.	Peripheral neuropathy	▪ Suppresses p38 MAPK/NF-kB stimulation and cytokine production	[156]
Doxorubicin-induced chronic cardiotoxicity in Wistar rats	25 mg/kg for five weeks, p.o.	Chemotherapy-induced cardiotoxicity	▪ Suppresses oxidative stress, inflammation and apoptosis	[166]
Cisplatin-induced nephrotoxicity in $CB2^{-/-}$ mice	1, 3 and 10 mg/kg, i.p.	Nephroprotective	▪ Mitigates kidney inflammation, oxidative/nitrative stress and apoptosis	[20]
Rotenone-induced neurodegeneration in Wistar rats	50 mg/kg for 4 weeks, i.p.	Parkinson's disease	▪ Attenuates oxidative stress, inflammation and restores dopaminergic neurons	[50]
MPTP-induced Parkinson's disease model in C57BL/6J mice	10 mg/kg for 5 days, i.p.	Parkinson's disease	▪ Attenuates oxidative stress, inflammation and restores dopaminergic neurons	[226]
Double transgenic APP/PS1 Alzheimer's disease mice	48 mg/kg for 10 weeks, p.o.	Alzheimer's disease	▪ Inhibits inflammation and β-amyloid formation	[240]
Two-vessel occlusion (2VO) model in Sprague-Dawley rats	16, 48 and 144 mg/kg for 4 weeks, i.p.	Post-stroke cognitive deficits	▪ Upregulates PI3K/Akt signaling pathway via CB2R activation	[252]
Middle cerebral artery occlusion-induced cerebral ischemia in SD rats	10 mg/kg, i.p.	Cerebral ischemia	▪ Modulates AMPK/CREB signaling activating cortical CB2R mitigated cerebral ischemic injury	[49]
Hypoperfusion/reperfusion in rat by transient bilateral common carotid artery occlusion and reperfusion	40 mg/kg, p.o.	Cerebral ischemia	▪ Reduces oxidative stress and inflammation by activating CB2R/PPAR-γ	[264]
Anxiety- and depression-like behaviors models in C57BL/6 mice	50 mg/kg, i.p.	Depression and anxiety	▪ Mitigates anxiety and depression activating CB2R	[271]
Chronic restraint plus stress-induced depression in Sprague-Dawley rats	25, 50 and 100 mg/kg for 28 days, i.p.	Depression	▪ Exerts neurotrophic and anti-inflammatory effects	[273]
Bile duct ligation-induced liver fibrosis in Wistar rats	5 mg/kg for 2 weeks, p.o.	Liver fibrosis	▪ Downregulates CB1R while enhances expression of MMP-1	[279]
Chronic binge alcohol feeding-induced steato-hepatitis in $CB2^{-/-}$ mice	10 mg/kg for 10 days, i.p.	Alcohol liver damage	▪ Attenuates oxidative stress, vascular inflammation, and hepatic metabolic pathways by activating CB2R	[287]
Nicotine addiction models in WT, CB2-KO and DAT-cre mice and Long Evans rats	3, 10, 25, 50, and 100 mg/kg, i.p.	Nicotine addiction	▪ Attenuates nicotine reward and seeking by CB2R/non-CB2R dependent mechanisms	[74]
Collagen antibody induced arthritis model in balb/c mice	10 mg/kg/100 μL for 14 days, p.o.	Arthritis	▪ Attenuates pro-inflammatory cytokines and downregulates MMP-3 and 9 and enhances anti-inflammatory IL-13	[63]

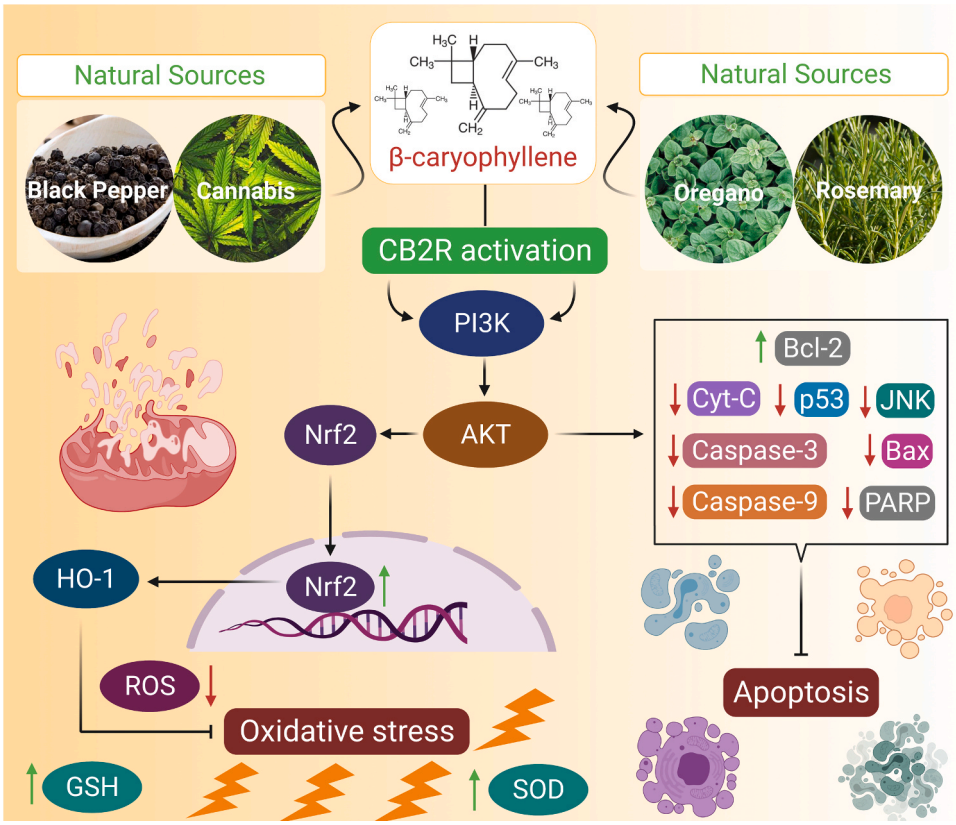

Fig. 1. The possible mechanism of CB2 receptor (CB2R) activation by β-caryophyllene (BCP) in alleviating oxidative stress and apoptosis.

methionine-265 [12]. Also, (*E*)-BCP has a C4–C5 double bond exhibiting a π–π stacking interaction with phenylalanine-117 (4.0 Å), and thus its geometry possibly has a pivotal role for hCB2 receptor binding, significant π–π stacking interactions between the (*E*)-BCP double bonds and phenylalanine-117 and tryptophan-258, respectively, easing receptor binding. However, BCP oxide does not have a double bond in position C4-C5, so it is unable to bind hCB2R [37].

Allosteric modulators (AMs) of CB2R are considered a potentially pivotal approach for modulating CB2R signaling. AMs bind to receptors allosteric sites which are topographically different comparative to that of the orthosteric sites, where endocannabinoids bind [38]. Upon binding, AMs modify the configuration of the receptors, eventually leading to either enhance or reduce of the efficacy and/or potency of endogenous or synthetic ligands acting concomitantly at orthosteric sites [39]. Thus, rather than a direct activation of CB2Rs, AMs may instead "fine-tune" the effects of endocannabinoids acting simultaneously at orthosteric sites. Because endogenous cannabinoids have increased during inflammatory process entirely in inflamed tissues, systemically administered CB2R-AMs (without intrinsic activity themselves) might suggest specific temporal and spatial modulation of CB2R signaling at the inflammation site, exerting effect only when and where increased levels of endogenous cannabinoids occur. This could enhance therapeutic efficiency while diminishing off-target, systemic toxicity [40,41].

Altogether, AMs display distinct pharmacological advantages over orthosteric ligands in respect of increased target specificity and decreased or null off-target adverse effects [42,43]. only a few AMs of the CB2R have been recognized so far and they have micromolar activity. For instance, BCP and dihydro-gambogic acid (DHGA) are the two stated negative allosteric modulators (NAMs) [44]. Even though BCP works as an agonist, BCP has also been revealed to act as an allosteric modulator. Maheswari et al. [44] have found that BCP has a higher selectivity to CB2R with unique ago-allosteric activities, depending on *in vitro* studies. They have reported that BCP is a negative ago-allosteric modulator with a pKi of 2.37 μM [44]. As well, the authors also found that BCP remarkably causes incomplete but saturable decrease in the binding of an orthosteric cannabinoid ligands at the CB2Rs, this exclusive binding distinctive is a feature of substances having allosteric modulatory properties [45,46]. Also, BCP shows features of an AM by increasing the dissociation rates of orthosteric ligands; [3H]CP-55,940 and [3H]WIN-55,212-2 from CB2Rs.

These findings have indicated that BCP could act as a NAM of CB2R binding. However, it is vital to note that the decrease in selective binding caused by NAMs is not due to direct competition with the ligands at the orthosteric site, but instead arises from negative cooperativity produced by the binding of the NAM to the allosteric site. BCP does not only alter the dissociation rates of CB2 radioligands from hCB2Rs, it also does so differently, based on the specific CB2R radioligands used (e.g., in a probe-dependent manner). For instance, BCP has resulted in a higher noticeable effect on the dissociation rates of [3H]WIN-55,212–2, comparative to [3H]CP55,940. Probe dependence is a well-known feature of AMs [47]. However, BCP has exerted little modulation on the functional properties of CB2R ligands, the allosteric modulatory properties of BCP on the ability of CB2 ligands to modulate signaling pathways other than adenylyl cyclase have yet to be investigated.

Additionally, Pandey et al. [48] have reported that binding of BCP to a putative allosteric pocket directly close to the orthosteric ligands has reduced the absolute value of the binding free energy of CP55,940, which is in harmony with the predicted effect of a NAM. As well, the presence of BCP as a NAM has helped in restricting the flexibility of this CP55,940-CB2R complex interaction, does not allow the main conformational alternations required for CP55,940 and CB2R activation. Since the recognition of CB2R selective properties, the protective effects of BCP-mediated CB2R activation and associated mechanisms have been well studied in preclinical models of various diseases, including rheumatoid arthritis [12], renal injury [20], ischemic stroke [49],

Parkinson's disease (PD) [50], liver fibrosis [51], colitis [52], and addiction [53]. In addition to CB2R, studies have revealed a host of other BCP targets, such as sirtuin 1 (SIRT1) [54], peroxisome proliferator-activated receptor (PPAR)-α [55], PPAR-γ, GABAergic signaling factors, transient receptor potential cation channel subfamily V, fatty acid amide hydrolase (FAAH), and cyclooxygenase-2 (COX-2) [56].

BCP has been showed to interact with and to upregulate members of the PPARs family. The binding of agonist to CB2R augments the MAP kinase activity that further controls the stimulation of PPARs via direct phosphorylation [57]. Numerous studies provide evidence that cannabinoids exert their anti-inflammatory activities, at least in part by activation of PPAR-α and PPAR-γ signaling [58,59]. Moreover, PPAR-γ has been displayed to be implicated in BCP-mediated neuroprotection [60] and tumor suppression roles [61], and lipid-lowering effects and vascular inflammation mitigation [62], anxiolytic, antioxidant, anti-arthritic and anti-inflammatory activities [62,63].

Cannabinoids are identified to interact or crosstalk with the PPARs family, such as PPAR-α, PPAR-α/δ, and PPAR-γ which are encoded by distinct genes and are controlled by steroids and lipid metabolites modulating lipid and glucose homeostasis and inflammation [54,64]. The stimulation of CB2R on the cell surface promotes the intracellular signaling cascade leading to the activation of PPARs [63]. CB2R activation has demonstrated to directly interact and stimulate PPAR-α and PPAR-γ. CB2R activation by BCP enhances the activation of PPAR-α and PPAR-γ signaling which shows various physiological and therapeutic activities in dyslipidemia, vascular inflammation, and insulin resistance [54,62]. Particularly, BCP activates PPAR-α via a direct interaction with the ligand-binding pocket, so modulating lipid metabolism [55]. BCP has shown to control cellular lipid metabolism in a PPAR-α-related manner by decreasing PPAR-α responsive gene expressions, intracellular triglyceride, uptake and oxidation of fatty acids. The equilibrium dissociation constants value of BCP for the PPAR-α was found 1.93 μM with an EC50 value of 3.2 μM [55]. The activation of PPAR-α and γ subtypes by cannabinoids including BCP attributes to numerous metabolic, analgesic, neuroprotective, and cardioprotective benefits. BCP by stimulating CB2R and both PPARs isoforms (PPAR-α, and PPAR-γ) remarkably provides a promising polypharmacological multitargeted approach for its pharmaceutical development and clinical application.

BCP exerts negligible toxicity on normal tissues and majority of the available studies demonstrate tissue protective effects. Additionally, it has also been approved by the United States Food and Drug Administration for use as a flavoring agent, food additive and taste enhancer in foods. Numerous therapeutic benefits and absence of psychotropic effects make BCP a promising candidate for therapeutic use, including the treatment of multiple chronic inflammatory diseases [12].

Therefore, the present article comprehensively reviews the pharmacological activities and pharmacotherapeutic potential of BCP, focusing mainly on the mechanisms mediating CB2R activation, and highlights the molecular mechanisms and signaling pathways underlying these therapeutic effects. The present narrative review summarizes recent insights into the CB2R selective pharmacological properties and therapeutic potential of BCP such as cardioprotective, hepatoprotective, neuroprotective, nephroprotective, gastroprotective, chemopreventive, antioxidant, anti-inflammatory, and immunomodulator (Fig. 2). The CB2R mediated therapeutic potential of BCP demonstrated in the *in vivo* and *in vitro* studies are presented in Tables 1 and 2, respectively.

The natural origin, wide abundance and time-tested dietary use of BCP is suggestive of its relative safety over synthetic ligands. The present review focuses only on the studies which clearly demonstrated the CB2R dependent pharmacological activities and therapeutic potential of BCP. The CB2R selective properties are likely to accentuate the perspectives on clinical and pharmaceutical development of BCP for therapeutic and preventive usage with a mechanism based pharmacological rationale. This review will encourage a focused approach on evaluating and deciphering the CB2R dependent therapeutic potential of BCP and rationalize development of BCP as a drug for human use based on pharmacological principles of therapeutics rather merely accounts its

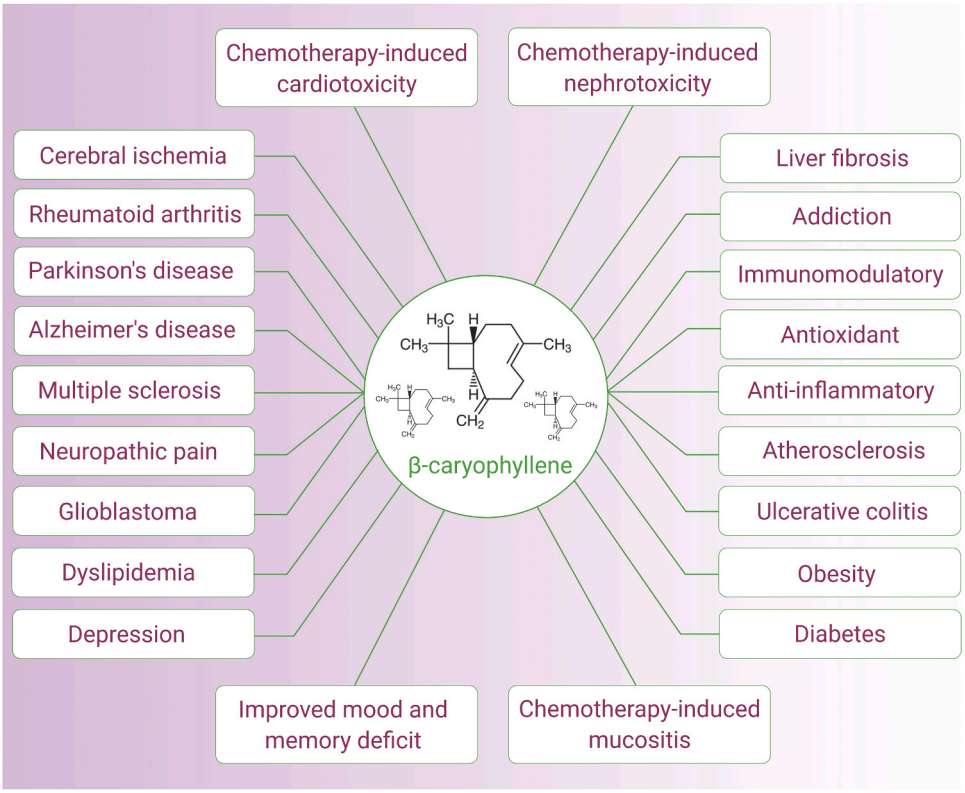

Fig. 2. Cannabinoid type 2 receptor (CB2R)-mediated pharmacological activities and therapeutic potential of β-caryophyllene (BCP).

Table 2
The *in vitro* studies demonstrating cannabinoid type 2 receptor (CB2R)-mediated therapeutic potential of β-caryophyllene (BCP).

Experimental model	BCP dose/incubation period	Effects	CB2R-mediated mechanisms	Ref.
C2C12 skeletal myotubes CB2R siRNA	1 μM, 48 h	Obesity and related complications	▪ Lipid oxidation involving the SIRT1/PGC-1α pathway	[54]
MIN6 β-cells	0.1–1 μM, 1 h	Hyperglycemia	▪ Glucose-stimulated insulin secretion mediated by Arf6	[84]
TNF-α-induced vascular inflammation in HUVECs	5 μM, 24 h	Atherosclerosis	▪ Modulates endothelial dysfunction by inhibiting IRF-1 and VCAM-1	[139]
U-373 and U87 glioma cells	20 and 30 μg/mL, 24 h	Cancer	▪ Decreases cell viability and induces apoptosis by activating PPAR-γ	[61]
MPP+-induced neurotoxicity in SH-SY5Y human neuroblastoma cells	1 and 2.5 μM, 24 h	Parkinson's disease	▪ Inhibits ROS, apoptosis, and p-JNK and upregulates HO-1 expression	[228]
Oxygen-glucose deprivation/ reoxygenation in rat cortical cultures	1 μM	Cerebral ischemia-reperfusion injury	▪ Modulates AMPK/CREB signaling	[49]
LPS-induced inflammation in oligodendrocyte (OLN-93) and microglial cells	0.2–25 μM, 24 h	Multiple sclerosis	▪ Inhibits oxidative stress and inflammation with restoration of M2 phenotype by activating CB2R/PPAR-γ	[208]
LPS-induced cytotoxicity in OLN-93 cells	0–50 μM, 24 h	Multiple sclerosis	▪ Nrf2/HO-1 signaling mediating CB2R/PPAR-γ activation	[60]
Hypoxia-induced neuro-inflammation in BV2 microglia	5 μM, 24 h	Neuroinflammation	▪ Inhibits NF-κB and release of proinflammatory cytokines	[214]
Glutamate-induced excitotoxicity in C6 rat glioma cells (CCL-107)	0.5–3 μM, 24 h (pre- and co-treatment)	Glioma	▪ Enhances antioxidant responses via Nrf2 activation	[215]
Ex vivo hippocampal sections	50 μM	Depression	▪ Promotes neurotrophic factors and inhibits inflammation	[273]
Palmitate-induced lipid accumulation in HepG2 cells	0–5 μM	Hepatic steatosis	▪ Inhibits lipid accumulation and activation of the CaMKK-β/AMPK signaling pathway	[284]
Antimycin A-induced injury in osteoblastic MC3T3-E1 cells	0.5, 1.0, and 5.0 μM	Osteoporosis	▪ Enhances osteocalcin secretion and matrix mineralization ▪ Mitigates oxidative stress and apoptosis	[294]
LPS-induced oral mucositis in gingival fibroblasts and epithelial cells	10 μg/mL	Mucositis	▪ Suppresses NF-kB and activates PPAR-γ and PGC-1α dependent on CB2R activation	[176]

nutraceutical indications.

2. Pharmacological properties of β-caryophyllene

2.1. Therapeutic potential of BCP in drug abuse

2.1.1. Alcohol use disorder

Alcohol use disorder (AUD) or alcoholism is a major global public health concern [65]. Increasing evidence demonstrates a correlation between ethanol dependence and abnormal ECS signaling, as evidenced by altered CB2R gene expression in the brain associated with alcohol consumption [66], which suggests that CB2R is a potential target for AUD treatment [67–69]. Al Mansouri et al. [53] reported that BCP dose-dependently reduced ethanol consumption and preference in a two-bottle (water and ethanol) preference test in mice without significantly altering total liquid intake or intake of various concentrations of saccharin or quinine, suggesting that BCP had no influence on taste sensation. Moreover, BCP suppressed ethanol-induced conditioned place preference (CPP) and exacerbated loss of righting reflex duration. Pretreatment with the selective CB2R antagonist AM630 abolished these responses, demonstrating CB2R-dependent mechanisms and indicating that CB2R activation is a promising target for AUD treatment.

2.1.2. Nicotine use disorder

Tobacco smoking and nicotine addiction have extensive detrimental effects on human health. Smoking behavior is sustained by nicotine-induced excitation of dopaminergic neurons in the ventral tegmental area by stimulating nicotinic acetylcholine receptors. While some therapies targeting dopaminergic function have shown remarkable efficacy for reducing tobacco usage and nicotine withdrawal symptoms, the relapse rate remains high after treatment cessation [70]. Recently, CB2R has been proposed as a promising pharmacological target for developing therapeutics for substance use disorders as this receptor is present in midbrain dopaminergic neurons and is implicated in addiction and reward-seeking behaviors [71]. Navarrete et al. [72] reported that nicotine-induced CPP, nicotine self-intake, and nicotine withdrawal symptoms were attenuated in CB2R knockout (KO) mice, indicating the role of CB2R in nicotine reward and dependence. In agreement with this finding, the selective CB2R agonist O-1966 in combination with a subclinical dose of nicotine affected nicotine-induced CPP [73]. Furthermore, He et al. [74] found that BCP dose-dependently inhibited nicotine self-intake and motivation to seek nicotine, whereas pretreatment with AM630 reversed this effect.

In addition, BCP mitigated rewards induced by direct electrical stimulation of brain reward pathways, optogenetic enhancement of dopaminergic activity in mice with conditional knockout of the dopamine transporter, and nicotine self-administration in rodents [74]. Thus, BCP has significant pharmacological activity in attenuating nicotine reward and seeking behavior, and these effects were not significantly associated with sedation. However, pretreating animals with AM630, a selective CB2 receptor antagonist significantly reversed the effect of BCP on nicotine self-administration but not by AM251, a selective CB1 receptor antagonist, indicating the implication of a CB2R dependent mechanism. Moreover, high-dose BCP prevented nicotine or food self-administration in both wild-type and CB2R KO mice, suggesting that both CB2R-dependent and CB2R-independent mechanisms contribute to the effects of BCP on addiction-related behaviors. Possible non-CB2R targets include endocannabinoid-degrading enzymes such as FAAH [56], μ-opioid receptors [75], and PPAR-γ or PPAR-α [62], all of which are implicated in nicotine addiction [76] and appetitive behaviors [77]. In a recent study, BCP did not significantly alter food self-administration or cocaine-induced hyperactivity in animals models using pharmacological blockade or genetic deletion of CB2R. The study showed that the actions of BCP were mediated by PPAR-α and PPAR-γ in reducing the cocaine self-administration [78].

2.2. Diabetes

Diabetes mellitus (DM), a widespread metabolic disorder, may arise due to either a lack of insulin production, defined as type 1 DM (T1DM), or reduced sensitivity or increased resistance to insulin, defined as type 2 DM (T2DM). DM involves enhanced uptake and utilization of glucose and eventually leads to hyperglycemia [79]. DM often leads to the development of numerous microvascular and macrovascular complications. Oxidative stress and inflammation are the main drivers of pathogenesis and complications of DM [80], and ECS is a known regulator of food consumption, glucose homeostasis, insulin secretion, and redox-inflammatory changes [81]. CB2Rs expressed in the islets of Langerhans are involved in endogenous endocannabinoid signaling and play a crucial role in endocrine secretion. CB2R activation enhances insulin release from β-cells by inducing intracellular Ca^{2+} signals [82], decreasing the secretion of proinflammatory mediators, and scavenging reactive free radical species [83].

Suijun et al. [84] reported that BCP dose-dependently promoted glucose-stimulated insulin secretion (GSIS) in MIN6 β-cells, whereas pretreatment with a CB2R inhibitor or genetic silencing abolished this secretagogue effect. A complex but coordinated signaling mechanism involving small G-proteins (e.g., Arf6, Cdc42, and Rac1) regulates the transport and fusion of insulin secretory vesicles to the plasma membrane [85]. Importantly, Arf6 and its downstream targets Rac1 and Cdc42 are involved in the regulation of GSIS [86]. Disruption of Cdc42 function is central to DM progression as Cdc42 not only participates in insulin synthesis but also regulates the mobilization of insulin granules and cell membrane exocytosis by activating a series of downstream effectors [87]. The Rho family GTPase Rac1 has been shown to regulate insulin-stimulated membrane translocation of glucose transporter 4 and ensuing glucose transport in cultured muscle cells [88]. Furthermore, BCP enhanced the expression levels of Arf6, Rac1, and Cdc42, a finding that suggests CB2R signaling as a novel regulatory mechanism for glucose homeostasis Suijun et al. [84]. The pharmacological mechanisms attribute to the antidiabetic actions of BCP are illustrated in Fig. 3.

2.3. Insulin resistance, dyslipidemia, and obesity

Insulin resistance is a common feature of most metabolic diseases, including T2DM, obesity, dyslipidemia, hypertension, atherosclerosis, and nonalcoholic fatty liver disorder [89–91]. Further, dyslipidemia is considered the most important clinical manifestation of DM and is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and predominance of small, dense low-density lipoprotein particles. Low HDL-C and elevated triglyceride levels along with hypertriglyceridemia lead to elevated free fatty acid levels, which may cause insulin resistance and dysfunction of β-cells [92,93]. Furthermore, free fatty acids are important regulators of inflammation, and hypertriglyceridemia may induce subclinical inflammation that subsequently leads to insulin resistance and β-cell dysfunction [94]. Accumulating evidence suggesting that overactivated ECS is associated with weight gain, reduced sensitivity to insulin, and glucose intolerance, leading to the development of metabolic diseases such as obesity, dyslipidemia, insulin resistance, and atherosclerosis [95].

Deregulated fatty acid oxidation contributes to the pathogenesis of obesity and T2DM [96], and Zheng et al. [54] showed that CB2R activation contributes to lipid homeostasis by regulating fatty acid oxidation at the transcriptional and non-transcriptional levels. During transcription, the transcription coactivator PPAR-γ coactivator 1a (PGC-1α)

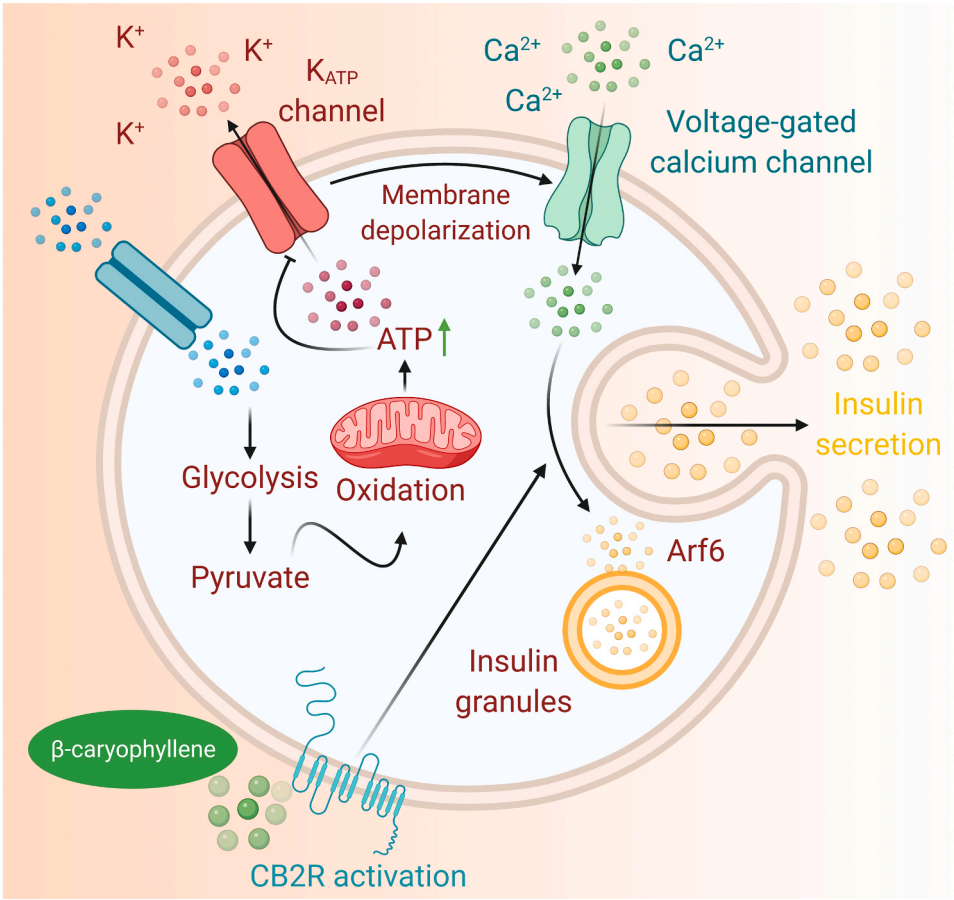

Fig. 3. Cannabinoid type 2 receptor (CB2R)-mediated antihyperglycemic activity of β-caryophyllene (BCP).

promotes the activities of nuclear receptors PPAR-α and estrogen-related receptor alpha (ERRα), which facilitate the transcription of enzymes involved in fatty acid oxidation [97]. Regulation of PGC-1α activity is facilitated by SIRT1 deacetylase, which enhances SIRT1-mediated nutrient signaling pathways, including the AMPK and cAMP response element-binding protein (CREB) pathway activated by nutrient restriction [98]. The SIRT1/PGC-1α pathway plays an important role in fatty acid oxidation. Zheng et al. [54] further showed that treatment of differentiated C2C12 myotubes with BCP stimulated SIRT1 deacetylase activity by enhancing CREB phosphorylation and led to improved deacetylation of PGC-1α. In C2C12 myotubes, BCP also upregulated genes associated with fatty acid oxidation, whereas selective CB2R KO using a targeted siRNA abrogated these beneficial effects of BCP. Additionally, in a recent study, glucose uptake, enzymes of both glycolytic and oxidative pathways and ATP production were evaluated in C2C12 myotubes using CB2R antagonists AM630 and SR144528. BCP was found to promote glucose uptake and ATP synthesis along with augmentation of glycolytic and oxidative pathways activating CB2R. BCP mediating CB2R dependent mechanisms appears an attractive pharmacological target to improve physiological glucose metabolism in skeletal muscles [99]. Altogether, these findings suggest the therapeutic potential of BCP against metabolic disorders such as dyslipidemia by targeting CB2R and the SIRT1/PGC-1α pathway.

PPARs regulate cellular proliferation, differentiation, and apoptosis in addition to glucose homeostasis and lipid metabolism [100,101]. PPAR-α is widely expressed in the liver, kidney, muscle, and heart. It modulates lipid metabolism by regulating the expression of genes involved in fatty acid uptake and oxidation in the liver and modulates plasma triglycerides and cholesterol [102]. Recently, BCP was shown to effectively curb dyslipidemia and vascular inflammation [103]. BCP was also found to suppress VCAM1, which promotes the adhesion of lymphocytes, monocytes, eosinophils, and basophils to the vascular endothelium and initiates plaque formation. Further, BCP restored the balance between endothelial and inducible forms of nitric oxide synthase, which are critical regulators of arterial caliber and blood pressure as well as the redox status of vascular cells. The aforementioned effects are attributed specifically to the CB2R agonist activity of BCP and ensuing activation of PPAR-γ receptors as pretreatment with either AM630 or the PPAR-γ antagonist bisphenol-A-diglycidyl ether (BADGE) abolished the BCP-mediated protective effects. Therefore, CB2R and PPAR-γ pathways contribute to the correction of the lipid profile and imbalance between nitric oxide and nitric oxide synthase isoforms that promote vascular inflammation. It is apparent that the PPAR-γ agonist property of BCP partially accounts for decreased fat mass and triglyceride levels along with increased HDL. However, these beneficial effects of BCP are mediated by CB2R activation, which further stimulates PGC1-α and improves the interaction between PPAR-γ and other transcriptional mediators, resulting in the upregulation of liver enzymes involved in fatty acid oxidation.

Youssef et al. [62] studied the effects of BCP on metabolic and neurobehavioral alterations in a rodent model of DM fed a high fat/-fructose diet (HFFD) and demonstrated CB2R/PPAR-γ mechanisms. BCP was found to mitigate insulin resistance, oxidative damage, and neuroinflammatory and neurobehavioral alterations induced by HFFD. The effects of BCP on glycemic parameters were mediated by CB2R activation but were largely independent of PPAR-γ, whereas antioxidant, anti-inflammatory, and anxiolytic responses were dependent on both CB2R and PPAR-γ activation. Furthermore, the antidepressant and memory-enhancing effects of BCP were CB2R-dependent and were mediated by increased expression of PGC-1α and brain-derived neurotrophic factor (BDNF), a neurotrophin essential for neuron repair, survival, and plasticity and cognitive function [104]. Abrogation of the protective effects of BCP by AM630 and BADGE pretreatment demonstrated that BCP improves mood, attention, and cognitive function via a CB2R/PGC-1α/BDNF pathway. The effects of BCP on lipid metabolism and insulin resistance are depicted in Fig. 4.

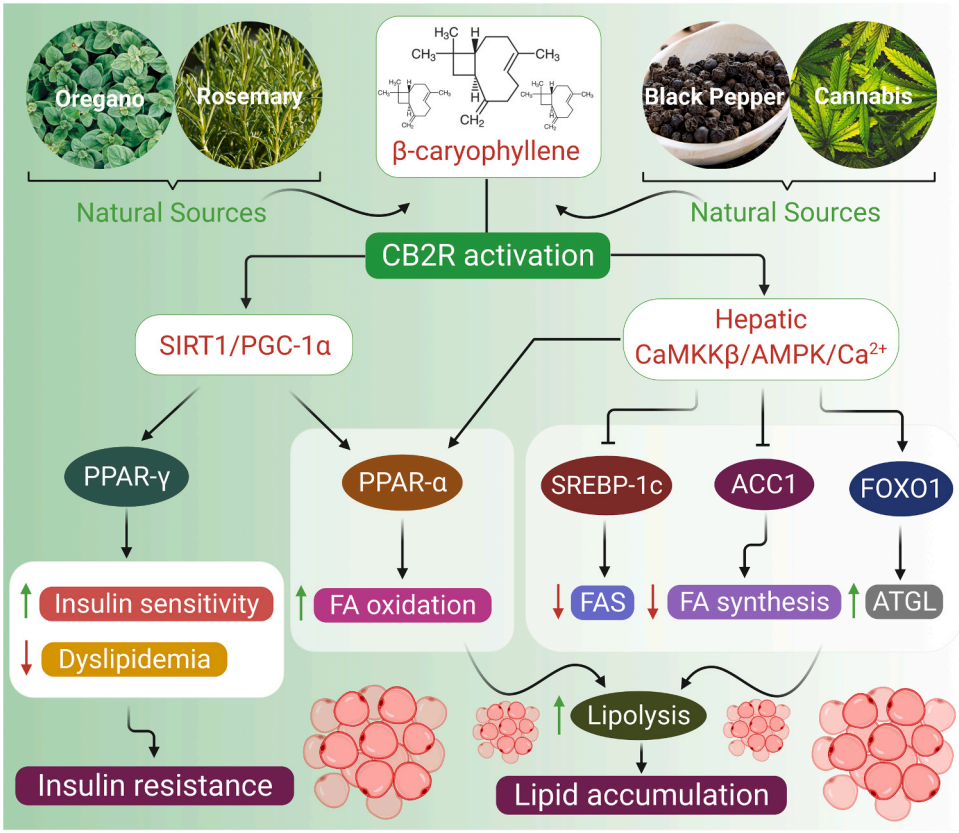

Fig. 4. The effect of BCP on lipid accumulation and insulin resistance via CB2 receptor activation.

2.4. Analgesia and anticipation

Pain is a subjective experience arising from sensory signals indicating potential tissue damage [105]. Neuropathic pain results from injury to the peripheral nerves, sensory ganglia, and spinal cord and its roots. Neuropathic pain is frequently associated with trauma, vascular or metabolic disorders, viral infections, neuroinflammation, and autoimmune diseases. These lesions and nerve injury provoke inflammatory responses, which are characterized by activation of microglial cells that synthesize and release proinflammatory cytokines. The persisting molecular and cellular alterations that arise in response to neural injury manifest as changes in pain sensitivity, such as hyperalgesia and allodynia, which may persist and are often difficult to treat effectively using current therapies [106].

The opioid and CB systems are involved in pain management [107], and both CB1R [108] and CB2R [109] have potent anti-nociceptive activities. Indeed, many substances acting on ECS have well documented anti-nociceptive and anti-inflammatory properties [110,111]. In addition, the significant effects of CB2R agonists against both acute and neuropathic pain and their detrimental adverse responses compared with those of CB1R agonists have been demonstrated [112,113]. Compared with CB1R, CB2R is expressed abundantly in peripheral tissues, predominantly in immune cells, and to a lesser extent in the central nervous system [114]. Nonetheless, studies have shown that the anti-nociceptive activity of CB2R is mediated directly or indirectly through activation of descending pain modulation pathways [115,116]. Selective CR2R agonists such as BCP have been found to stimulate the endogenous secretion of β-endorphin peptide precursors from keratinocytes, which produce analgesic effects by activating peripheral μ-opioid receptors in primary afferent neurons [117]. Alternately, analgesia may result from direct CB2R stimulation in the periphery [118] or in brain regions that control pain such as the thalamus, cerebellum, and brainstem [109,119,120]. Therefore, selective targeting of CB2R holds promise for treating pain disorders.

The analgesic actions of BCP have been studied in murine models of inflammation and neuropathic pain induced by formalin or partial ligation of the sciatic nerve [121]. BCP diminished inflammatory (late phase) pain responses in control $CB2R^{+/+}$ mice but not in $CB2R^{-/-}$ mice, whereas it did not affect acute (early phase) responses. Moreover, the analgesia induced by BCP was abolished by pretreatment with the selective CB2R antagonist SR144528. More importantly, chronic treatment with various doses of BCP for 14 days significantly mitigated mechanical allodynia and reduced thermal hyperalgesia on the side of unilateral sciatic nerve ligation. In contrast, chronic BCP treatment did not mitigate partial nerve ligation-induced mechanical allodynia and thermal hyperalgesia in $CB2R^{-/-}$ mice.

The activation of spinal glial cells and ensuing release of proinflammatory mediators have been implicated in the development of neuropathic pain [122]. Microglia are believed to mediate this process by upregulating proinflammatory mediators, thereby triggering astrocyte and microglial activation [123]. BCP also reduced microglial cell density in the spinal dorsal horn. Collectively, these results indicate that BCP attenuates inflammatory and neuropathic pain by suppressing astrocytosis and microgliosis via CB2R activation. Paula-Freire et al. [75] demonstrated the anti-nociceptive activity of BCP in acute and chronic pain models involving opioid and CB pathways. Using the hot plate paw-withdrawal test for thermal nociception and formalin test for inflammatory pain, the occurrence of acute pain was assessed. Thermal hypernociception and von Frey mechanical hypernociception tests were used to assess chronic nociception following chronic constriction injury of the sciatic nerve. BCP treatment reduced both acute and chronic pain by inhibiting proinflammatory cytokines. Pretreatment with naloxone and AM630 reversed the anti-nociceptive activity of BCP and revealed the involvement of μ-opioid receptors and CB2R pathways, respectively.

Kuwahata et al. [124] examined the effect of intraplantar (i.pl.) injection of BCP on a murine model of partial sciatic nerve ligation (PSNL)-induced mechanical allodynia and elucidated the involvement of peripheral CB2R on the anti-allodynic effect of BCP. Injury to the sciatic nerve led to prolonged mechanical allodynia and thermal hyperalgesia [125]. BCP injected into the ipsilateral hind paw of PSNL mice dose-dependently mitigated mechanical allodynia but had no effect on the contralateral hind paw, indicating that BCP has a localized anti-allodynic effect on peripheral nociceptors. BCP appears to exert anti-allodynic activity by stimulating peripheral CB2Rs but not CB1Rs as the anti-allodynic effects of BCP are abolished following pretreatment with AM630 but not the CB1R antagonist AM251. For instance, activation of peripheral CB2R could reduce primary afferent neuron sensitization by suppressing the production of sensitizing factors released from neighboring mast and immune cells. Another possible mechanism of indirect anti-nociceptive activity is stimulation of local release of β-endorphin from keratinocytes, which could suppress pain by activating neuronal μ-opioid receptors. Keratinocytes are abundant in the skin and have been reported to express CB2R [126]. Collectively, these results indicate that BCP can suppress neuropathic pain through peripheral CB2R activation.

Katsuyama et al. [127] elucidated the anti-nociceptive effect of i.pl. BCP in capsaicin-induced acute pain and assessed the contributions of peripheral CB or opioid mechanisms as well as the effect of BCP on the anti-nociceptive activity of morphine. Sakurada et al. observed that a short-lasting paw-licking/biting reaction following subcutaneous injection of capsaicin into the hind paw of mice was dose-dependently suppressed by morphine [128]. The stimulation of nociceptive primary afferents by capsaicin was shown to lead to the release of nociceptive neurotransmitters in the dorsal spinal cord [129,130]. Injection of BCP into the plantar surface of the hind paw dose-dependently reduced capsaicin-induced nociceptive behavior, an effect abolished by pretreatment with AM630 but not AM251. Pretreatment with the selective μ-opioid receptor blockers naloxone and β-funaltrexamine also prevented the inhibitory action of BCP on capsaicin-induced nociception. Importantly, pretreatment with methiodide, a peripherally acting antagonist against μ-opioid receptors, and antisera against β-endorphin antagonized the anti-nociceptive actions of BCP. However, the anti-nociceptive effect of morphine was enhanced by a lower concentration of BCP. In addition, the anti-nociception produced by the combination of BCP and morphine was significantly blocked by naloxone pretreatment. It was concluded that this antinociception is attributable to CB2R activation in the periphery by BCP, which in turn releases local endogenous β-endorphin from keratinocytes and activates μ-opioid receptors. Similar to local BCP injection, peripheral BCP injection combined with morphine could be beneficial by minimizing the adverse effects of morphine.

The anti-nociceptive efficacy of BCP has also been examined against other agents, including clinical compounds known to induce inflammation and chronic pain states. Aly et al. [131] assessed whether BCP could inhibit the neuropathic pain and inflammation produced by the nucleoside reverse transcriptase inhibitor 2'-3'-dideoxycytidine (ddC, zalcitabine). Treatment with BCP, minocycline, or pentoxifylline significantly attenuated mechanical allodynia induced by ddC. In contrast, pretreatment with AM630 but not AM251 abrogated the anti-allodynic effect of BCP. Furthermore, BCP ameliorated the expression of proinflammatory cytokines in the paw skin and brain. Mitogen-activated protein kinases (MAPKs), including p38 MAPK, extracellular signal-regulated kinase (ERK)1/2, and c-jun N-terminal kinase (JNK), are known mediators of neuronal sensitization and neuropathic pain. The activation (via phosphorylation) of p38 MAPK promotes inflammation by activating microglial cells [132], and increased expression of phosphorylated ERK1/2 has been implicated in the pathophysiology of pain in the peripheral nervous system (PNS) and central nervous system (CNS) [133]. Treatment with BCP significantly suppressed ddC-induced elevation of phosphorylated ERK1/2 levels but had no effect on phosphorylated p38 levels. Thus, BCP inhibited ddC-induced mechanical allodynia, probably through CB2R activation

and ensuing attenuation of inflammation. Oral BCP treatment simultaneously with antiretroviral drug therapy may improve the tolerability and thus potential efficacy of these agents for diseases by preventing inflammation and neuropathic pain. This suggested the potential adjuvant use of BCP and development of CB2R agonists for mechanical allodynia. The plausible mechanisms of CB2R-dependent analgesic/anti-nociceptive and allodynic effects of BCP observed till date in experimental studies are summarized in a schematic presentation in Fig. 5.

2.5. Atherosclerosis

Atherosclerosis is a chronic inflammatory condition of the arteries and is associated with increased morbidity and mortality globally. It increases the risks of myocardial infarction, stroke, and peripheral artery [134]. Elevated serum levels of cholesterol and triglycerides and chronic inflammation resulting in secretion of proinflammatory mediators such as cytokines appear to act synergistically in plaque formation. Therefore, suppression of the central immune pathways linking proinflammatory cytokines is an important strategy for atherosclerosis treatment [135].

Both human umbilical vein endothelial cells (HUVECs) and pulmonary artery endothelial cells express CB2Rs [136], and considerable evidence accrued over the past several decades demonstrates that CB2R regulates many pathogenic processes critical to atherosclerosis. Steffens et al. [137] first demonstrated the role of CB2R in atherosclerosis *in vivo* by showing that low-dose oral tetrahydrocannabinol reduced both plaque size and macrophage numbers in ApoE$^{-/-}$ mice compared with those in untreated control mice and that co-administration of the CB2R selective antagonist SR144528 abolished these effects. Netherland et al. [138] also found that CB2R activation decreased macrophage infiltration, inflammation, and the progression of atheromatous plaques. Zhang et al. [139] reported that BCP dose-dependently reduced the attachment of human monocytic cells to the aortic surface in a mouse model of atherosclerosis induced by a high-fat diet plus lipopolysaccharide (LPS) treatment. This recruitment of monocytes to the vascular surface was facilitated by the expression of adhesion molecules on endothelial cells induced by tumor necrosis factor (TNF)-α. BCP attenuated TNF-α-stimulated expression of VCAM-1 on the cell surface but had no effect on the expression of ICAM-1. BCP also suppressed macrophage infiltration to the aortic surface and decreased serum concentrations of cholesterol and triglycerides. A previous study reported that activation of interferon regulatory factor 1 (IRF-1) by TNF-α is essential for the expression of VCAM-1 but not ICAM-1 and E-selectin [140]. In addition to inflammatory cell adhesion, IRF-1 can upregulate inducible nitric oxide synthase (iNOS), which is another mediator of endothelial inflammation [141]. BCP was found to hinder the expression of IRF-1. Activation of IRF-1 depends on the stimulation of upstream signaling molecules such as JAK2 and STAT1. BCP attenuated the phosphorylation of JAK2/STAT1 and consequent expression of IRF-1 in HUVECs challenged with TNF-α, demonstrating the role of JAK2/STAT1/IRF-1 signaling in atherosclerogenic inflammation. The repressive effects of BCP on IRF-1 and VCAM-1 expression were abolished by SR144528 or siCB2R, supporting the potential importance of CB2R signaling in atherosclerosis by modulating endothelial dysfunction.

2.6. Cancer

Glioblastoma (GBM) is the most common and aggressive type of malignant brain cancer in adults and is characterized by uncontrolled cell proliferation and exaggerated angiogenesis, promoting tumor growth [142]. Signaling through MAPKs and the stress-associated transcription factor nuclear factor κB (NF-κB) is a critical modulator of GBM cell growth and proliferation [143]. NF-κB regulates the expression

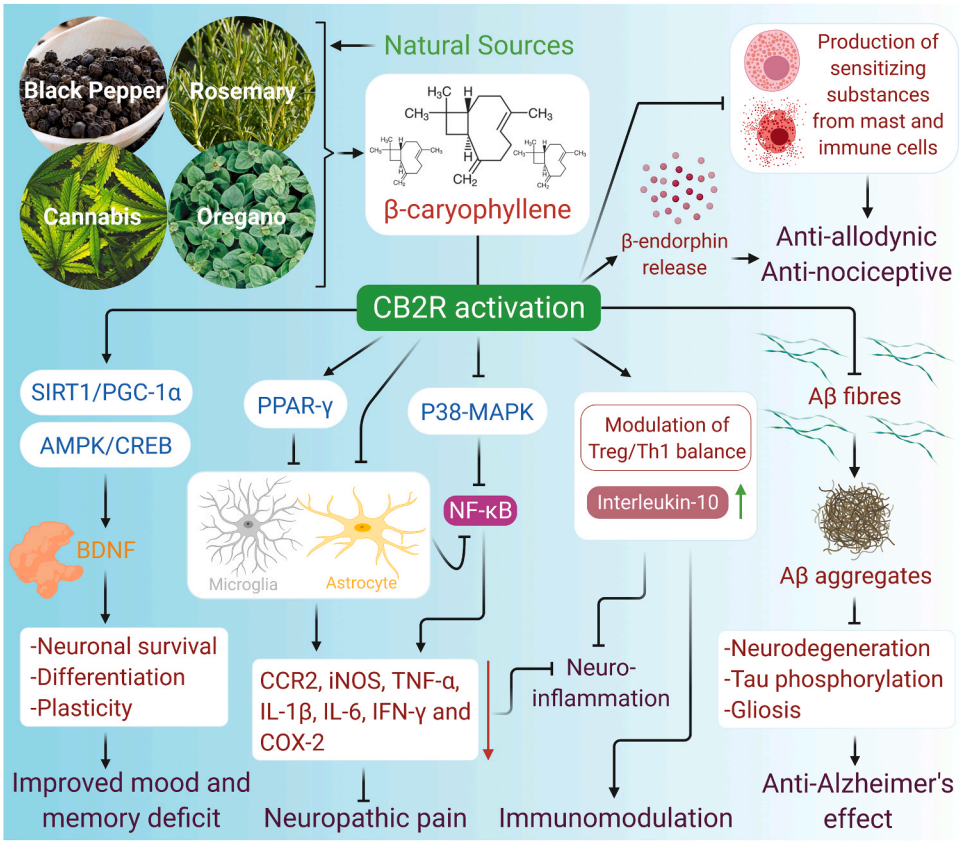

Fig. 5. Cannabinoid type 2 receptor (CB2R)-mediated anti-allodynic and neuroprotective mechanisms of β-caryophyllene (BCP).

of genes involved in inflammation and enhances the synthesis and release of proinflammatory mediators from GBM cells [144]. Considering the limited therapeutic options and poor survival, it is crucial to develop new therapies to improve disease prognosis and quality of life. Both CB1R and CB2R are expressed by GBM cells and are implicated in controlling growth, differentiation and survival of the cells [145]. CB2R activation induced apoptotic and/or autophagic cell death and inhibited the proliferation, activation, motility, and secretion of inflammatory cytokines by GMB cells [146]. In the human GBM-derived cell line U-373 and human glioma stem-like cell line U87, BCP reduced cell viability, inhibited cell proliferation and cell cycle progression, and enhanced apoptotic cell death, as evidenced by increased expression of the apoptotic effector proteases caspase-3 and caspase-9 [61]. These effects were associated with the upregulation of the pro-apoptotic protein BAX and downregulation of the anti-apoptotic protein Bcl-2. Bcl-2 may bind Beclin-1, which upon activation regulates autophagic cell death. Autophagy facilitates tumorigenesis by promoting tumor proliferation and invasiveness [147]. Conversely, BCP reduced the expression of Beclin-1, LC3, and p62/SQSTM1, suggesting a possible switch between autophagy and apoptosis. Consequently, BCP as a CB2R agonist may act as a tumor suppressor GBM treatment.

Previous studies have shown that CBs reduced inflammation via inhibition of upstream and downstream signaling-mediated inflammatory processes, with possible crosstalk between CB2R and PPAR-γ [62,63]. Stimulation of PPAR-γ was shown to decrease the secretion of proinflammatory mediators [148]. BCP significantly decreased the expression levels of NF-κB and TNF-α and activated PPAR-γ, demonstrating the anti-inflammatory mechanism of BCP. In addition, BCP significantly decreased JNK expression, which was associated with the anti-proliferative response, whereas AM630 abolished the changes in caspase-3, PPAR, and JNK expression levels and partially restored GMB cell viability.

2.7. Chemotherapy-induced organ toxicity

Paclitaxel (Taxol®) is an effective drug against multiple malignant tumors, but its tolerability is limited by side effects such as peripheral neuropathy. This chemotherapy-induced peripheral neuropathy (CIPN) involves several mechanisms, including loss of nerve fibers that innervate the epidermis, mitochondrial impairment, deregulated transient receptor potential channels, and peripheral as well as central inflammatory processes [149]. Previous studies have demonstrated the role of microglial cells and production of proinflammatory mediators [150–152], but there are no efficacious strategies for treating CIPN. Several studies have reported that ECS can mitigate multiple forms of acute and chronic brain injury, including excitotoxicity from excessive glutamatergic activation and associated mitochondrial dysfunction, inflammation, and oxidative injury. Cannabinoids have demonstrated analgesic efficacy against several pain conditions, and the response is associated with anti-hyperalgesic and anti-inflammatory activities [153]. Although the effects of CBs in neuropathic pain conditions have been extensively investigated, the exact mechanisms underlying their anti-nociceptive activity remain disputed [121,154,155].

In a murine model of paclitaxel-induced peripheral neuropathy, Segat et al. [156] found that BCP attenuated allodynia, and this response was blocked by AM630 pretreatment. The concomitant administration of BCP with paclitaxel also enhanced CB2R expression in the spinal cord. Growing evidence indicates a pivotal role of p38 MAPK in chronic pain as it is stimulated in response to nerve injury and results in increased synthesis of several proinflammatory cytokines involved in pain mediation [132,157]. Additionally, NF-κB is activated in neurons and microglial cells following nerve damage, and this activation is linked to both chronic inflammation and subsequent neurodegeneration [158]. Its stimulation in microglial cells results in the production of many inflammatory mediators that can sensitize peripheral and central nociceptive neurons and drive pain progression [159]. These mediators include interleukin (IL)-1β [160], which aggravates pain in dorsal horn neurons [159] and activates both p38 MAPK and NF-κB in adjacent microglial cells, resulting in further secretion of cytokines [132,158]. BCP attenuated paclitaxel-induced activation of p38 MAPK and NF-κB and reduced both the expression of the microglial activation marker Iba-1 and tissue IL-1β levels. Collectively, these findings suggest that BCP can mitigate paclitaxel-induced peripheral neuropathy via CB2R activation in the CNS and consequently suppress p38 MAPK/NF-κB activation and cytokine production.

The anthracycline antibiotic doxorubicin (DOX) is also effective against many hematopoietic and solid malignancies [161], but its clinical value is hindered by dose-dependent cardiotoxicity leading to dilated cardiomyopathy and congestive heart failure. The pathomechanisms of DOX-associated cardiotoxicity include reactive oxygen species (ROS)-mediated oxidative stress, lipid peroxidation, inflammation, and apoptotic cell death [162]. CB2R is expressed in myocardium [163] as well as in vascular endothelial and smooth muscle cells [164]. The activation of CB2R holds therapeutic promise as it leads to the mitigation of self-sustaining oxidative stress, inflammation, and apoptosis of myocardial cells [165]. Meeran et al. [166] showed that BCP protected against DOX-induced cardiotoxicity, as evidenced by reduced serum levels of cardiomyocyte enzymes (CK-MB and LDH), preserved histology and ultrastructure, and restored heart function. This rescue was dependent on antioxidant effects as BCP pretreatment also enhanced antioxidant enzyme activities, restored intracellular glutathione (GSH) levels, and reduced lipid peroxidation. In addition, BCP reduced inflammation, as evidenced by lower levels of inflammatory enzymes (iNOS, COX-2), proinflammatory cytokines, and NF-κB. Additionally, BCP decreased the expression levels of the apoptotic markers Bax, p53, cleaved PARP, and caspase-3 and increased the expression level of Bcl-2. BCP treatment increased myocardial expression of CB2R and PPAR-γ, whereas DOX-challenged rats pretreated with AM630 showed remarkably decreased CB2R and PPAR-γ expression levels. Thus, CB2R activation may be a novel target and BCP a promising candidate for prevention of chemotherapy-induced cardiotoxicity.

Cisplatin is a common platinum-based chemotherapeutic agent that is used for treating bladder, cervical, ovarian, lung, and testicular cancers among others. One of the major side effects of cisplatin is nephrotoxicity, which is dose-limiting and currently without effective therapies [167]. Oxidative and nitrative stress associated with inflammation are central pathogenic processes in cisplatin-induced nephrotoxicity [168,169]. CB2R is expressed in the kidney, primarily by mesangial cells of the renal cortex, podocytes of the glomerulus [170], and proximal tubule cells [171], and activation of CB2R had a protective effect on the structure and function of nephrons in animal models of chronic kidney injury [172,173]. Horváth et al. [20] reported that BCP treatment dose-dependently ameliorated cisplatin-induced renal dysfunction, morphological damage, and kidney inflammation, as evidenced by significant reductions in the levels of proinflammatory chemokines (IL-1β and TNF-α), levels of macrophage inflammatory proteins (MCP-1 and MIP-2), which attract inflammatory cells to the injury site, the cell adhesion molecule ICAM-1, and infiltration of leukocytes and macrophages. BCP also attenuated oxidative/nitrative stress, as evidenced by a significant decrease in the expression levels of NOX-2, NOX-4, 3-NT, and 4-HNE. Intrinsic and poly(ADP-ribose) polymerase (PARP)-dependent pathways activated in response to ROS and reactive nitrogen species also contribute to cisplatin-induced nephrotoxicity [168] by promoting apoptosis or necrosis [174]. BCP significantly reduced cisplatin-induced caspase 3/7 activity, DNA fragmentation, and PARP activation in renal tissues of mice, these effects were abrogated by CB2R KO, confirming the dependence on CB2R. Therefore, CB2R activation appears to be a promising target to prevent cisplatin-induced nephrotoxicity by mitigating inflammation, oxidative/nitrosative stress, and apoptosis.

Oral mucositis is the most common and a debilitating complication of cancer treatment, particularly chemotherapy and radiotherapy. It is characterized by severe inflammation that results in erythematous and

ulcerative lesions of the oral mucosa, dysphagia, and an inability to maintain normal nutritional intake, leading to the interruption of life-saving therapies [175]. Picciolo et al. [176] evaluated the efficacy of BCP against LPS-induced oral mucositis in gingival fibroblasts and epithelial cells. BCP decreased the levels of inflammatory mediators, including TNF-α and IL-1β, and upregulated the levels of the anti-inflammatory cytokine IL-13. Furthermore, BCP inhibited the expression of NF-κB and upregulated the levels of PGC-1α and PPAR-γ, suggested that BCP modulates upstream signals that stimulate the first phase of the inflammatory process. In contrast, AM630 abrogated the salutary effects of BCP. Oral mucositis is associated with excessive secretion of IL-6 [177] and subsequent stimulation of the transcription factor STAT3 [178], which induces the secretion of additional inflammatory cytokines such as IL-17A, which coordinates the recruitment of inflammatory cells to the mucosa. Treatment with BCP significantly attenuated the expression of STAT-3, IL-6, and IL-17A in gingival fibroblasts and epithelial cells, suggesting that BCP halted the second phase of inflammation. However, AM630 reversed the effects of BCP on STAT-3, IL-6, and IL-17A. Thus, BCP demonstrated remarkable efficiency in an *in vitro* model of oral mucositis, and CB2R activation may serve as a potential target for developing efficient therapeutics for oral mucositis. BCP effectively interrupted the transition from acute to chronic inflammation via suppression of NF-κB and activation of CB2R and PPAR-γ.

2.8. Inflammatory bowel diseases (IBDs)

Inflammatory bowel diseases (IBDs), including ulcerative colitis and Crohn's disease, are characterized by massive infiltration of inflammatory cells into intestinal tissues, secretion of proinflammatory mediators, and increased generation of free radicals that results in damage to the intestinal lumen and influences the lumen's response to luminal commensal flora and pathogens [179,180]. High levels of endocannabinoids and overexpression of CB2R have been reported in the colon of patients with IBD [181]. This elevated CB2R expression level is directly associated with the number of macrophages, helper and cytotoxic T cells, monocytes, and neutrophils [10,182], which are correlated with IBD [183]. Available data support the notion that endocannabinoids exert anti-inflammatory effects in the colon by PPAR-γ pathway activation [184,185].

Bento et al. [52] evaluated the effects of oral BCP in a murine model of colitis induced by dextran sulfate sodium (DSS), which led to mucosal damage accompanied by infiltration of neutrophils and macrophages. BCP decreased disease activity, attenuated body weight loss, and inhibited expression of the neutrophil marker myeloperoxidase and the macrophage marker N-acetylglucosaminidase. Treatment with BCP also reduced the expression levels of TNF-α, IL-1β, INF-γ, and keratinocyte-derived chemokine (CXCL1/KC), factors known to drive the recruitment of inflammatory cells [186,187]. Conversely, BCP increased the expression levels of IL-4 and FoxP3, the most specific markers for regulatory T (Treg) cells. MAPK signaling via transcriptional factors NF-κB and CREB is the main proinflammatory transduction pathway associated with colitis [188]. The T helper type 1 (TH1) cytokines, including INF-γ, TNF-α, and IL-1β are regulated by CREB in colitis [189]. BCP significantly inhibited CREB activation by DSS, suggesting that this effect is linked to decreased levels of TH1 cytokines and increased levels of TH2 cytokines such as IL-4.

In addition, BCP treatment improved acute colitis by suppressing the activation of ERK1/2, IKKα/β, NF-κB, caspase-3, and the proliferative marker Ki-67, indicating reduced inflammation, cell proliferation, and cell death. BCP also reduced the secretion of CXCL1/KC, MIP-2, and TNF-α in macrophages challenged with LPS. Pretreatment with AM630 or GW9662, PPAR-γ antagonist, abrogated the protective effects conferred by BCP against macroscopic colon damage, reduced colon length, and reduced myeloperoxidase (MPO) activity induced by DSS. Furthermore, abrogation of these inhibitory effects on proinflammatory cytokine production (TNF-α and CINC-1) in IEC-6 cells showed that CB2R and PPAR-γ activation mediated the anti-inflammatory effect. Three potential pathways are involved in the stimulation of PPAR-γ by endocannabinoids: direct action on PPAR-γ, transformation of cannabinoids to metabolites that stimulate PPAR-γ, and indirect activation through interactions with cell surface receptors and intracellular signaling pathways. These data suggest that BCP-mediated dual activation of CB2R and PPAR-γ pathways is a promising strategy for the treatment of IBD.

2.9. Multiple sclerosis and other neuroinflammatory diseases

Multiple sclerosis (MS) is a CNS disorder caused by autoimmune attack of the myelin sheaths surrounding axons, resulting in disruption of axonal transmission and associated sensory and motor deficits. The induction of experimental autoimmune encephalomyelitis (EAE) by injection of myelin antigens, including proteolipid protein peptide and myelin oligodendrocyte glycoprotein, is the most commonly used animal model for studying the features of MS [190]. Several studies have reported that cannabimimetic drugs, mainly CB2R agonists, can slow the progression of demyelinating diseases [191–193] by preventing leukocyte proliferation, stimulating T cell and macrophage apoptosis, and inhibiting the release of inflammatory mediators [192]. CB2R-expressing immune cells play important roles in the regulation of T cell migration, reduction of cytokine secretion [194], and antigen presentation [195], suggesting that CB2R agonists suppress EAE progression. Similarly, an increasing number of preclinical and human studies have shown that cannabinoids regulate spasticity in MS [196]. These CB2R-dependent neuroprotective mechanisms of BCP are depicted in Fig. 5.

Alberti et al. [197] reported that BCP pretreatment of extracted lymphocytes stimulated with the EAE inducer myelin oligodendrocyte glycoprotein (MOG) fragment 35–55 upregulated the production of IL-10 and downregulated the production of IFN-γ, effects abolished by the CB2R antagonist AM630. BCP also ameliorated motor paralysis, loss of body weight, and mechanical hyperalgesia characteristic of the pre-motor phase of EAE. Additionally, BCP treatment decreased the expression levels of Iba-1, iNOS, and neurofilament-H, attenuated both glial cell activation and oxidative injury, and prevented subsequent demyelination. It is thought that CD4+ Th cells are responsible for mediating inflammation in EAE and other autoimmune disorders. Prophylactic treatment with BCP significantly reduced both CD4+ and CD8+ T cell populations and prevented CD8+ and CD4+ T cell stimulation in lymphatic tissues. A shift in Th1 and Th17 cytokines is believed to trigger pathological inflammation in MS [198] and BCP normalized the Th1/Treg cell balance concomitant with the prevention of demyelination via CB2R activation. Collectively, BCP appears to inhibit the progression of EAE and other autoimmune diseases by interrupting proinflammatory cell activity, suppressing T cell infiltration into CNS, and enhancing the activity of Treg cells.

Neuroinflammation has been shown to have a direct correlation to neurodegenerative diseases, including dementia, MS, PD, and Alzheimer's disease (AD) [199]. Alterations in microglial phenotype and activity are major contributors to these neuroinflammatory processes across disease types. Microglial cells are brain-resident phagocytic cells that can be classified as type 1 (M1), with generally proinflammatory activity, and type 2 (M2), with generally anti-inflammatory activity [200], and the relative balance between these types is a critical determinant of inflammatory status. Thus, control of this balance is a major focus of research on potential therapies for neurodegenerative and neuropsychiatric diseases. Overactivation of M1 microglial cells in multiple disease states can induce neuronal damage through the release of cytotoxic and inflammatory mediators such as nitric oxide, ROS, and proinflammatory cytokines [201]. In contrast, M2-polarized microglial cells can abolish inflammatory and immune responses by secreting anti-inflammatory cytokines such as IL-10 and IL-4 and by promoting

the conversion of arginine to ornithine and urea via arginase-1, which in turn suppresses NOS activity and nitric oxide synthesis. Moreover, M2 cells have a novel function in tissue repair, which may depend in part on the generation of ornithine and associated metabolites. Thus, long-lasting stimulation of M1 microglia leads to neuronal injury and destruction, whereas M2 cells promote regeneration and healing [200].

Oligodendrocytes play a primary role in the formation of myelin and axonal assembly in the CNS [202]. Loss of myelin and oligodendrocyte cell death are hallmarks of MS and other demyelinating disorders [203]. Administration of LPS to animals is a widely used model for MS as this results in infiltration of immune and microglial cells to produce proinflammatory cytokines and induce oligodendrocyte apoptosis [203]. Notably, CB2R has attracted enormous interest as a possible therapeutic target due to the absence of psychotropic effects upon stimulation (unlike with CB1R stimulation), abundant expression in immune cells [204], and documented neuromodulatory and immunomodulatory activities [205]. Several studies have revealed that CB2R activation can diminish proinflammatory cytokine release and enhance anti-inflammatory cytokine release following damaging stimuli, thereby promoting neuronal survival [206,207].

Askari and Shafiee-Nick [208] reported that BCP treatment of LPS-induced microglial cells significantly increased cell proliferation and viability and intracellular GSH levels while reducing ROS levels, and pretreatment with AM-630 or GW9662 abolished these effects. Furthermore, BCP treatment attenuated the LPS-induced increase in levels of inflammatory mediators, including cytokines and prostaglandins, and enhanced secretion of IL-10, which promoted a shift toward the M2 phenotype and reduced the M1 cell population [209]. These effects were abolished by AM630 or GW9662. Co-administration of the sphingomyelinase (SMase) inhibitor imipramine with BCP significantly enhanced the cytoprotective efficacy of BCP, as evidenced by increased cell viability, intracellular GSH level, and IL-10 level and decreased accumulation of ROS and inflammatory mediators, including cytokines and prostaglandins. BCP also significantly increased urea and Arg-1 levels; this effect was enhanced by co-treatment with imipramine and reversed by pretreatment with AM-630 or GW9662. In addition, low-dose BCP treatment significantly decreased the M1/M2, NO/urea, and iNOS/Arg-1 ratios, effects that were further enhanced by imipramine pre-administration and reversed by AM-630 pretreatment. Thus, lower BCP doses can produce anti-inflammatory responses through activation of CB2R, whereas higher concentrations can exert anti-inflammatory and protective effects via activation of both PPAR-γ receptor and CB2R. Stimulation of SMase by the CB2R-activated βγ-subunit resulted in the release of ceramides, which increased the expression and activity of PPAR-γ receptor [210]. BCP reversed the LPS-induced M1/M2 imbalance, induced the secretion of anti-inflammatory mediators, and elevated GSH levels, thereby decreasing proinflammatory and oxidative stress. In addition, higher concentrations of BCP overactivated the CB2R βγ-subunit, resulting in greater SMase activation, increased secretion of ceramides, and further activation of the PPAR-γ pathway, whereas low concentrations of BCP showed more selective anti-inflammatory effects. Taken together, BCP can modulate microglial cells and might have clinical and pharmacological potential in neurodegenerative diseases.

Askari and Shafiee-Nick [60] also found that BCP significantly inhibited LPS-induced toxicity and attenuated increased production of NO, ROS, and TNF-α in the oligodendrocyte cell line OLN-93, whereas AM630 or GW9662 abolished the beneficial actions of BCP on cell proliferation, oxidative stress, inflammatory status, and proinflammatory cytokine secretion. However, GW9662 completely abrogated the protective effects of high-dose BCP only but not the protective effects associated with low concentrations. These findings suggest that protection of OLN-93 cells by high-dose BCP was mediated mainly via activation of CB2R and PPAR-γ signaling pathways. The SMase inhibitors fluoxetine and imipramine significantly enhanced the protective effect of BCP on cell viability and NO, ROS, TNF-α, and GSH levels. Furthermore, BCP significantly increased the expression levels of PPAR-γ, a response abolished by AM630 pretreatment. Furthermore, BCP pretreatment significantly enhanced the levels of Nrf2 and HO-1, effects again abrogated by AM630 pretreatment. These results indicate that BCP can protect against LPS-induced cytotoxicity via activation of multiple signaling pathways, including the Nrf2/HO-1/antioxidant axis in addition to PPAR-γ and CB2R pathways. The data demonstrate that low-dose BCP may have therapeutic value against neurodegenerative and neuroinflammatory diseases.

Brain injury following transient or sustained disruption of neural blood flow (stroke) can be divided into two phases, an early phase resulting from metabolic failure, excitotoxicity, and oxidative damage largely confined to the ischemic region and a delayed process of more expansive secondary injury associated with neuroinflammation, neural apoptosis, and glial activation [211]. Activated microglia play a significant role in the onset of neuroinflammatory processes in stroke [212], thus, selective activation of CB2R has been examined as a potential treatment [213]. Guo et al. [214] found that BCP pretreatment reduced cytotoxicity and attenuated the secretion of proinflammatory cytokines by activated BV2 microglia under hypoxia. BCP also reduced ROS production by mitochondria and prevented activation of NF-κB-dependent transcription. All these protective effects of BCP were blocked by CB2R siRNA transfection. Assis et al. [215] reported that different concentrations of BCP significantly inhibited glutamate-induced cytotoxicity of C6 rat glioma cells by preventing ROS generation and upregulating antioxidant capacity via Nrf2. These responses were abrogated by AM630 treatment. Neuronal death in the early stages after ischemic stroke results from a mutually reinforcing chain of events including overestimation of glutamatergic NMDA receptors, ensuing intracellular calcium overload, excessive ROS generation [216], loss of mitochondrial membrane potential (ΔΨm) [217], failure of the mitochondrial respiratory chain, decreased ATP generation, and apoptosis [218]. Thus, these demonstrations of preserved antioxidant capacity and reduced neuroinflammatory signaling suggest that CB2R activation via BCP may provide broad spectrum protection against ischemic damage.

2.10. Neurodegenerative disorders

2.10.1. Parkinson's disease (PD)

PD is caused by progressive loss of dopaminergic neurons mainly in the substantia nigra pars compacta (SNpc), which results in resting tremors, bradykinesia, and muscle rigidity along with impaired gait and posture [219]. Mitochondrial dysfunction, increased production and accumulation of free radicals, and initiation of apoptosis are key pathogenic events in PD. Activation of CB2R has been shown to suppress neuroinflammation by attenuating microglial and astrocyte activation in the SNpc and striatum [220,221], restore neuronal function, promote neuronal survival, and ameliorate functional deficits [222–225]. Javed et al. [50] found that BCP inhibited the decrease in GSH, SOD, and catalase levels and reduced the accumulation of the membrane peroxidation marker malondialdehyde (MDA) in rodents exposed to the neurotoxic pesticide rotenone, a widely used inducer of PD-like pathology. BCP also prevented loss of SNpc dopaminergic neurons and striatal dopamine nerve fibers, decreased astrocyte and microglia activation, as evidenced by reduced expression of GFAP and Iba-1, respectively, and attenuated the release of proinflammatory cytokines and inflammatory mediators. These actions were abolished by AM630 pretreatment, indicating that BCP protects against rotenone-induced neurodegeneration by CB2R-dependent anti-inflammatory and antioxidant mechanisms. This antiparkinsonian activity of BCP-mediated CB2R activation was further demonstrated in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD [226]. In this model, MPTP is converted to the neurotoxin 1-methyl- 4-phenylpyridinium (MPP+), which causes selective death of dopaminergic neurons in the SNpc [227]. BCP significantly improved MPTP-induced behavioral and motor impairments, inhibited loss of SNpc dopaminergic neurons,

suppressed local activation of astrocytes and microglia, and attenuated release of proinflammatory cytokines within the nigrostriatal system. Consistent with mediation by CB2Rs, all these effects were blocked by AM630 pretreatment. The neuroprotective mechanisms of BCP were further demonstrated by Wang et al. [228] using human neuroblastoma cells (SH-SY5Y) subjected to MPP+-induced neurotoxicity. BCP reduced ROS accumulation and extracellular accumulation of lactate dehydrogenase (LDH), a marker for cell death, and restored both cellular GSH levels and glutathione peroxidases (GPx) activity. BCP also inhibited expression of caspase-3 and Bax, upregulated Bcl-2, and suppressed the ΔΨm depolarization induced by MPP+. Again, all these effects were blocked by AM630. In addition, BCP decreased the expression of phosphorylated JNK and upregulated heme oxygenase-1 (HO-1), providing further evidence that BCP can prevent MPP+-induced oxidative stress. Of note, HO-1 is upregulated in the serum and SNpc of PD patients [229], underscoring the contribution of oxidative stress to disease progression and the clinical potential of CB2R activation. Blockade of JNK signaling is another potential treatment strategy as these pathways are implicated in apoptotic cell death [230].

2.10.2. Alzheimer's disease (AD)

AD is a neurodegenerative disorder causing cognitive impairment and dementia. The pathological features of AD are defective cholinergic neurotransmission, neurofibrillary tangles, and amyloid plaques, which upon deposition induces neuroinflammation and neurodegeneration [231]. Additionally, astrocytic and microglial activation also contribute to neuroinflammation in patients with AD [232]. Previous studies have suggested that cannabinoids have anti-inflammatory efficacy and can be used as preventive therapy for AD [233,234], and a number of animal models and human postmortem studies have demonstrated high expression of CB2R by glial cells in the vicinity of amyloid plaques [222, 235–237]. Activation of CB2R has also been shown to improve cognition and attenuate neuroinflammation in animal models of AD [238,239].

Cheng et al. [240] studied the effects of BCP in a double transgenic APP/PS1 AD mouse model that recapitulates many of the neurological features of AD, including amyloidosis and neuroinflammation, and assessed the mediating roles of CB2R and PPAR-γ. BCP inhibited age-dependent cognitive decline in these transgenic mice, a response correlated with lower β-amyloid deposition in the hippocampus and cerebral cortex along with decreased expression of inflammatory mediators in the cerebral cortex. Additionally, BCP prevented astrogliosis and microglial activation as evidenced by downregulation of GFAP and Iba-1. Agonists of PPAR-γ such as rosiglitazone have also been reported to ameliorate AD pathology and improve cognitive function in animal models [241,242] and to slow memory and cognitive decline in AD patients [243,244]. In animal models, AM630 or GW9662 abolished the neuroprotective effects of BCP. Thus, BCP or other CB2R agonists may be promising therapeutics for AD.

Vascular dementia (VD) is a chronic progressive syndrome that results from repeated ischemic cerebrovascular episodes [245] and is the second leading cause of dementia after AD [246]. VD is characterized by progressive cognitive and behavioral impairment that results from reduced cerebral blood flow in brain regions as hippocampus and white matter [247]. Ashton et al. reported CB2R upregulation in models of ischemia [248] that mirrored the delayed time course of degeneration, suggesting primary localization in macrophages or leukocytes recruited into the injured brain. In accord with this finding, CB2R upregulation has been detected in various forms of brain injury [249]. Moreover, CB2R activation has been shown to reduce neuroinflammation [250]. The anti-ischemic activities of CB2R activation involve reduction of leukocyte rolling and vascular adhesion, thereby limiting entry into the brain and secretion of proinflammatory cytokines that activate microglial cells and macrophages [251].

Lou et al. [252] demonstrated the protective efficacy of a BCP/hydroxypropyl-β-cyclodextrin inclusion complex (HPbCD/BCP) on impaired cognitive function in a rat model of VD. This HPbCD carrier was developed for complexation of non-polar molecules to improve stability, aqueous solubility, dissolution rate, and bioavailability [253]. Indeed, PbCD/BCP enhanced the bioavailability of BCP and mitigated cognitive and memory deficits in the two-vessel occlusion (2VO) model of chronic cerebral ischemia. Furthermore, PbCD/BCP attenuated the number of abnormal and apoptotic hippocampal neurons as evidenced by reduced TUNEL staining. Moreover, HPbCD/BCP activated the PI3K/Akt signaling pathway, which is strongly implicated in neuroprotection and associated with learning and memory abilities [254] and upregulated CB2R in the hippocampus and white matter. AM630 pretreatment downregulated CB2R, PI3K, and Akt levels, suggesting that CB2R activation is required for PI3K/Akt pathway signaling and protection cerebral damage.

2.10.3. Ischemic brain injury

Ischemic brain injury results from a complex web of pathogenic processes including NMDA receptor overstimulation, loss of intracellular Ca^{2+} homeostasis, ΔΨm depolarization, loss of mitochondrial metabolism, oxidative damage to macromolecules and membranes, and inflammatory signaling [255]. Given these complex mutually interacting processes, there are many potential therapeutic targets, but there are still no broadly efficacious neuroprotective therapeutics that do not produce intolerable or toxic side effects.

Evidence herein reveals substantial contributions of endocannabinoid signaling to metabolic homeostasis, antioxidant capacity, immunomodulation, and brain responses to stress, strongly suggesting functions as endogenous neuroprotective agents against cerebral ischemia [251,256]. For instance, the endocannabinoid and CB2R agonist arachidonoyl-glycerol (2-AG) protected neurons against malonate toxicity by preventing increased COX-2 expression and subsequent conversion of 2-AG to inflammatory prostaglandin E_2 glyceryl ester (PGE_2-G) [257]. Furthermore, PPAR-α mediated the anti-inflammatory activities of the non-cannabinoids palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), which act as endogenous agonists at this receptor [258,259].

The neuroprotective efficacy of BCP and the underlying mechanisms have been demonstrated in multiple ischemic models [49]. BCP attenuated ΔΨm depolarization and reduced injury to rat cortical neurons subjected to oxygen-glucose deprivation/re-oxygenation (OGD/R), and these protective effects were abolished by pretreatment with AM630 but not by AM251. BCP also reduced intracellular oxidative stress and apoptotic cell death, possibly by activating the AMPK/CREB/BNDF pathway. It has been demonstrated that AMPK is upregulated in neurons during glucose deprivation, ischemia, and hypoxia [260], and this response can either protect neurons [261] or aggravate injury depending on the context [262], while CREB activation by upstream AMPK signaling generally promotes survival by upregulating the transcription of neurotrophins and other cytoprotectants [263]. Selective inhibitors of AMPK and CREB reversed these neuroprotective effects, consistent with essential functions in BCP actions. A clinically significant finding is that BCP given after induction of ischemia reduced infarct size and inflammation, upregulated the phosphorylation of CREB, and enhanced BNDF expression in neurons, responses abrogated by AM630 pretreatment. Thus, CB2R activation may be a viable protective strategy against ischemic brain damage following stroke in the emergency setting.

Poddighe et al. [264] reported that BCP inhibited increased lipoperoxidation in rat frontal cortex and plasma following transient bilateral common carotid artery occlusion and reperfusion (BCCAO/R). In addition, a single acute BCP dose stimulated the ECS by enhancing 2-AG, AEA, PEA, and OEA expression levels as well as the expression of CB1R and CB2R in frontal cortex, and reduced plasma AEA in both sham and BCCAO/R rats. Among endocannabinoid analogs, PEA may be particularly important in endogenous defense against neuroinflammation by suppressing COX-2 activity [265]. Another potentially deleterious response to BCCAO/R is the decrease in docosahexaenoic acid (DHA), a normally abundant polyunsaturated fatty acid [266], and

BCP treatment also inhibited this BCCAO/R-induced decrease in DHA. Moreover, BCP significantly reduced COX-2 expression and upregulated PPAR-α. Collectively, these findings indicate that pretreatment with BCP suppresses neuroinflammation and protects neurons against BCCAO/R by quelling oxidative stress and neuroinflammation via activation of CB2R and PPAR-α pathways.

2.10.4. Depression

Depression is a debilitating mood disorder with high global prevalence. It is characterized by disturbed mood, appetite loss, social withdrawal, and a lack of interest and pleasure in enjoyable activities (anhedonia). Despite several decades of research, understanding of pathogenesis is still incomplete due to the involvement of multiple brain networks [267]. Lower expression of CB2R was reported in the hippocampus of animal models with a depression-like condition induced by stress [268], and CB2R activation can ameliorate depression- and anxiety-like behaviors [269]. Indeed, CB2R ligands have shown pharmacological benefits similar to currently used anxiolytic and antidepressant drugs such as benzodiazepines and selective serotonin reuptake inhibitors but without the deleterious adverse effects such as sedation, ataxia, amnesia, and dependence associated with some anxiolytics [270].

Bahi et al. [271] reported that BCP improved sociability and reduced anxiety- and depressive-like behaviors observed in the elevated plus maze test (including relative time in the open and closed arms and number of entries into the open and closed arms). BCP also increased time spent in the center of an open field with no alteration in locomotor activity, again suggestive of anxiolytic actions. Additionally, BCP reduced the number of buried marbles and digging time in the marble burying test, attenuated immobility in the tail suspension and forced swim tests, and reduced latency to feed in the novelty-suppressed feeding test, suggesting therapeutic actions against compulsion, behavioral despair, and anxiety, respectively. Pretreatment with AM630 reversed these anxiolytic- and antidepressant-like effects of BCP, indicating the involvement of CB2R signaling, and further suggesting that these disease states can be treated through non-serotonergic and GABAergic modulation [272].

Hwang et al. [273] investigated the antidepressant and anti-inflammatory effects of BCP in the chronic restraint plus stress (CR+S) rat depression model and further examined associated changes in hippocampal inflammatory markers and plasticity. Administration of different doses of BCP significantly decreased behavioral despair as evidenced by reduced immobility in the tail suspension and forced swim tests. In addition, BCP ameliorated the increase in hippocampal COX-2 and decreases in hippocampal BDNF and CB2R expression levels induced by stress, suggesting that BCP has neurotrophic and anti-inflammatory actions in the brain. Moreover, the effects of BCP on inflammatory processes and depression were assessed by electrophysiological measurements in LPS-treated hippocampal slices. BCP reversed LPS-induced augmentation of long-term depression (LTD), a form of NMDAR-dependent synaptic plasticity at glutamatergic synapses associated with cognitive deficits [274].

In conclusion, BCP has been demonstrated to ameliorate behavioral and inflammatory responses related to chronic stress, suggesting clinical value for the treatment of depression and anxiety disorders. The CB2R-dependent protective mechanisms of BCP on anxiety, depression, and cognitive dysfunction are presented in Fig. 5.

2.11. Liver diseases

Cholestatic liver disease results from functional impairment of bile secretion by hepatic cells due to obstruction at any stage in the excretory pathway and may lead to irreversible liver fibrosis [275]. The prevalence of liver fibrosis, characterized by the replacement of functional tissue with fibrotic scar tissue, has increased in recent years. Both CB1R and CB2R expression levels are markedly upregulated in liver cirrhosis, a condition in which the cellular structure is dominated by liver myofibroblasts [276]. Endogenous stimulation of CB2Rs reduced liver fibrosis by inhibiting the proliferation and promoting the apoptosis of fibrogenic cells [276]. Additionally, it has been shown that CB2R activation prevents or abrogates liver fibrogenesis by exerting anti-inflammatory activities in both liver and non-liver tissues [277]. Moreover, CB2R stimulation protects against hepatic damage, inflammation, and fibrosis in animal models, suggesting a novel pharmacological target for the treatment of chronic liver diseases [83,278].

Mahmoud et al. [279] reported that BCP or the selective CB1R agonist hemopressin reduced liver collagen fiber deposition, normalized levels of the liver function enzymes alanine aminotransferase (ALT) and aspartate transaminase, reduced bilirubin and hydroxyproline levels, and enhanced expression of matrix metalloproteinase (MMP)-1, which suppresses fibrogenesis by degrading excess type-I collagen fibers, in the rat bile duct ligation model [280]. BCP treatment also attenuated hepatocyte apoptosis as evidenced by increased Bcl2-positive cell number, possibly by reducing collagen and hydroxyproline in liver tissues. These effects were abolished by AM630, implicating CB2R signaling. AMPK pathway activators have also garnered attention as potential therapeutics for obesity, diabetes, and hepatic steatosis [281]. AMPK activation leads to the phosphorylation and suppression of acetyl-CoA carboxylase 1 (ACC1), a rate-limiting enzyme for synthesis of fatty acids. AMPK also phosphorylates sterol regulatory element-binding protein 1c (SREBP-1c) precursor and inhibits its cleavage as well as its translocation to the nucleus and transcriptional activity, which reduces expression of fatty acid synthase (FAS) [282]. Additionally, AMPK phosphorylates FoxO1 following translocation to the nucleus, resulting in increased expression of adipose triglyceride lipase (ATGL) [283]. Kamikubo et al. [284] assessed the effects of medicinal foods on hepatic lipid accumulation by measuring the activation of AMPK in palmitate-overloaded HepG2 cells. BCP significantly reduced SREBP-1c translocation to the nucleus and FoxO1 translocation to the cytoplasm, resulting in FAS downregulation, and upregulated ATGL. BCP also reduced accumulation of intracellular lipid in palmitate-exposed HepG2 cells and dose-dependently increased AMPK and ACC1 phosphorylation. These actions on the phosphorylation of AMPK and ACC1 were reversed by treatment with an AMPK inhibitor, underscoring the importance of the AMPK signaling pathway in BCP-mediated reduction of hepatic lipid accumulation. This BCP-dependent activation of AMPK results from a rise in intracellular Ca^{2+} and ensuing activation of Ca^{2+}-calmodulin-dependent protein kinase kinase-β (CaMKKβ), as the CaMKKβ inhibitor STO609 fully abolished the effects of BCP on AMPK and ACC1 phosphorylation and blocked the reduction in lipid accumulation [285]. Moreover, pretreatment with AM630 blocked this BCP-mediated rise in intracellular Ca^{2+}, AMPK and ACC1 phosphorylation, and the reduction in lipid accumulation. CB2R knockdown by siRNA further confirmed that BCP actions in hepatocytes are dependent on activation of CB2R and the AMPK pathway.

Alcoholic liver disease (ALD), a common complication in alcoholics, involves a broad spectrum of hepatic lesions, from steatosis to cirrhosis. The molecular mechanisms underlying ALD are complex and include cellular injuries, inflammatory processes, oxidative stress, regeneration, and bacterial translocation. Alcoholic hepatitis is the most severe form of alcohol-induced liver disease [286]. Administration of BCP demonstrated benefits against steatohepatitis in mice subjected to chronic binge alcohol feeding [287], a model that mimics the main pathological characteristics of early ALD, including liver injury, changes in proinflammatory mediators, and steatosis [288]. Chronic administration of BCP enhanced liver function enzyme activities, ameliorated oxidative and nitrosative stress, and improved liver histology in this model. BCP also mitigated the proinflammatory phenotype (M1) switch of Kupffer cells (resident liver phagocytic cells) and upregulated F4/80+, CD68+, and Iba-1+ (M2) macrophages [289]. In addition, alcohol-fed mice exhibited elevated expression of CD11b, a biomarker of proinflammatory monocytes and macrophages, and of activated M1

phenotype biomarkers such as IL1ß, IL-6, and the chemokines CCL2 and CXCL2. In addition, alcoholic liver exhibited increased expression of "M2" activation markers arginase 1 (Arg1) and CD163. Conversely, other biomarkers of "M2" activation, including mannose receptor C type 2, macrophage galactose-type C-type lectin 1, C-type lectin domain family 7 member A (Clec7a), and IL-10 were decreased in alcohol-fed mice. Thus, chronic ethanol consumption appears to drive Kupffer cell polarization toward the M1 phenotype and increases the M1/M2 ratio. This shift was reduced by BCP treatment. In addition, BCP significantly decreased ICAM-1, E-selectin, and P-selectin expression levels and neutrophil infiltration, consistent with attenuation of hepatic vascular inflammation. Furthermore, BCP inhibited the decreased expression of PPAR-α, hyperacetylation of proteins, and PPAR-α-dependent signaling induced by chronic and binge alcohol feeding. These hepatoprotective effects of BCP were abolished by CB2R KO, confirming the role of CB2R and suggesting that BCP may be useful for the treatment of ALD.

2.12. Bone disorders

Osteoblastic cells synthesize bone matrix and are responsible for its mineralization. Dysfunctional osteoblasts are implicated in the pathogenesis of osteoporosis, a bone disorder of the elderly in which reduce bone production, increased resorption, or both results in loss of bone mass, increasing the risk of breakage, postural deformation, and limited mobility [290]. The cannabinoid system likely contributes to the maintenance of normal bone mass through CB2 signaling as CB2R are abundantly expressed in osteoblasts, osteocytes, and osteoclasts [291, 292], and multiple studies have demonstrated that CB2R regulates osteoclast activity and differentiation, bone formation, and bone resorption [293]. Further, a CB2R agonist mitigated bone loss in ovariectomized animals and increased cortical thickness by inhibiting the bone dissolution activity of osteoclasts and by stimulating endocortical bone synthesis.

Shan et al. [294] demonstrated that BCP increased collagen synthesis, alkaline phosphatase activity, osteocalcin secretion, and mineralization of osteoblastic MC3T3-E1 cells. Additionally, BCP pretreatment attenuated antimycin A-induced ROS accumulation and apoptosis, potentially by restoring GSH concentration and catalase activity. Furthermore, BCP treatment increased expression of Nrf2 and HO-1. CB2R was expressed in MC3T3-E1 cells and the actions of BCP on osteocalcin secretion and matrix mineralization were abrogated by CB2R siRNA. The available data indicate that BCP improves bone formation and maintains bone mass by promoting extracellular matrix mineralization via CB2R-dependent mechanisms.

2.13. Rheumatoid arthritis

Rheumatoid arthritis is a common inflammatory autoimmune disorder characterized by synovial hypertrophy and joint damage due to innate and adaptive immune responses [295]. Activation of the inflammatory response is mediated by NF-κB, which drives the expression and secretion of multiple matrix metalloproteinases (MMPs) to augment joint degradation [296].

Corticolimbic endocannabinoid signaling is implicated in the pathogenesis of osteoarthritis, so its modulation could be beneficial for the control of osteoarthritis [297]. BCP has shown analgesic [13] as well as anti-inflammatory and antioxidant activities in arthritic rats [298]. CB2R activation prevents upstream and downstream inflammatory signaling pathways and can relieve the pain associated with inflammatory disorders.

Irrera et al. [63] examined the anti-arthritic efficacy of BCP and the contributions of PPAR-γ in a collagen antibody-induced arthritis (CAIA) model. Administration of BCP reduced disease severity, attenuated the levels of several inflammatory mediator, such as TNF-α, IL-1β, and IL-6, and enhanced expression of the anti-inflammatory cytokine IL-13. Additionally, BCP downregulated matrix metalloproteinases 3 and 9 in joints. The joints of arthritic mice showed enhanced expression levels of COX-2 and NF-κB, and decreased expression levels of PGC-1α and PPAR-γ, changes ameliorated by BCP. Furthermore, BCP upregulated PGC-1α and PPAR-γ in human chondrocytes stimulated with LPS. These protective effects were blocked by AM630, suggesting mediation via activation of CB2R and PPAR-γ. The CB2R dependent pathways contributing to the anti-inflammatory actions of BCP in bone and other tissues are illustrated in Fig. 6.

3. BCP as a nutraceutical

Nutrition is one of the vital elements in promoting healthy ageing and curbing the life style diseases where immune-inflammatory and oxidative changes play major role in disease onset and progression [299–302]. In recent years nutritional supplements gained popularity for their health benefits, protective role and therapeutic potential [303]. Recently, an evolutionary link to food selection and metabolic stress adaptation has been proposed in particular reference to the cannabimimetic phytochemicals in the diet [303]. Food rich in natural modulators of ECS may have potential to favorably modulate CB1/CB2Rs and may attribute a balance action on both receptors [304,305]. Dietary secondary metabolites from edible plants including vegetables and spices able to enhance the activity of CB2R may provide adaptive metabolic advantages and counteract inflammation [304,306,307]. In particular, the foods able to produce CB2R activation may thus play a role in the nutrition transition of Western high-calorie diets [303]. In past few years, the role of cannabimimetic food as a nutraceutical strategy has been proposed potentially useful for possible therapeutic benefits based on evidence-based data and mechanism [308]. It has been speculated that the intake of BCP may plausibly shift the CB1/CB2 receptor activation ratio away from CB1 receptor activation. The role of CB2R in resolving inflammation and pain, relieving stress, boosting immunity and mitigating oxidative stress has been demonstrated [309]. Therefore, the cannabimimetic role of BCP in diets could be beneficial in promoting health and general well-being owing to the potential anti-inflammatory and tissue protective properties [303].

BCP is one of the common ingredients in a large number of dietary plants which are commonly consumed through diets in our-day-to day life [310]. According to an estimate the average per day consumption of BCP through edible plants including vegetables and spices is fewer than ten milligrams [303]. Though, the daily intake of BCP may vary depends upon the dietary cultures and practices involving diet rich in edible plants containing spices and vegetables. It is believed that BCP being one of the common components of the herb based traditional medicines and cuisines of Mediterranean, Indian subcontinent, Middle East and Far East Asian countries has potential to modulate the ECS particularly the CB2R [304,311–313]. BCP has also been reported bioavailable upon oral consumption, considered a lipophilic ingredient and shown effective than their synthetic congeners [314]. It has been showed to be present in many beverages which are consumed as a nutritional supplement and believed to be useful in correcting metabolic dysregulations [315]. Different parts of cannabis with lesser proportions of psychotropic constituents are often used as feed for animals as well as food, beverages including tea and milkshakes for human use [316–318]. Thus, the fruits, florescence, seeds, leaves, oil and plant extract rich in BCP can be used in beverages and foods a useful nutritional or dietary supplement [310]. Considering the popular notion, we are what we eat and eat what we are, BCP rich vegetables and spices consumed in diets could be useful in promotion of healthy ageing and curbing various low grade sustained immune-inflammatory diseases [309,310].

4. "Entourage effect" of BCP with other cannabinoid compounds

In recent years, cannabinoid-cannabinoid or terpenoid-cannabinoid interactions have been believed to exert "entourage effect" which was first described in cannabis by Ben-Shabat and colleagues [319]. The

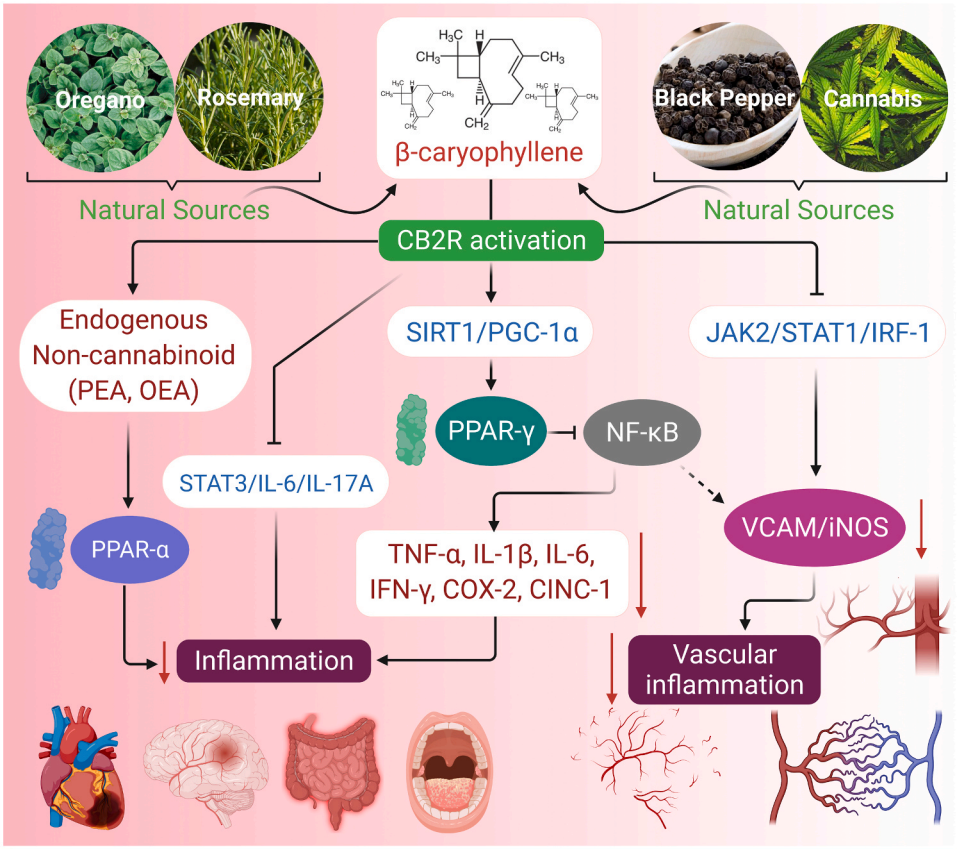

Fig. 6. Cannabinoid type 2 receptor (CB2R)-dependent anti-inflammatory effects of β-caryophyllene (BCP).

"entourage effect", which is presumed to be observed following synergistic interaction between terpenes and cannabinoids are considered to positively contribute to the effect of cannabinoids [319]. As stated earlier that BCP is one of the important constituents in cannabis, the plant which consist of about 600 chemicals including 140 phytocannabinoids (21–22 carbon compounds) and more than hundred mono- and sesqui-terpenes. The terpene constituents are known to play role in respiration, photosynthesis and defense against pests and provide flavor and aroma. In a pioneering review, Russo has proposed a synergy in plant extract over individual phytochemicals owing to the mixture of many phytoconstituents in the extract including cannabinoids, terpenes, flavonoids and that contribute in achieving maximal pharmacological effect [320]. Though the phenomenon of entourage effect has been challenged by some studies showing absence of entourage effects as terpenoids fail to modulate phytocannabinoids signaling or CB1 or CBR in cannabis [321,322]. In another study, terpenes fail to alter radioligand binding but BCP showed to displace [3H]-CP55,940 modestly revealing an agonist action [322]. The plausible effects and reasons still need to be investigated and proved. Furthermore, the entourage effect has been supported by an ancient knowledge originated from use of cannabis in Indian traditions from the time immemorial. BCP provides unique smell to the extract of cannabis and it is often used in training the dogs employed for sniffing cannabinoid compounds for drug abuse purposes [323]. Cannabis (seeds and flowers), which is popularly known as Bhang in India and has been used in food and drink as early as 2000 BC in ancient India. Cannabis beverages commonly known as Bhang Thandai or lassi is consumed as a popular drink on several occasions in India. Another vital ingredient in this cannabis beverage is pepper, which is one of the most common spice in the Indian cuisines. Since ancient time the cocktail of pepper and cannabis are used together. In addition to black pepper, this cannabis beverages preparations also consists of blends of almonds, pumpkin seeds, watermelon seeds, mango, cantaloupe seeds, saffron, cardamom, rose petals and water or milk. BCP has also been identified in cow's milk following a BCP rich fodder [324,325]. The pepper also consists of a constituent, guineensine which has been shown a potent anandamide (AEA) reuptake inhibitor [304,326]. To make this beverage, many components used to enhance taste and aroma, including pepper that is vital to provide a balancing property to the paranoia effect of cannabis. This plausibly explained by the entourage effect of terpenes present in these edible plants and interactions of terpenes with cannabinoids present in the cannabis. The addition of pepper affords a rebalancing approach in high run and calming off the effect of cannabis. Since, the cannabinoids and the cannabis plant seem to be the most current great hope for treating untreatable disorders, the particular phytocannabinoid–terpenoid interactions, the so called "entourage effect" must be continuously examined as it might be due to the involvement of "minor cannabinoids" and cannabis terpenoids to the plant overall pharmacological effects. The entourage effect is reasonably related to be due to receptor or enzyme mediated effect on particular receptors or the enzymes.

5. Concluding remarks

The present review highlights the therapeutic potential of BCP endowed with CB2R agonist properties against myriad of physiological and pathological processes. BCP modulates CB2R signaling suppress inflammation, accelerate fatty acid oxidation, boosts antioxidant capacity, prevents apoptosis and positively modulates metabolic and homeostatic functions among other effects, leading to amelioration of numerous pathological processes. Many preparations rich in BCP along with other phytocannabinoids and terpenoids viz., Bedrocan®, Sativex®, Marinol®, Bedrobinol®, Namisol®, Arvisol®, Fenoxidol™, Epidiolex® etc. got approval for use as drugs or health supplements and found successful against various indications.

BCP natural occurrence, negligible systemic toxicity, dietary bioavailability, and time-tested human consumption makes it a potentially safe and effective food and beverages for promotion of general health and well-being. Further, being non-psychotropic and wide availability in edible plants other than cannabis, BCP is not subjected to any medicolegal and regulatory concerns and can be encouraged for use as nutritional or dietary supplement. Hence, the efficacy and safety of BCP alone as drug candidate should be investigated further for pharmaceutical and nutraceutical applications. We reasonably suggest that BCP could be an alternative or add on agent with the modern synthetic drugs to limit dose related toxicity and provide a synergistic and/or additive effect.

To conclude, BCP with CB2R selective properties is an unique natural molecule of importance for pharmaceutical development and clinical usage with a pharmacological rationale of therapeutics.

CRediT authorship contribution statement

Shreesh Ojha conceptualized the hypotheses. Hebaallah Mamdouh Hashiesh performed literature search and wrote first draft. Niraj Kumar Jha draw the schemes and drafted the artwork. Hebaallah Mamdouh Hashiesh drafted the tables. Charu Sharma, Hebaallah Mamdouh Hashiesh, Bassem Sadek, Niraj Kumar Jha, Juma Al Kaabi and Shreesh Ojha significantly contributed in editing and revisions of the manuscript. All authors read, edited and approved the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2021.111639.

References

[1] A.E. Bonnet, Y. Marchalant, Potential therapeutical contributions of the endocannabinoid system towards aging and Alzheimer's disease, Aging Dis. 6 (5) (2015) 400–405.
[2] H.C. Lu, K. Mackie, An introduction to the endogenous cannabinoid system, Biol. Psychiatry 79 (7) (2016) 516–525.
[3] B. Bie, J. Wu, J.F. Foss, M. Naguib, An overview of the cannabinoid type 2 receptor system and its therapeutic potential, Curr. Opin. Anaesthesiol. 31 (4) (2018) 407–414.
[4] N.D. Volkow, R.D. Baler, W.M. Compton, S.R. Weiss, Adverse health effects of marijuana use, N. Engl. J. Med. 370 (23) (2014) 2219–2227.
[5] L. Deng, J. Guindon, B.L. Cornett, A. Makriyannis, K. Mackie, A.G. Hohmann, Chronic cannabinoid receptor 2 activation reverses paclitaxel neuropathy without tolerance or cannabinoid receptor 1-dependent withdrawal, Biol. Psychiatry 77 (5) (2015) 475–487.
[6] N. Leleu-Chavain, M. Body-Malapel, J. Spencer, P. Chavatte, P. Desreumaux, R. Millet, Recent advances in the development of selective CB(2) agonists as promising anti-inflammatory agents, Curr. Med. Chem. 19 (21) (2012) 3457–3474.
[7] S. Han, J. Thatte, D.J. Buzard, R.M. Jones, Therapeutic utility of cannabinoid receptor type 2 (CB(2)) selective agonists, J. Med. Chem. 56 (21) (2013) 8224–8256.
[8] D. An, S. Peigneur, L.A. Hendrickx, J. Tytgat, Targeting cannabinoid receptors: current status and prospects of natural products, Int. J. Mol. Sci. 21 (14) (2020) 5064.
[9] S. Munro, K.L. Thomas, M. Abu-Shaar, Molecular characterization of a peripheral receptor for cannabinoids, Nature 365 (6441) (1993) 61–65.
[10] S. Galiègue, S. Mary, J. Marchand, D. Dussossoy, D. Carrière, P. Carayon, M. Bouaboula, D. Shire, G. Le Fur, P. Casellas, Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations, Eur. J. Biochem. 232 (1) (1995) 54–61.
[11] Kd.C. Machado, M.T. Islam, E.S. Ali, R. Rouf, S.J. Uddin, S. Dev, J.A. Shilpi, M. C. Shill, H.M. Reza, A.K. Das, S. Shaw, M.S. Mubarak, S.K. Mishra, A.Ad.C. Melo-Cavalcante, A systematic review on the neuroprotective perspectives of beta-caryophyllene, Phytother. Res. (2018) 2376–2388.
[12] J. Gertsch, M. Leonti, S. Raduner, I. Racz, J.-Z. Chen, X.-Q. Xie, K.-H. Altmann, M. Karsak, A. Zimmer, Beta-caryophyllene is a dietary cannabinoid, Proc. Natl. Acad. Sci. 105 (26) (2008) 9099.
[13] K. Fidyt, A. Fiedorowicz, L. Strządała, A. Szumny, β-Caryophyllene and β-caryophyllene oxide-natural compounds of anticancer and analgesic properties, Cancer Med. 5 (10) (2016) 3007–3017.
[14] A.C. Howlett, Cannabinoid receptor signaling. Handbook of Experimental Pharmacology, 2005, pp. 53–79.
[15] A.S. Hauser, M.M. Attwood, M. Rask-Andersen, H.B. Schiöth, D.E. Gloriam, Trends in GPCR drug discovery: new agents, targets and indications, Nat. Rev. Drug Discov. 16 (12) (2017) 829–842.
[16] J. Gertsch, R.G. Pertwee, V. Di Marzo, Phytocannabinoids beyond the cannabis plant – do they exist? Br. J. Pharmacol. 160 (3) (2010) 523–529.
[17] A. Dhopeshwarkar, K. Mackie, CB2 cannabinoid receptors as a therapeutic target-what does the future hold? Mol. Pharmacol. 86 (4) (2014) 430–437.
[18] D.G. Demuth, A. Molleman, Cannabinoid signalling, Life Sci. 78 (6) (2006) 549–563.
[19] M.S. Ibsen, M. Connor, M. Glass, Cannabinoid CB(1) and CB(2) receptor signaling and bias, Cannabis Cannabinoid Res. 2 (1) (2017) 48–60.
[20] B. Horváth, P. Mukhopadhyay, M. Kechrid, V. Patel, G. Tanchian, D.A. Wink, J. Gertsch, P. Pacher, β-Caryophyllene ameliorates cisplatin-induced nephrotoxicity in a cannabinoid 2 receptor-dependent manner, Free Radic. Biol. Med. 52 (8) (2012) 1325–1333.
[21] M.T. Islam, Diterpenes and their derivatives as potential anticancer agents, Phytother. Res. 31 (5) (2017) 691–712.
[22] C. Ghelardini, N. Galeotti, L. Di Cesare Mannelli, G. Mazzanti, A. Bartolini, Local anaesthetic activity of beta-caryophyllene, Farmaco 56 (5–7) (2001) 387–389 (Societa chimica italiana: 1989).
[23] Atta-ur-Rahman, V.U. Ahmad. 13C NMR of Natural Products, Springer, Berlin/Heidelberg, Germany, 1992, pp. 583–584.
[24] I.G. Collado, J.R. Hanson, A.J. Macías-Sánchez, Recent advances in the chemistry of caryophyllene, Nat. Prod. Rep. 15 (2) (1998) 187–204.
[25] H. Shirahama, E. Osawa, T. Matsumoto, Conformational studies on humulene by means of empirical force field calculations. Role of stable conformers of humulene in biosynthetic and chemical reactions, J. Am. Chem. Soc. 102 (9) (1980) 3208–3213.
[26] D. Yang, L. Michel, J.-P. Chaumont, J. Millet-Clerc, Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis, Mycopathologia 148 (2) (2000) 79–82.
[27] S. Sain, P.K. Naoghare, S.S. Devi, A. Daiwile, K. Krishnamurthi, P. Arrigo, T. Chakrabarti, Beta caryophyllene and caryophyllene oxide, isolated from Aegle marmelos, as the potent anti-inflammatory agents against lymphoma and neuroblastoma cells, Anti-inflamm. Anti-Allergy Agents Med. Chem. 13 (1) (2014) 45–55.
[28] S. Di Giacomo, L. Abete, R. Cocchiola, G. Mazzanti, M. Eufemi, A. Di Sotto, Caryophyllane sesquiterpenes inhibit DNA-damage by tobacco smoke in bacterial and mammalian cells, Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 111 (2018) 393–404.
[29] H.-I. Jang, K.-J. Rhee, Y.-B. Eom, Antibacterial and antibiofilm effects of α-humulene against Bacteroides fragilis, Can. J. Microbiol. 66 (6) (2020) 389–399.
[30] M. Ambrož, M. Šmatová, M. Šadibolová, E. Pospíšilová, P. Hadravská, M. Kašparová, V.H. Skarková, V. Králová, L. Skálová, Sesquiterpenes α-humulene and β-caryophyllene oxide enhance the efficacy of 5-fluorouracil and oxaliplatin in colon cancer cells, Acta Pharm. 69 (1) (2019) 121–128 (Zagreb, Croatia).
[31] H. Chen, J. Yuan, J. Hao, Y. Wen, Y. Lv, L. Chen, X. Yang, α-Humulene inhibits hepatocellular carcinoma cell proliferation and induces apoptosis through the inhibition of Akt signaling, Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 134 (2019), 110830.
[32] A. Wanas, M. Radwan, Z. Mehmedic, M. Jacob, I. Khan, M. Elsohly, Antifungal activity of the volatiles of high potency Cannabis sativa L. against Cryptococcus neoformans, Rec. Nat. Prod. 10 (2015) 214–220.
[33] J. Legault, P.A. Côté, S. Ouellet, S. Simard, A. Pichette, Iso-caryophyllene cytotoxicity induced by lipid peroxidation and membrane permeabilization in L-929 cells, J. Appl. Pharm. Sci. 3 (2013) 25–31.
[34] J. Legault, A. Pichette, Potentiating effect of beta-caryophyllene on anticancer activity of alpha-humulene, isocaryophyllene and paclitaxel, J. Pharm. Pharmacol. 59 (12) (2007) 1643–1647.
[35] A. Di Sotto, R. Mancinelli, M. Gullì, M. Eufemi, C.L. Mammola, G. Mazzanti, S. Di, Chemopreventive potential of Caryophyllane sesquiterpenes: an overview of preliminary evidence, Cancers 12 (10) (2020).
[36] K.E. Baser, G. Buchbauer (Eds.), Handbook of Essential Oils, CRC Press, Boca Raton, 2016.
[37] G. Oliveira, K.C. Machado, K.C. Machado, A. da Silva, C.M. Feitosa, F.R. de Castro Almeida, Non-clinical toxicity of β-caryophyllene, a dietary cannabinoid: absence

of adverse effects in female Swiss mice, Regul. Toxicol. Pharmacol. RTP 92 (2018) 338–346.
[38] P. Keov, P.M. Sexton, A. Christopoulos, Allosteric modulation of G protein-coupled receptors: a pharmacological perspective, Neuropharmacology 60 (1) (2011) 24–35.
[39] F.J. Ehlert, Analysis of allosterism in functional assays, J. Pharmacol. Exp. Ther. 315 (2) (2005), 740-54.
[40] L.T. May, V.A. Avlani, P.M. Sexton, A. Christopoulos, Allosteric modulation of G protein-coupled receptors, Curr. Pharm. Des. 10 (17) (2004) 2003–2013.
[41] P.J. Conn, A. Christopoulos, C.W. Lindsley, Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders, Nat. Rev. Drug Discov. 8 (1) (2009) 41–54.
[42] A. Christopoulos, Allosteric binding sites on cell-surface receptors: novel targets for drug discovery, Nat. Rev. Drug Discov. 1 (3) (2002) 198–210.
[43] L.T. May, K. Leach, P.M. Sexton, A. Christopoulos, Allosteric modulation of G protein-coupled receptors, Annu. Rev. Pharmacol. Toxicol. 47 (2007) 1–51.
[44] R. Maheswari, Characterization of allosteric modulators of CB2 receptors as novel therapeutics for inflammatory diseases, Univ. Ark. Med. Sci. (2011) 198.
[45] V. Di Marzo, The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation, Pharmacol. Res. 60 (2) (2009) 77–84.
[46] V. Di Marzo, Endocannabinoids: synthesis and degradation, Rev. Physiol. Biochem. Pharmacol. 160 (2008) 1–24.
[47] R.A. Ross, H.C. Brockie, L.A. Stevenson, V.L. Murphy, F. Templeton, A. Makriyannis, R.G. Pertwee, Agonist-inverse agonist characterization at CB1 and CB2 cannabinoid receptors of L759633, L759656, and AM630, Br. J. Pharmacol. 126 (3) (1999) 665–672.
[48] P. Pandey, K.K. Roy, R.J. Doerksen, Negative allosteric modulators of cannabinoid receptor 2: protein modeling, binding site identification and molecular dynamics simulations in the presence of an orthosteric agonist, J. Biomol. Struct. Dyn. 38 (1) (2020) 32–47.
[49] I.Y. Choi, C. Ju, A.M. Anthony Jalin, D.I. Lee, P.L. Prather, W.K. Kim, Activation of cannabinoid CB2 receptor-mediated AMPK/CREB pathway reduces cerebral ischemic injury, Am. J. Pathol. 182 (3) (2013) 928–939.
[50] H. Javed, S. Azimullah, M.E. Haque, S.K. Ojha, Cannabinoid type 2 (CB2) receptors activation protects against oxidative stress and neuroinflammation associated dopaminergic neurodegeneration in rotenone model of Parkinson's disease, Front. Neurosci. 10 (2016) 321, 321-321.
[51] M.A. Calleja, J.M. Vieites, T. Montero-Meléndez, M.I. Torres, M.J. Faus, A. Gil, A. Suárez, The antioxidant effect of β-caryophyllene protects rat liver from carbon tetrachloride-induced fibrosis by inhibiting hepatic stellate cell activation, Br. J. Nutr. 109 (3) (2013) 394–401.
[52] A.F. Bento, R. Marcon, R.C. Dutra, R.F. Claudino, M. Cola, D.F. Leite, J.B. Calixto, β-Caryophyllene inhibits dextran sulfate sodium-induced colitis in mice through CB2 receptor activation and PPARγ pathway, Am. J. Pathol. 178 (3) (2011) 1153–1166.
[53] S. Al Mansouri, S. Ojha, E. Al Maamari, M. Al Ameri, S.M. Nurulain, A. Bahi, The cannabinoid receptor 2 agonist, β-caryophyllene, reduced voluntary alcohol intake and attenuated ethanol-induced place preference and sensitivity in mice, Pharmacol. Biochem. Behav. 124 (2014) 260–268.
[54] X. Zheng, T. Sun, X. Wang, Activation of type 2 cannabinoid receptors (CB2R) promotes fatty acid oxidation through the SIRT1/PGC-1alpha pathway, Biochem. Biophys. Res. Commun. 436 (3) (2013) 377–381.
[55] C. Wu, Y. Jia, J.H. Lee, H.J. Jun, H.S. Lee, K.Y. Hwang, S.J. Lee, Trans-caryophyllene is a natural agonistic ligand for peroxisome proliferator-activated receptor-α, Bioorg. Med. Chem. Lett. 24 (14) (2014) 3168–3174.
[56] A. Chicca, D. Caprioglio, A. Minassi, V. Petrucci, G. Appendino, O. Taglialatela-Scafati, J. Gertsch, Functionalization of β-caryophyllene generates novel polypharmacology in the endocannabinoid system, ACS Chem. Biol. 9 (7) (2014) 1499–1507.
[57] S.E. O'Sullivan, D.A. Kendall, Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease, Immunobiology 215 (8) (2010) 611–616.
[58] Z. Ament, J.A. West, E. Stanley, T. Ashmore, L.D. Roberts, J. Wright, A. W. Nicholls, J.L. Griffin, PPAR-pan activation induces hepatic oxidative stress and lipidomic remodelling, Free Radic. Biol. Med. 95 (2016) 357–368.
[59] S.E. O'Sullivan, An update on PPAR activation by cannabinoids, Br. J. Pharmacol. 173 (12) (2016) 1899–1910.
[60] V.R. Askari, R. Shafiee-Nick, Promising neuroprotective effects of β-caryophyllene against LPS-induced oligodendrocyte toxicity: a mechanistic study, Biochem. Pharmacol. 159 (2019) 154–171.
[61] N. Irrera, A. D'Ascola, G. Pallio, A. Bitto, F. Mannino, V. Arcoraci, M. Rottura, A. Ieni, L. Minutoli, D. Metro, M. Vaccaro, D. Altavilla, F. Squadrito, β-caryophyllene inhibits cell proliferation through a direct modulation of CB2 receptors in glioblastoma cells, Cancers 12 (4) (2020) 1038 (Basel).
[62] D.A. Youssef, H.M. El-Fayoumi, M.F. Mahmoud, Beta-caryophyllene alleviates diet-induced neurobehavioral changes in rats: the role of CB2 and PPAR-gamma receptors, Biomed. Pharmacother. 110 (2019) 145–154.
[63] N. Irrera, A. D'Ascola, G. Pallio, A. Bitto, E. Mazzon, F. Mannino, V. Squadrito, V. Arcoraci, L. Minutoli, G.M. Campo, A. Avenoso, E.B. Bongiorno, M. Vaccaro, F. Squadrito, D. Altavilla, β-caryophyllene mitigates collagen antibody induced arthritis (CAIA) in mice through a cross-talk between CB2 and PPAR-γ receptors, Biomolecules 9 (8) (2019) 326.
[64] E. D'Aniello, T. Fellous, F.A. Iannotti, A. Gentile, M. Allarà, F. Balestrieri, R. Gray, P. Amodeo, R.M. Vitale, V. Di Marzo, Identification and characterization of phytocannabinoids as novel dual PPARα/γ agonists by a computational and in vitro experimental approach, Biochim. Biophys. Acta Gen. Subj. 1863 (3) (2019) 586–597.
[65] B.F. Grant, R.B. Goldstein, T.D. Saha, S.P. Chou, J. Jung, H. Zhang, R.P. Pickering, W.J. Ruan, S.M. Smith, B. Huang, D.S. Hasin, Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III, JAMA Psychiatry 72 (8) (2015) 757–766.
[66] E.S. Onaivi, H. Ishiguro, J.P. Gong, S. Patel, P.A. Meozzi, L. Myers, A. Perchuk, Z. Mora, P.A. Tagliaferro, E. Gardner, A. Brusco, B.E. Akinshola, Q.R. Liu, S. S. Chirwa, B. Hope, J. Lujilde, T. Inada, S. Iwasaki, D. Macharia, L. Teasenfitz, T. Arinami, G.R. Uhl, Functional expression of brain neuronal CB2 cannabinoid receptors are involved in the effects of drugs of abuse and in depression, Ann. N. Y. Acad. Sci. 1139 (2008) 434–449.
[67] C.S. Breivogel, S.R. Childers, The functional neuroanatomy of brain cannabinoid receptors, Neurobiol. Dis. 5 (6 Pt. B) (1998) 417–431.
[68] B.S. Basavarajappa, The endocannabinoid signaling system: a potential target for next-generation therapeutics for alcoholism, Mini Rev. Med. Chem. 7 (8) (2007) 769–779.
[69] E.S. Onaivi, Cannabinoid receptors in brain: pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications, Int. Rev. Neurobiol. 88 (2009) 335–369.
[70] C.J. Jordan, Z.X. Xi, Discovery and development of varenicline for smoking cessation, Expert Opin. Drug Discov. 13 (7) (2018) 671–683.
[71] C.J. Jordan, Z.X. Xi, Progress in brain cannabinoid CB(2) receptor research: from genes to behavior, Neurosci. Biobehav. Rev. 98 (2019) 208–220.
[72] F. Navarrete, M. Rodríguez-Arias, E. Martín-García, D. Navarro, M.S. García-Gutiérrez, M.A. Aguilar, A. Aracil-Fernández, P. Berbel, J. Miñarro, R. Maldonado, J. Manzanares, Role of CB2 cannabinoid receptors in the rewarding, reinforcing, and physical effects of nicotine, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 38 (12) (2013) 2515–2524.
[73] B.M. Ignatowska-Jankowska, P.P. Muldoon, A.H. Lichtman, M.I. Damaj, The cannabinoid CB2 receptor is necessary for nicotine-conditioned place preference, but not other behavioral effects of nicotine in mice, Psychopharmacology 229 (4) (2013) 591–601.
[74] Y. He, E. Galaj, G.H. Bi, X.F. Wang, E. Gardner, Z.X. Xi, β-Caryophyllene, a dietary terpenoid, inhibits nicotine taking and nicotine seeking in rodents, Br. J. Pharmacol. 177 (9) (2020) 2058–2072.
[75] L.I. Paula-Freire, M.L. Andersen, V.S. Gama, G.R. Molska, E.L. Carlini, The oral administration of trans-caryophyllene attenuates acute and chronic pain in mice, Phytomed. Int. J. Phytother. Phytopharmacol. 21 (3) (2014) 356–362.
[76] D. Krause, M. Warnecke, C.G. Schuetz, M. Soyka, K.M. Manz, L. Proebstl, F. Kamp, A.I. Chrobok, O. Pogarell, G. Koller, The impact of the opioid antagonist naloxone on experimentally induced craving in nicotine-dependent individuals, Eur. Addict. Res. 24 (5) (2018) 255–265.
[77] J. Fu, S. Gaetani, F. Oveisi, J. Lo Verme, A. Serrano, F. Rodríguez De Fonseca, A. Rosengarth, H. Luecke, B. Di Giacomo, G. Tarzia, D. Piomelli, Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha, Nature 425 (6953) (2003) 90–93.
[78] E. Galaj, G.-H. Bi, A. Moore, K. Chen, Y. He, E. Gardner, Z.-X. Xi, Beta-caryophyllene inhibits cocaine addiction-related behavior by activation of PPARα and PPARγ: repurposing a FDA-approved food additive for cocaine use disorder, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 46 (4) (2021) 860–870.
[79] H.-N. Choi, S.-M. Jeong, G.H. Huh, J.-I. Kim, Quercetin ameliorates insulin sensitivity and liver steatosis partly by increasing adiponectin expression in ob/ob mice, Food Sci. Biotechnol. 24 (1) (2015) 273–279.
[80] G. Kaur, Amelioration of obesity, glucose intolerance, and oxidative stress in high-fat diet and low-dose streptozotocin-induced diabetic rats by combination consisting of "curcumin with piperine and quercetin", ISRN Pharmacol. 2012 (2012), 957283.
[81] G. Gruden, F. Barutta, G. Kunos, P. Pacher, Role of the endocannabinoid system in diabetes and diabetic complications, Br. J. Pharmacol. 173 (7) (2016) 1116–1127.
[82] P. Juan-Picó, E. Fuentes, F.J. Bermúdez-Silva, F. Javier Díaz-Molina, C. Ripoll, F. Rodríguez de Fonseca, A. Nadal, Cannabinoid receptors regulate Ca(2+) signals and insulin secretion in pancreatic beta-cell, Cell Calcium 39 (2) (2006) 155–162.
[83] B. Horváth, L. Magid, P. Mukhopadhyay, S. Bátkai, M. Rajesh, O. Park, G. Tanchian, R.Y. Gao, C.E. Goodfellow, M. Glass, R. Mechoulam, P. Pacher, A new cannabinoid CB2 receptor agonist HU-910 attenuates oxidative stress, inflammation and cell death associated with hepatic ischaemia/reperfusion injury, Br. J. Pharmacol. 165 (8) (2012) 2462–2478.
[84] W. Suijun, Y. Zhen, G. Ying, W. Yanfang, A role for trans-caryophyllene in the moderation of insulin secretion, Biochem. Biophys. Res. Commun. 444 (4) (2014) 451–454.
[85] A. Kowluru, Small G proteins in islet beta-cell function, Endocr. Rev. 31 (1) (2010) 52–78.
[86] B. Jayaram, I. Syed, C.N. Kyathanahalli, C.J. Rhodes, A. Kowluru, Arf nucleotide binding site opener [ARNO] promotes sequential activation of Arf6, Cdc42 and Rac1 and insulin secretion in INS 832/13 β-cells and rat islets, Biochem. Pharmacol. 81 (8) (2011) 1016–1027.
[87] Q.-Y. Huang, X.-N. Lai, X.-L. Qian, L.-C. Lv, J. Li, J. Duan, X.-H. Xiao, L.-X. Xiong, Cdc42: a novel regulator of insulin secretion and diabetes-associated diseases, Int. J. Mol. Sci. 20 (1) (2019) 179.
[88] S. Nozaki, S. Ueda, N. Takenaka, T. Kataoka, T. Satoh, Role of RalA downstream of Rac1 in insulin-dependent glucose uptake in muscle cells, Cell. Signal. 24 (11) (2012) 2111–2117.

[89] J. Hirosumi, G. Tuncman, L. Chang, C.Z. Gorgun, K.T. Uysal, K. Maeda, M. Karin, G.S. Hotamisligil, A central role for JNK in obesity and insulin resistance, Nature 420 (6913) (2002) 333–336.

[90] V.T. Samuel, G.I. Shulman, The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux, J. Clin. Investig. 126 (1) (2016) 12–22.

[91] G. Priya, S. Kalra, A review of insulin resistance in type 1 diabetes: is there a place for adjunctive metformin? Diabetes Ther. 9 (1) (2018) 349–361.

[92] I. Briaud, J.S. Harmon, C.L. Kelpe, V.B. Segu, V. Poitout, Lipotoxicity of the pancreatic beta-cell is associated with glucose-dependent esterification of fatty acids into neutral lipids, Diabetes 50 (2) (2001) 315–321.

[93] Y. Lee, H. Hirose, M. Ohneda, J.H. Johnson, J.D. McGarry, R.H. Unger, Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships, Proc. Natl. Acad. Sci. USA 91 (23) (1994) 10878–10882.

[94] L.I. Rachek, Free fatty acids and skeletal muscle insulin resistance, Prog. Mol. Biol. Transl. Sci. 121 (2014) 267–292.

[95] V.N. Subramaniam, A.R. Menezes, A. DeSchutter, C.J. Lavie, The cardiovascular effects of marijuana: are the potential adverse effects worth the high? Mol. Med. 116 (2) (2019) 146–153.

[96] G. Boden, G.I. Shulman, Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction, Eur. J. Clin. Investig. 32 (Suppl. 3) (2002) S14–S23.

[97] S.R. Pyper, N. Viswakarma, S. Yu, J.K. Reddy, PPARalpha: energy combustion, hypolipidemia, inflammation and cancer, Nucl. Recept. Signal. 8 (2010) 002.

[98] Z. Gerhart-Hines, J.E. Dominy Jr., S.M. Blattler, M.P. Jedrychowski, A.S. Banks, J. H. Lim, H. Chim, S.P. Gygi, P. Puigserver, The cAMP/PKA pathway rapidly activates SIRT1 to promote fatty acid oxidation independently of changes in NAD (+), Mol. Cell 44 (6) (2011) 851–863.

[99] F. Geddo, S. Antoniotti, G. Querio, I.C. Salaroglio, C. Costamagna, C. Riganti, M. P. Gallo, Plant-derived trans-β-caryophyllene boosts glucose metabolism and ATP synthesis in skeletal muscle cells through cannabinoid type 2 receptor stimulation, Nutrients 13 (3) (2021).

[100] S.J. Bensinger, P. Tontonoz, Integration of metabolism and inflammation by lipid-activated nuclear receptors, Nature 454 (7203) (2008) 470–477.

[101] A.C. Li, C.J. Binder, A. Gutierrez, K.K. Brown, C.R. Plotkin, J.W. Pattison, A. F. Valledor, R.A. Davis, T.M. Willson, J.L. Witztum, W. Palinski, C.K. Glass, Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPARalpha, beta/delta, and gamma, J. Clin. Investig. 114 (11) (2004) 1564–1576.

[102] P. Escher, W. Wahli, Peroxisome proliferator-activated receptors: insight into multiple cellular functions, Mutat. Res. 448 (2) (2000) 121–138.

[103] D.A. Youssef, H.M. El-Fayoumi, M.F. Mahmoud, Beta-caryophyllene protects against diet-induced dyslipidemia and vascular inflammation in rats: involvement of CB2 and PPAR-gamma receptors, Chem. Biol. Interact. 297 (2019) 16–24.

[104] C.D. Wrann, J.P. White, J. Salogiannnis, D. Laznik-Bogoslavski, J. Wu, D. Ma, J. D. Lin, M.E. Greenberg, B.M. Spiegelman, Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway, Cell Metab. 18 (5) (2013) 649–659.

[105] A.I. Basbaum, D.M. Bautista, G. Scherrer, D. Julius, Cellular and molecular mechanisms of pain, Cell 139 (2) (2009) 267–284.

[106] M. Costigan, J. Scholz, C.J. Woolf, Neuropathic pain: a maladaptive response of the nervous system to damage, Annu. Rev. Neurosci. 32 (2009) 1–32.

[107] J. Giordano, The neurobiology of nociceptive and anti-nociceptive systems, Pain Physician 8 (3) (2005) 277–290.

[108] B. Costa, D. Siniscalco, A.E. Trovato, F. Comelli, M.L. Sotgiu, M. Colleoni, S. Maione, F. Rossi, G. Giagnoni, AM404, an inhibitor of anandamide uptake, prevents pain behaviour and modulates cytokine and apoptotic pathways in a rat model of neuropathic pain, Br. J. Pharmacol. 148 (7) (2006) 1022–1032.

[109] M.D. Jhaveri, S.J.R. Elmes, D. Richardson, D.A. Barrett, D.A. Kendall, R. Mason, V. Chapman, Evidence for a novel functional role of cannabinoid CB(2) receptors in the thalamus of neuropathic rats, Eur. J. Neurosci. 27 (7) (2008) 1722–1730.

[110] A. Dyson, M. Peacock, A. Chen, J.-P. Courade, M. Yaqoob, A. Groarke, C. Brain, Y. Loong, A. Fox, Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat, Pain 116 (1–2) (2005) 129–137.

[111] M. Beltramo, The cannabinoid system and pain: towards new drugs? J. Soc. Biol. 203 (1) (2009) 99–106.

[112] J. Guindon, A.G. Hohmann, Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain, Br. J. Pharmacol. 153 (2) (2008) 319–334.

[113] J.J. Xu, P. Diaz, F. Astruc-Diaz, S. Craig, E. Munoz, M. Naguib, Pharmacological characterization of a novel cannabinoid ligand, MDA19, for treatment of neuropathic pain, Anesth. Analg. 111 (1) (2010) 99–109.

[114] B.K. Atwood, K. Mackie, CB2: a cannabinoid receptor with an identity crisis, Br. J. Pharmacol. 160 (3) (2010) 467–479.

[115] M.M. Ibrahim, M.L. Rude, N.J. Stagg, H.P. Mata, J. Lai, T.W. Vanderah, F. Porreca, N.E. Buckley, A. Makriyannis, T.P. Malan Jr., CB2 cannabinoid receptor mediation of antinociception, Pain 122 (1–2) (2006) 36–42.

[116] G.C. Hsieh, M. Pai, P. Chandran, B.A. Hooker, C.Z. Zhu, A.K. Salyers, E. J. Wensink, C. Zhan, W.A. Carroll, M.J. Dart, B.B. Yao, P. Honore, M.D. Meyer, Central and peripheral sites of action for CB_2 receptor mediated analgesic activity in chronic inflammatory and neuropathic pain models in rats, Br. J. Pharmacol. 162 (2) (2011) 428–440.

[117] M.M. Ibrahim, F. Porreca, J. Lai, P.J. Albrecht, F.L. Rice, A. Khodorova, G. Davar, A. Makriyannis, T.W. Vanderah, H.P. Mata, T.P. Malan, CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids, Proc. Natl. Acad. Sci. USA 102 (8) (2005) 3093–3098.

[118] U. Anand, W.R. Otto, D. Sanchez-Herrera, P. Facer, Y. Yiangou, Y. Korchev, R. Birch, C. Benham, C. Bountra, I.P. Chessell, P. Anand, Cannabinoid receptor CB2 localisation and agonist-mediated inhibition of capsaicin responses in human sensory neurons, Pain 138 (3) (2008) 667–680.

[119] W. Yamamoto, T. Mikami, H. Iwamura, Involvement of central cannabinoid CB2 receptor in reducing mechanical allodynia in a mouse model of neuropathic pain, Eur. J. Pharmacol. 583 (1) (2008) 56–61.

[120] P.W. Brownjohn, J.C. Ashton, Spinal cannabinoid CB2 receptors as a target for neuropathic pain: an investigation using chronic constriction injury, Neuroscience 203 (2012) 180–193.

[121] A.L. Klauke, I. Racz, B. Pradier, A. Markert, A.M. Zimmer, J. Gertsch, A. Zimmer, The cannabinoid CB_2 receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain, Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 24 (4) (2014) 608–620.

[122] J. Scholz, C.J. Woolf, The neuropathic pain triad: neurons, immune cells and glia, Nat. Neurosci. 10 (11) (2007) 1361–1368.

[123] F.Y. Tanga, V. Raghavendra, J.A. DeLeo, Quantitative real-time RT-PCR assessment of spinal microglial and astrocytic activation markers in a rat model of neuropathic pain, Neurochem. Int. 45 (2–3) (2004) 397–407.

[124] H. Kuwahata, S. Katsuyama, T. Komatsu, H. Nakamura, M. Corasaniti, G. Bagetta, S. Sakurada, T. Sakurada, K. Takahama, Local peripheral effects of β-caryophyllene through CB2 receptors in neuropathic pain in mice, Pharmacol. Pharm. 3 (4) (2012), 397-40.

[125] Z. Seltzer, R. Dubner, Y. Shir, A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury, Pain 43 (2) (1990) 205–218.

[126] R. Baron, R. Baron, Mechanisms of disease: neuropathic pain—a clinical perspective, Nat. Clin. Pract. Neurol. 2 (2006) 95–106.

[127] S. Katsuyama, H. Mizoguchi, H. Kuwahata, T. Komatsu, K. Nagaoka, H. Nakamura, G. Bagetta, T. Sakurada, S. Sakurada, Involvement of peripheral cannabinoid and opioid receptors in β-caryophyllene-induced antinociception, Eur. J. Pain 17 (5) (2013) 664–675.

[128] T. Sakurada, H. Yogo, K. Katsumata, K. Tan-No, S. Sakurada, K. Kisara, M. Ohba, Differential antinociceptive effects of sendide, a NK1-receptor antagonist, and morphine in the capsaicin test, Brain Res. 649 (1) (1994) 319–322.

[129] L.S. Sorkin, D.J. McAdoo, Amino acids and serotonin are released into the lumbar spinal cord of the anesthetized cat following intradermal capsaicin injections, Brain Res. 607 (1–2) (1993) 89–98.

[130] R. Gamse, A. Molnar, F. Lembeck, Substance P release from spinal cord slices by capsaicin, Life Sci. 25 (7) (1979) 629–636.

[131] E. Aly, M.A. Khajah, W. Masocha, β-Caryophyllene, a CB2-receptor-selective phytocannabinoid, suppresses mechanical allodynia in a mouse model of antiretroviral-induced neuropathic pain, Molecules 25 (1) (2019) 106.

[132] R.R. Ji, M.R. Suter, p38 MAPK, microglial signaling, and neuropathic pain, Mol. Pain 3 (2007) 33.

[133] T. Maruta, T. Nemoto, K. Hidaka, T. Koshida, T. Shirasaka, T. Yanagita, R. Takeya, I. Tsuneyoshi, Upregulation of ERK phosphorylation in rat dorsal root ganglion neurons contributes to oxaliplatin-induced chronic neuropathic pain, PLoS One 14 (11) (2019), 0225586.

[134] A. Gisterå, G.K. Hansson, The immunology of atherosclerosis, Nat. Rev. Nephrol. 13 (6) (2017) 368–380.

[135] J.F. de Boer, M. Schonewille, A. Dikkers, M. Koehorst, R. Havinga, F. Kuipers, U. J. Tietge, A.K. Groen, Transintestinal and biliary cholesterol secretion both contribute to macrophage reverse cholesterol transport in rats-brief report, Arterioscler. Thromb. Vasc. Biol. 37 (4) (2017) 643–646.

[136] G. Haraldsen, D. Kvale, B. Lien, I.N. Farstad, P. Brandtzaeg, Cytokine-regulated expression of E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in human microvascular endothelial cells, J. Immunol. 156 (7) (1996) 2558–2565 (Baltim., Md.: 1950).

[137] M. Steffens, J. Zentner, J. Honegger, T.J. Feuerstein, Binding affinity and agonist activity of putative endogenous cannabinoids at the human neocortical CB1 receptor, Biochem. Pharmacol. 69 (1) (2005) 169–178.

[138] C.D. Netherland, T.G. Pickle, A. Bales, D.P. Thewke, Cannabinoid receptor type 2 (CB2) deficiency alters atherosclerotic lesion formation in hyperlipidemic Ldlr-null mice, Atherosclerosis 213 (1) (2010) 102–108.

[139] Z. Zhang, C. Yang, X. Dai, Y. Ao, Y. Li, Inhibitory effect of trans-caryophyllene (TC) on leukocyte-endothelial attachment, Toxicol. Appl. Pharmacol. 329 (2017) 326–333.

[140] L. Dou, H.F. Liang, D.A. Geller, Y.F. Chen, X.P. Chen, The regulation role of interferon regulatory factor-1 gene and clinical relevance, Hum. Immunol. 75 (11) (2014) 1110–1114.

[141] J.M. Warfel, F. D'Agnillo, Anthrax lethal toxin enhances TNF-induced endothelial VCAM-1 expression via an IFN regulatory factor-1-dependent mechanism, J. Immunol. 180 (11) (2008) 7516–7524 (Baltim., Md.: 1950).

[142] C. Adamson, O.O. Kanu, A.I. Mehta, C. Di, N. Lin, A.K. Mattox, D.D. Bigner, Glioblastoma multiforme: a review of where we have been and where we are going, Expert Opin. Investig. Drugs 18 (8) (2009) 1061–1083.

[143] M.N. Abbas, S. Kausar, H. Cui, Therapeutic potential of natural products in glioblastoma treatment: targeting key glioblastoma signaling pathways and epigenetic alterations, Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex. 22 (7) (2020) 963–977.

[144] Y.T. Yeung, K.L. McDonald, T. Grewal, L. Munoz, Interleukins in glioblastoma pathophysiology: implications for therapy, Br. J. Pharmacol. 168 (3) (2013) 591–606.

[145] A. Ellert-Miklaszewska, I. Ciechomska, B. Kaminska, Cannabinoid signaling in glioma cells, Adv. Exp. Med. Biol. 986 (2013) 209–220.
[146] C.A. Dumitru, I.E. Sandalcioglu, M. Karsak, Cannabinoids in glioblastoma therapy: new applications for old drugs, Front. Mol. Neurosci. 11 (2018) 159, 159-159.
[147] R. Singh, A.M. Cuervo, Autophagy in the cellular energetic balance, Cell Metab. 13 (5) (2011) 495–504.
[148] M. Pistis, S.E. O'Sullivan, The role of nuclear hormone receptors in cannabinoid function, Adv. Pharmacol. 80 (2017) 291–328 (San. Diego, Calif.).
[149] A.S. Jaggi, N. Singh, Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy, Toxicology 291 (1–3) (2012) 1–9.
[150] M. Pevida, A. Lastra, A. Hidalgo, A. Baamonde, L. Menéndez, Spinal CCL2 and microglial activation are involved in paclitaxel-evoked cold hyperalgesia, Brain Res. Bull. 95 (2013) 21–27.
[151] J. Ruiz-Medina, A. Baulies, S.A. Bura, O. Valverde, Paclitaxel-induced neuropathic pain is age dependent and devolves on glial response, Eur. J. Pain 17 (1) (2013) 75–85.
[152] H. Zhang, J.A. Boyette-Davis, A.K. Kosturakis, Y. Li, S.Y. Yoon, E.T. Walters, P. M. Dougherty, Induction of monocyte chemoattractant protein-1 (MCP-1) and its receptor CCR2 in primary sensory neurons contributes to paclitaxel-induced peripheral neuropathy, J. Pain Off. J. Am. Pain Soc. 14 (10) (2013) 1031–1044.
[153] P.G. Fine, M.J. Rosenfeld, The endocannabinoid system, cannabinoids, and pain, Rambam Maimonides Med. J. 4 (4) (2013) 0022.
[154] E. Burgos, D. Gómez-Nicola, D. Pascual, M.I. Martín, M. Nieto-Sampedro, C. Goicoechea, Cannabinoid agonist WIN 55,212-2 prevents the development of paclitaxel-induced peripheral neuropathy in rats. Possible involvement of spinal glial cells, Eur. J. Pharmacol. 682 (1–3) (2012) 62–72.
[155] G. Vera, P.A. Cabezos, M.I. Martín, R. Abalo, Characterization of cannabinoid-induced relief of neuropathic pain in a rat model of cisplatin-induced neuropathy, Pharmacol. Biochem. Behav. 105 (2013) 205–212.
[156] G.C. Segat, M.N. Manjavachi, D.O. Matias, G.F. Passos, C.S. Freitas, R. Costa, J. B. Calixto, Antiallodynic effect of β-caryophyllene on paclitaxel-induced peripheral neuropathy in mice, Neuropharmacology 125 (2017) 207–219.
[157] C.C. Reyes-Gibby, J. Wang, S.J. Yeung, S. Shete, Informative gene network for chemotherapy-induced peripheral neuropathy, BioData Min. 8 (2015) 24.
[158] E. Niederberger, G. Geisslinger, The IKK-NF-kappaB pathway: a source for novel molecular drug targets in pain therapy? FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 22 (10) (2008) 3432–3442.
[159] Y. Kawasaki, L. Zhang, J.K. Cheng, R.R. Ji, Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord, J. Neurosci. 28 (20) (2008) 5189–5194.
[160] R.R. Ji, R.Wt Gereau, M. Malcangio, G.R. Strichartz, MAP kinase and pain, Brain Res. Rev. 60 (1) (2009) 135–148.
[161] G. Minotti, P. Menna, E. Salvatorelli, G. Cairo, L. Gianni, Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity, Pharmacol. Rev. 56 (2) (2004) 185–229.
[162] M. Linschoten, A.J. Teske, M.J. Cramer, E. van der Wall, F.W. Asselbergs, Chemotherapy-related cardiac dysfunction: a systematic review of genetic variants modulating individual risk, Circ. Genom. Precis. Med. 11 (1) (2018), 001753.
[163] S. Bátkai, P. Pacher, Endocannabinoids and cardiac contractile function: pathophysiological implications, Pharmacol. Res. 60 (2) (2009) 99–106.
[164] M. Rajesh, P. Mukhopadhyay, S. Bátkai, G. Haskó, L. Liaudet, J.W. Huffman, A. Csiszar, Z. Ungvari, K. Mackie, S. Chatterjee, P. Pacher, CB2-receptor stimulation attenuates TNF-alpha-induced human endothelial cell activation, transendothelial migration of monocytes, and monocyte-endothelial adhesion, Am. J. Physiol. Heart Circ. Physiol. 293 (4) (2007) H2210–H2218.
[165] P. Pacher, S. Bátkai, G. Kunos, The endocannabinoid system as an emerging target of pharmacotherapy, Pharmacol. Rev. 58 (3) (2006) 389–462.
[166] M.F.N. Meeran, H. Al Taee, S. Azimullah, S. Tariq, E. Adeghate, S. Ojha, β-caryophyllene, a natural bicyclic sesquiterpene attenuates doxorubicin-induced chronic cardiotoxicity via activation of myocardial cannabinoid type-2 (CB(2)) receptors in rats, Chem. Biol. Interact. 304 (2019) 158–167.
[167] N. Pabla, Z. Dong, Cisplatin nephrotoxicity: mechanisms and renoprotective strategies, Kidney Int. 73 (9) (2008) 994–1007.
[168] H. Pan, P. Mukhopadhyay, M. Rajesh, V. Patel, B. Mukhopadhyay, B. Gao, G. Haskó, P. Pacher, Cannabidiol attenuates cisplatin-induced nephrotoxicity by decreasing oxidative/nitrosative stress, inflammation, and cell death, J. Pharmacol. Exp. Ther. 328 (3) (2009) 708–714.
[169] P. Mukhopadhyay, B. Horváth, Z. Zsengellér, J. Zielonka, G. Tanchian, E. Holovac, M. Kechrid, V. Patel, I.E. Stillman, S.M. Parikh, J. Joseph, B. Kalyanaraman, P. Pacher, Mitochondrial-targeted antioxidants represent a promising approach for prevention of cisplatin-induced nephropathy, Free Radic. Biol. Med. 52 (2) (2012) 497–506.
[170] F. Barutta, F. Piscitelli, S. Pinach, G. Bruno, R. Gambino, M.P. Rastaldi, G. Salvidio, V. Di Marzo, P. Cavallo Perin, G. Gruden, Protective role of cannabinoid receptor type 2 in a mouse model of diabetic nephropathy, Diabetes 60 (9) (2011) 2386–2396.
[171] K.A. Jenkin, A.J. McAinch, E. Grinfeld, D.H. Hryciw, Role for cannabinoid receptors in human proximal tubular hypertrophy, Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol. 26 (6) (2010) 879–886.
[172] C. Zoja, M. Locatelli, D. Corna, S. Villa, D. Rottoli, V. Nava, R. Verde, F. Piscitelli, V. Di Marzo, J. Fingerle, J.M. Adam, B. Rothenhaeusler, G. Ottaviani, A. Bénardeau, M. Abbate, G. Remuzzi, A. Benigni, Therapy with a selective cannabinoid receptor type 2 agonist limits albuminuria and renal injury in mice with type 2 diabetic nephropathy, Nephron 132 (1) (2016) 59–69.
[173] K.A. Jenkin, L. O'Keefe, A.C. Simcocks, J.F. Briffa, M.L. Mathai, A.J. McAinch, D. H. Hryciw, Renal effects of chronic pharmacological manipulation of CB2 receptors in rats with diet-induced obesity, Br. J. Pharmacol. 173 (7) (2016) 1128–1142.
[174] C. Szabó, H. Ischiropoulos, R. Radi, Peroxynitrite: biochemistry, pathophysiology and development of therapeutics, Nat. Rev. Drug Discov. 6 (8) (2007) 662–680.
[175] L.S. Elting, D.M. Keefe, S.T. Sonis, A.S. Garden, F.K. Spijkervet, A. Barasch, R. B. Tishler, T.P. Canty, M.K. Kudrimoti, M. Vera-Llonch, Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life, Cancer 113 (10) (2008) 2704–2713.
[176] G. Picciolo, G. Pallio, D. Altavilla, M. Vaccaro, G. Oteri, N. Irrera, F. Squadrito, β-caryophyllene reduces the inflammatory phenotype of periodontal cells by targeting CB2 receptors, Biomedicines 8 (6) (2020) 164.
[177] A. Hernández-Caldera, R. Vernal, R. Paredes, P. Veloso-Matta, J. Astorga, M. Hernández, Human periodontal ligament fibroblasts synthesize C-reactive protein and Th-related cytokines in response to interleukin (IL)-6 trans-signalling, Int. Endod. J. 51 (6) (2018) 632–640.
[178] U. Bharadwaj, M.M. Kasembeli, P. Robinson, D.J. Tweardy, Targeting Janus kinases and signal transducer and activator of transcription 3 to treat inflammation, fibrosis, and cancer: rationale, progress, and caution, Pharmacol. Rev. 72 (2) (2020) 486–526.
[179] M.A. McGuckin, R. Eri, L.A. Simms, T.H. Florin, G. Radford-Smith, Intestinal barrier dysfunction in inflammatory bowel diseases, Inflamm. Bowel Dis. 15 (1) (2009) 100–113.
[180] S. Cuzzocrea, Emerging biotherapies for inflammatory bowel disease, Expert Opin. Emerg. Drugs 8 (2) (2003) 339–347.
[181] G. D'Argenio, M. Valenti, G. Scaglione, V. Cosenza, I. Sorrentini, V. Di Marzo, Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 20 (3) (2006) 568–570.
[182] M.A. Engel, C.A. Kellermann, G. Burnat, E.G. Hahn, T. Rau, P.C. Konturek, Mice lacking cannabinoid CB1-, CB2-receptors or both receptors show increased susceptibility to trinitrobenzene sulfonic acid (TNBS)-induced colitis, J. Physiol. Pharmacol. Off. J. Pol. Physiol. Soc. 61 (1) (2010) 89–97.
[183] K. Maresz, G. Pryce, E.D. Ponomarev, G. Marsicano, J.L. Croxford, L.P. Shriver, C. Ledent, X. Cheng, E.J. Carrier, M.K. Mann, G. Giovannoni, R.G. Pertwee, T. Yamamura, N.E. Buckley, C.J. Hillard, B. Lutz, D. Baker, B.N. Dittel, Direct suppression of CNS autoimmune inflammation via the cannabinoid receptor CB1 on neurons and CB2 on autoreactive T cells, Nat. Med. 13 (4) (2007) 492–497.
[184] J. Liu, H. Li, S.H. Burstein, R.B. Zurier, J.D. Chen, Activation and binding of peroxisome proliferator-activated receptor gamma by synthetic cannabinoid ajulemic acid, Mol. Pharmacol. 63 (5) (2003) 983–992.
[185] S.E. O'Sullivan, E.J. Tarling, A.J. Bennett, D.A. Kendall, M.D. Randall, Novel time-dependent vascular actions of delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma, Biochem. Biophys. Res. Commun. 337 (3) (2005) 824–831.
[186] J.N. Barker, M.L. Jones, C.L. Swenson, V. Sarma, R.S. Mitra, P.A. Ward, K. J. Johnson, J.C. Fantone, V.M. Dixit, B.J. Nickoloff, Monocyte chemotaxis and activating factor production by keratinocytes in response to IFN-gamma, J. Immunol. 146 (4) (1991) 1192–1197 (Baltimore, Md.: 1950).
[187] A.F. Bento, D.F. Leite, R.F. Claudino, D.B. Hara, P.C. Leal, J.B. Calixto, The selective nonpeptide CXCR2 antagonist SB225002 ameliorates acute experimental colitis in mice, J. Leukoc. Biol. 84 (4) (2008) 1213–1221.
[188] C.E. Vitor, C.P. Figueiredo, D.B. Hara, A.F. Bento, T.L. Mazzuco, J.B. Calixto, Therapeutic action and underlying mechanisms of a combination of two pentacyclic triterpenes, alpha- and beta-amyrin, in a mouse model of colitis, Br. J. Pharmacol. 157 (6) (2009) 1034–1044.
[189] B. Egger, M. Bajaj-Elliott, T.T. MacDonald, R. Inglin, V.E. Eysselein, M. W. Büchler, Characterisation of acute murine dextran sodium sulphate colitis: cytokine profile and dose dependency, Digestion 62 (4) (2000) 240–248.
[190] L. Steinman, Assessment of animal models for MS and demyelinating disease in the design of rational therapy, Neuron 24 (3) (1999) 511–514.
[191] O. Haugh, J. Penman, A.J. Irving, V.A. Campbell, The emerging role of the cannabinoid receptor family in peripheral and neuro-immune interactions, Curr. Drug Targets 17 (16) (2016) 1834–1840.
[192] V. Katchan, P. David, Y. Shoenfeld, Cannabinoids and autoimmune diseases: a systematic review, Autoimmun. Rev. 15 (6) (2016) 513–528.
[193] R. Kaur, S.R. Ambwani, S. Singh, Endocannabinoid system: a multi-facet therapeutic target, Curr. Clin. Pharmacol. 11 (2) (2016) 110–117.
[194] J. Ehrhart, D. Obregon, T. Mori, H. Hou, N. Sun, Y. Bai, T. Klein, F. Fernandez, J. Tan, R.D. Shytle, Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation, J. Neuroinflamm. 2 (2005) 29.
[195] N.E. Buckley, K.L. McCoy, E. Mezey, T. Bonner, A. Zimmer, C.C. Felder, M. Glass, A. Zimmer, Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB(2) receptor, Eur. J. Pharmacol. 396 (2–3) (2000) 141–149.
[196] W.G. Notcutt, Clinical use of cannabinoids for symptom control in multiple sclerosis, Neurother. J. Am. Soc. Exp. Neurother. 12 (4) (2015) 769–777.
[197] T.B. Alberti, W.L. Barbosa, J.L. Vieira, N.R. Raposo, R.C. Dutra, (-)-β-Caryophyllene, a CB2 receptor-selective phytocannabinoid, suppresses motor paralysis and neuroinflammation in a murine model of multiple sclerosis, Int. J. Mol. Sci. 18 (4) (2017).

[198] L.E. Harrington, R.D. Hatton, P.R. Mangan, H. Turner, T.L. Murphy, K.M. Murphy, C.T. Weaver, Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages, Nat. Immunol. 6 (11) (2005) 1123–1132.
[199] G. Pasqualetti, D.J. Brooks, P. Edison, The role of neuroinflammation in dementias, Curr. Neurol. Neurosci. Rep. 15 (4) (2015) 17.
[200] F.O. Martinez, S. Gordon, The M1 and M2 paradigm of macrophage activation: time for reassessment, F1000Prime Rep. 6 (2014), 13-13.
[201] S. Sugama, T. Takenouchi, B.P. Cho, T.H. Joh, M. Hashimoto, H. Kitani, Possible roles of microglial cells for neurotoxicity in clinical neurodegenerative diseases and experimental animal models, Inflamm. Allergy Drug Targets 8 (4) (2009) 277–284.
[202] L. Peferoen, M. Kipp, P. van der Valk, J.M. van Noort, S. Amor, Oligodendrocyte-microglia cross-talk in the central nervous system, Immunology 141 (3) (2014) 302–313.
[203] J.W. Prineas, J.D. Parratt, Oligodendrocytes and the early multiple sclerosis lesion, Ann. Neurol. 72 (1) (2012) 18–31.
[204] L. Lin, T. Yihao, F. Zhou, N. Yin, T. Qiang, Z. Haowen, C. Qianwei, T. Jun, Z. Yuan, Z. Gang, F. Hua, Y. Yunfeng, C. Zhi, Inflammatory regulation by driving microglial M2 polarization: neuroprotective effects of cannabinoid receptor-2 activation in intracerebral hemorrhage, Front. Immunol. 8 (2017), 112-112.
[205] V. Chiurchiù, A. Leuti, M. Maccarrone, Cannabinoid signaling and neuroinflammatory diseases: a melting pot for the regulation of brain immune responses, J. NeuroImmune Pharmacol. Off. J. Soc. NeuroImmune Pharmacol. 10 (2) (2015) 268–280.
[206] N. Barrie, N. Manolios, The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease, Eur. J. Rheumatol. 4 (3) (2017) 210–218.
[207] S.F. Lisboa, F.V. Gomes, F.S. Guimaraes, A.C. Campos, Microglial cells as a link between cannabinoids and the immune hypothesis of psychiatric disorders, Front. Neurol. 7 (2016) 5.
[208] V.R. Askari, R. Shafiee-Nick, The protective effects of β-caryophyllene on LPS-induced primary microglia M(1)/M(2) imbalance: a mechanistic evaluation, Life Sci. 219 (2019) 40–73.
[209] R.L. Lopes, T.J. Borges, R.F. Zanin, C. Bonorino, IL-10 is required for polarization of macrophages to M2-like phenotype by mycobacterial DnaK (heat shock protein 70), Cytokine 85 (2016) 123–129.
[210] A. Dhopeshwarkar, K. Mackie, CB2 cannabinoid receptors as a therapeutic target-what does the future hold? Mol. Pharmacol. 86 (4) (2014) 430–437.
[211] S.E. Lakhan, A. Kirchgessner, M. Hofer, Inflammatory mechanisms in ischemic stroke: therapeutic approaches, J. Transl. Med. 7 (2009) 97.
[212] A. Gerhard, B. Neumaier, E. Elitok, G. Glatting, V. Ries, R. Tomczak, A. C. Ludolph, S.N. Reske, In vivo imaging of activated microglia using [11C] PK11195 and positron emission tomography in patients after ischemic stroke, Neuroreport 11 (13) (2000) 2957–2960.
[213] S. Murikinati, E. Jüttler, T. Keinert, D.A. Ridder, S. Muhammad, Z. Waibler, C. Ledent, A. Zimmer, U. Kalinke, M. Schwaninger, Activation of cannabinoid 2 receptors protects against cerebral ischemia by inhibiting neutrophil recruitment, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 24 (3) (2010) 788–798.
[214] K. Guo, X. Mou, J. Huang, N. Xiong, H. Li, Trans-caryophyllene suppresses hypoxia-induced neuroinflammatory responses by inhibiting NF-κB activation in microglia, J. Mol. Neurosci. MN 54 (1) (2014) 41–48.
[215] L.C. Assis, M.R. Straliotto, D. Engel, M.A. Hort, R.C. Dutra, A.F. de Bem, β-Caryophyllene protects the C6 glioma cells against glutamate-induced excitotoxicity through the Nrf2 pathway, Neuroscience 279 (2014) 220–231.
[216] M.J. Niciu, B. Kelmendi, G. Sanacora, Overview of glutamatergic neurotransmission in the nervous system, Pharmacol. Biochem. Behav. 100 (4) (2012) 656–664.
[217] G. Bai, K.V. Rama Rao, C.R. Murthy, K.S. Panickar, A.R. Jayakumar, M. D. Norenberg, Ammonia induces the mitochondrial permeability transition in primary cultures of rat astrocytes, J. Neurosci. Res. 66 (5) (2001) 981–991.
[218] I.Y. Choi, S.J. Lee, C. Ju, W. Nam, H.C. Kim, K.H. Ko, W.K. Kim, Protection by a manganese porphyrin of endogenous peroxynitrite-induced death of glial cells via inhibition of mitochondrial transmembrane potential decrease, Glia 31 (2) (2000) 155–164.
[219] A.L. Bartels, K.L. Leenders, Parkinson's disease: the syndrome, the pathogenesis and pathophysiology, Cortex J. Devoted Study Nerv. Syst. Behav. 45 (8) (2009) 915–921.
[220] C. Benito, R.M. Tolón, M.R. Pazos, E. Núñez, A.I. Castillo, J. Romero, Cannabinoid CB2 receptors in human brain inflammation, Br. J. Pharmacol. 153 (2) (2008) 277–285.
[221] J. Fernández-Ruiz, C. García, O. Sagredo, M. Gómez-Ruiz, E. de Lago, The endocannabinoid system as a target for the treatment of neuronal damage, Expert Opin. Ther. Targets 14 (4) (2010) 387–404.
[222] B.G. Ramírez, C. Blázquez, T.G. del Pulgar, M. Guzmán, M.L. de Ceballos, Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation, J. Neurosci. 25 (8) (2005) 1904.
[223] J. Palazuelos, T. Aguado, M.R. Pazos, B. Julien, C. Carrasco, E. Resel, O. Sagredo, C. Benito, J. Romero, I. Azcoitia, J. Fernández-Ruiz, M. Guzmán, I. Galve-Roperh, Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity, Brain 132 (11) (2009) 3152–3164.
[224] J. Palazuelos, N. Davoust, B. Julien, E. Hatterer, T. Aguado, R. Mechoulam, C. Benito, J. Romero, A. Silva, M. Guzmán, S. Nataf, I. Galve-Roperh, The CB(2) cannabinoid receptor controls myeloid progenitor trafficking: involvement in the pathogenesis of an animal model of multiple sclerosis, J. Biol. Chem. 283 (19) (2008) 13320–13329.
[225] D.A. Price, A.A. Martinez, A. Seillier, W. Koek, Y. Acosta, E. Fernandez, R. Strong, B. Lutz, G. Marsicano, J.L. Roberts, A. Giuffrida, WIN55,212-2, a cannabinoid receptor agonist, protects against nigrostriatal cell loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease, Eur. J. Neurosci. 29 (11) (2009) 2177–2186.
[226] J.M. Viveros-Paredes, R.E. González-Castañeda, J. Gertsch, V. Chaparro-Huerta, R.I. López-Roa, E. Vázquez-Valls, C. Beas-Zarate, A. Camins-Espuny, M.E. Flores-Soto, Neuroprotective effects of β-caryophyllene against dopaminergic neuron injury in a murine model of Parkinson's disease induced by MPTP, Pharmaceuticals 10 (3) (2017) (Basel, Switzerland).
[227] J.W. Langston, L.S. Forno, J. Tetrud, A.G. Reeves, J.A. Kaplan, D. Karluk, Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure, Ann. Neurol. 46 (4) (1999) 598–605.
[228] G. Wang, W. Ma, J. Du, β-Caryophyllene (BCP) ameliorates MPP+ induced cytotoxicity, Biomed. Pharmacother. 103 (2018) 1086–1091.
[229] R. Motterlini, R. Foresti, Heme oxygenase-1 as a target for drug discovery, Antioxid. Redox Signal. 20 (11) (2013) 1810–1826.
[230] G. Wang, J. Pan, S.D. Chen, Kinases and kinase signaling pathways: potential therapeutic targets in Parkinson's disease, Prog. Neurobiol. 98 (2) (2012) 207–221.
[231] D.M. Walsh, D.J. Selkoe, Deciphering the molecular basis of memory failure in Alzheimer's disease, Neuron 44 (1) (2004) 181–193.
[232] T. Wyss-Coray, Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat. Med. 12 (9) (2006) 1005–1015.
[233] V.A. Campbell, A. Gowran, Alzheimer's disease; taking the edge off with cannabinoids? Br. J. Pharmacol. 152 (5) (2007) 655–662.
[234] N. Stella, Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas, Glia 58 (9) (2010) 1017–1030.
[235] C. Benito, E. Núñez, R.M. Tolón, E.J. Carrier, A. Rábano, C.J. Hillard, J. Romero, Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains, J. Neurosci. 23 (35) (2003) 11136–11141.
[236] M. Solas, P.T. Francis, R. Franco, M.J. Ramirez, CB2 receptor and amyloid pathology in frontal cortex of Alzheimer's disease patients, Neurobiol. Aging 34 (3) (2013) 805–808.
[237] A.G. Horti, Y. Gao, H.T. Ravert, P. Finley, H. Valentine, D.F. Wong, C.J. Endres, A. V. Savonenko, R.F. Dannals, Synthesis and biodistribution of [11C]A-836339, a new potential radioligand for PET imaging of cannabinoid type 2 receptors (CB2), Bioorg. Med. Chem. 18 (14) (2010) 5202–5207.
[238] J. Wu, B. Bie, H. Yang, J.J. Xu, D.L. Brown, M. Naguib, Activation of the CB2 receptor system reverses amyloid-induced memory deficiency, Neurobiol. Aging 34 (3) (2013) 791–804.
[239] A.M. Martín-Moreno, B. Brera, C. Spuch, E. Carro, L. García-García, M. Delgado, M.A. Pozo, N.G. Innamorato, A. Cuadrado, M.L. de Ceballos, Prolonged oral cannabinoid administration prevents neuroinflammation, lowers β-amyloid levels and improves cognitive performance in Tg APP 2576 mice, J. Neuroinflamm. 9 (2012) 8.
[240] Y. Cheng, Z. Dong, S. Liu, β-Caryophyllene ameliorates the Alzheimer-like phenotype in APP/PS1 mice through CB2 receptor activation and the PPARγ pathway, Pharmacology 94 (1–2) (2014) 1–12.
[241] G. Landreth, Q. Jiang, S. Mandrekar, M. Heneka, PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease, Neurother. J. Am. Soc. Exp. NeuroTher. 5 (3) (2008) 481–489.
[242] L. Escribano, A.M. Simón, E. Gimeno, M. Cuadrado-Tejedor, R. López de Maturana, A. García-Osta, A. Ricobaraza, A. Pérez-Mediavilla, J. Del Río, D. Frechilla, Rosiglitazone rescues memory impairment in Alzheimer's transgenic mice: mechanisms involving a reduced amyloid and tau pathology, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 35 (7) (2010) 1593–1604.
[243] G.S. Watson, B.A. Cholerton, M.A. Reger, L.D. Baker, S.R. Plymate, S. Asthana, M. A. Fishel, J.J. Kulstad, P.S. Green, D.G. Cook, S.E. Kahn, M.L. Keeling, S. Craft, Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study, Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry 13 (11) (2005) 950–958.
[244] D.S. Geldmacher, T. Fritsch, M.J. McClendon, G. Landreth, A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease, Arch. Neurol. 68 (1) (2011) 45–50.
[245] A.-M. Enciu, S.N. Constantinescu, L.M. Popescu, D.F. Mureşanu, B.O. Popescu, Neurobiology of vascular dementia, J. Aging Res. 2011 (2011), 401604-401604.
[246] J. Gunstad, A.M. Brickman, R.H. Paul, J. Browndyke, D.J. Moser, B.R. Ott, N. Gordon, O. Haque, R.A. Cohen, Progressive morphometric and cognitive changes in vascular dementia, Arch. Clin. Neuropsychol. Off. J. Natl. Acad. Neuropsychol. 20 (2) (2005) 229–241.
[247] H. Liu, J. Zhang, Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress, Int. J. Neurosci. 122 (9) (2012) 494–499.
[248] J.C. Ashton, R.M. Rahman, S.M. Nair, B.A. Sutherland, M. Glass, I. Appleton, Cerebral hypoxia-ischemia and middle cerebral artery occlusion induce expression of the cannabinoid CB2 receptor in the brain, Neurosci. Lett. 412 (2) (2007) 114–117.
[249] A. Arévalo-Martín, D. García-Ovejero, O. Gómez, A. Rubio-Araiz, B. Navarro-Galve, C. Guaza, E. Molina-Holgado, F. Molina-Holgado, CB2 cannabinoid receptors as an emerging target for demyelinating diseases: from neuroimmune

interactions to cell replacement strategies, Br. J. Pharmacol. 153 (2) (2008) 216–225.
[250] E.J. Carrier, S. Patel, C.J. Hillard, Endocannabinoids in neuroimmunology and stress, Curr. Drug Targets CNS Neurol. Disord. 4 (6) (2005) 657–665.
[251] C.J. Hillard, Role of cannabinoids and endocannabinoids in cerebral ischemia, Curr. Pharm. Des. 14 (23) (2008) 2347–2361.
[252] J. Lou, Z. Teng, L. Zhang, J. Yang, L. Ma, F. Wang, X. Tian, R. An, M. Yang, Q. Zhang, L. Xu, Z. Dong, β-Caryophyllene/hydroxypropyl-β-cyclodextrin inclusion complex improves cognitive deficits in rats with vascular dementia through the cannabinoid receptor type 2-mediated pathway, Front. Pharmacol. 8 (2017), 2-2.
[253] V. Aiassa, A. Zoppi, I. Albesa, M.R. Longhi, Inclusion complexes of chloramphenicol with β-cyclodextrin and aminoacids as a way to increase drug solubility and modulate ROS production, Carbohydr. Polym. 121 (2015) 320–327.
[254] L. Enriquez-Barreto, G. Cuesto, N. Dominguez-Iturza, E. Gavilán, D. Ruano, C. Sandi, A. Fernández-Ruiz, G. Martín-Vázquez, O. Herreras, M. Morales, Learning improvement after PI3K activation correlates with de novo formation of functional small spines, Front. Mol. Neurosci. 6 (2014), 54-54.
[255] M.A. Moskowitz, E.H. Lo, C. Iadecola, The science of stroke: mechanisms in search of treatments, Neuron 67 (2) (2010) 181–198.
[256] D. Centonze, L. Battistini, M. Maccarrone, The endocannabinoid system in peripheral lymphocytes as a mirror of neuroinflammatory diseases, Curr. Pharm. Des. 14 (23) (2008), 2370-42.
[257] J. Zhang, C. Chen, Endocannabinoid 2-arachidonoylglycerol protects neurons by limiting COX-2 elevation, J. Biol. Chem. 283 (33) (2008) 22601–22611.
[258] J. Lo Verme, J. Fu, G. Astarita, G. La Rana, R. Russo, A. Calignano, D. Piomelli, The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide, Mol. Pharmacol. 67 (1) (2005) 15–19.
[259] Y. Sun, S.P. Alexander, M.J. Garle, C.L. Gibson, K. Hewitt, S.P. Murphy, D. A. Kendall, A.J. Bennett, Cannabinoid activation of PPAR alpha; a novel neuroprotective mechanism, Br. J. Pharmacol. 152 (5) (2007) 734–743.
[260] P. Weisová, D. Dávila, L.P. Tuffy, M.W. Ward, C.G. Concannon, J.H.M. Prehn, Role of 5′-adenosine monophosphate-activated protein kinase in cell survival and death responses in neurons, Antioxid. Redox Signal. 14 (10) (2010) 1863–1876.
[261] C. Culmsee, J. Monnig, B.E. Kemp, M.P. Mattson, AMP-activated protein kinase is highly expressed in neurons in the developing rat brain and promotes neuronal survival following glucose deprivation, J. Mol. Neurosci. 17 (1) (2001) 45–58.
[262] L.D. McCullough, Z. Zeng, H. Li, L.E. Landree, J. McFadden, G.V. Ronnett, Pharmacological inhibition of AMP-activated protein kinase provides neuroprotection in stroke, J. Biol. Chem. 280 (21) (2005) 20493–20502.
[263] D.M. Thomson, S.T. Herway, N. Fillmore, H. Kim, J.D. Brown, J.R. Barrow, W. W. Winder, AMP-activated protein kinase phosphorylates transcription factors of the CREB family, J. Appl. Physiol. 104 (2) (2008) 429–438 (Bethesda, Md.: 1985).
[264] L. Poddighe, G. Carta, M.P. Serra, T. Melis, M. Boi, S. Lisai, E. Murru, L. Muredda, M. Collu, S. Banni, M. Quartu, Acute administration of beta-caryophyllene prevents endocannabinoid system activation during transient common carotid artery occlusion and reperfusion, Lipids Health Dis. 17 (1) (2018) 23.
[265] B. Costa, S. Conti, G. Giagnoni, M. Colleoni, Therapeutic effect of the endogenous fatty acid amide, palmitoylethanolamide, in rat acute inflammation: inhibition of nitric oxide and cyclo-oxygenase systems, Br. J. Pharmacol. 137 (4) (2002) 413–420.
[266] T.D. Niemoller, N.G. Bazan, Docosahexaenoic acid neurolipidomics, Prostaglandins Other Lipid Mediat. 91 (3–4) (2010) 85–89.
[267] P. Belujon, A.A. Grace, Dopamine system dysregulation in major depressive disorders, Int. J. Neuropsychopharmacol. 20 (12) (2017) 1036–1046.
[268] K. Mackie, Cannabinoid receptors as therapeutic targets, Annu. Rev. Pharmacol. Toxicol. 46 (2006) 101–122.
[269] E.M. Marco, M.S. García-Gutiérrez, F.J. Bermúdez-Silva, F.A. Moreira, F. Guimarães, J. Manzanares, M.P. Viveros, Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects, Front. Behav. Neurosci. 5 (2011) 63.
[270] M.M. Mitler, Nonselective and selective benzodiazepine receptor agonists–where are we today? Sleep 23 (Suppl. 1) (2000) S39–S47.
[271] A. Bahi, S. Al Mansouri, E. Al Memari, M. Al Ameri, S.M. Nurulain, S. Ojha, β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice, Physiol. Behav. 135 (2014) 119–124.
[272] P.M. Galdino, M.V. Nascimento, I.F. Florentino, R.C. Lino, J.O. Fajemiroye, B. A. Chaibub, J.R. de Paula, T.C. de Lima, E.A. Costa, The anxiolytic-like effect of an essential oil derived from Spiranthera odoratissima A. St. Hil. leaves and its major component, β-caryophyllene, in male mice, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 38 (2) (2012) 276–284.
[273] E.S. Hwang, H.B. Kim, S. Lee, M.J. Kim, K.J. Kim, G. Han, S.Y. Han, E.A. Lee, J. H. Yoon, D.O. Kim, S. Maeng, J.H. Park, Antidepressant-like effects of β-caryophyllene on restraint plus stress-induced depression, Behav. Brain Res. 380 (2020), 112439.
[274] M. De Roo, P. Klauser, P.M. Garcia, L. Poglia, D. Muller, Spine dynamics and synapse remodeling during LTP and memory processes, Prog. Brain Res. 169 (2008) 199–207.
[275] P. Hammel, A. Couvelard, D. O'Toole, A. Ratouis, A. Sauvanet, J.F. Fléjou, C. Degott, J. Belghiti, P. Bernades, D. Valla, P. Ruszniewski, P. Lévy, Regression of liver fibrosis after biliary drainage in patients with chronic pancreatitis and stenosis of the common bile duct, N. Engl. J. Med. 344 (6) (2001) 418–423.
[276] B. Julien, P. Grenard, F. Teixeira-Clerc, J.T. Van Nhieu, L. Li, M. Karsak, A. Zimmer, A. Mallat, S. Lotersztajn, Antifibrogenic role of the cannabinoid receptor CB2 in the liver, Gastroenterology 128 (3) (2005) 742–755.
[277] A. Louvet, F. Teixeira-Clerc, M.N. Chobert, V. Deveaux, C. Pavoine, A. Zimmer, F. Pecker, A. Mallat, S. Lotersztajn, Cannabinoid CB2 receptors protect against alcoholic liver disease by regulating Kupffer cell polarization in mice, Hepatology 54 (4) (2011) 1217–1226 (Baltimore, Md.).
[278] F. Teixeira-Clerc, M.-P. Belot, S. Manin, V. Deveaux, T. Cadoudal, M.-N. Chobert, A. Louvet, A. Zimmer, T. Tordjmann, A. Mallat, S. Lotersztajn, Beneficial paracrine effects of cannabinoid receptor 2 on liver injury and regeneration, Hepatology 52 (3) (2010) 1046–1059 (Baltimore, Md.).
[279] M.F. Mahmoud, S.E. Swefy, R.A. Hasan, A. Ibrahim, Role of cannabinoid receptors in hepatic fibrosis and apoptosis associated with bile duct ligation in rats, Eur. J. Pharmacol. 742 (2014) 118–124.
[280] K.Y. Kim, I. Choi, S.S. Kim, Progression of hepatic stellate cell activation is associated with the level of oxidative stress rather than cytokines during CCl4-induced fibrogenesis, Mol. Cells 10 (3) (2000) 289–300.
[281] B. Viollet, M. Foretz, B. Guigas, S. Horman, R. Dentin, L. Bertrand, L. Hue, F. Andreelli, Activation of AMP-activated protein kinase in the liver: a new strategy for the management of metabolic hepatic disorders, J. Physiol. 574 (Pt. 1) (2006) 41–53.
[282] Y. Li, S. Xu, M.M. Mihaylova, B. Zheng, X. Hou, B. Jiang, O. Park, Z. Luo, E. Lefai, J.Y.J. Shyy, B. Gao, M. Wierzbicki, T.J. Verbeuren, R.J. Shaw, R.A. Cohen, M. Zang, AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice, Cell Metab. 13 (4) (2011) 376–388.
[283] H. Yun, S. Park, M.J. Kim, W.K. Yang, D.U. Im, K.R. Yang, J. Hong, W. Choe, I. Kang, S.S. Kim, J. Ha, AMP-activated protein kinase mediates the antioxidant effects of resveratrol through regulation of the transcription factor FoxO1, FEBS J. 281 (19) (2014) 4421–4438.
[284] R. Kamikubo, K. Kai, K. Tsuji-Naito, M. Akagawa, Beta-caryophyllene attenuates palmitate-induced lipid accumulation through AMPK signaling by activating CB2 receptor in human HepG2 hepatocytes, Mol. Nutr. Food Res. 60 (10) (2016) 2228–2242.
[285] D.G. Hardie, The AMP-activated protein kinase pathway – new players upstream and downstream, J. Cell Sci. 117 (23) (2004) 5479–5487.
[286] A. Louvet, P. Mathurin, Alcoholic liver disease: mechanisms of injury and targeted treatment, Nat. Rev. Gastroenterol. Hepatol. 12 (4) (2015) 231–242.
[287] Z.V. Varga, C. Matyas, K. Erdelyi, R. Cinar, D. Nieri, A. Chicca, B.T. Nemeth, J. Paloczi, T. Lajtos, L. Corey, G. Hasko, B. Gao, G. Kunos, J. Gertsch, P. Pacher, β-Caryophyllene protects against alcoholic steatohepatitis by attenuating inflammation and metabolic dysregulation in mice, Br. J. Pharmacol. 175 (2) (2018) 320–334.
[288] A. Bertola, S. Mathews, S.H. Ki, H. Wang, B. Gao, Mouse model of chronic and binge ethanol feeding (the NIAAA model), Nat. Protoc. 8 (3) (2013) 627–637.
[289] M. Wang, Q. You, K. Lor, F. Chen, B. Gao, C. Ju, Chronic alcohol ingestion modulates hepatic macrophage populations and functions in mice, J. Leukoc. Biol. 96 (4) (2014) 657–665.
[290] T. Urano, S. Inoue, Genetics of osteoporosis, Biochem. Biophys. Res. Commun. 452 (2) (2014) 287–293.
[291] A. Sophocleous, E. Landao-Bassonga, R.J. Van't Hof, A.I. Idris, S.H. Ralston, The type 2 cannabinoid receptor regulates bone mass and ovariectomy-induced bone loss by affecting osteoblast differentiation and bone formation, Endocrinology 152 (6) (2011) 2141–2149.
[292] R.G. Pertwee, Pharmacology of cannabinoid CB1 and CB2 receptors, Pharmacol. Ther. 74 (2) (1997) 129–180.
[293] A. Idris, S. Ralston, Role of cannabinoids in the regulation of bone remodeling, Front. Endocrinol. 3 (136) (2012).
[294] J. Shan, L. Chen, K. Lu, Protective effects of trans-caryophyllene on maintaining osteoblast function, IUBMB Life 69 (1) (2017) 22–29.
[295] J.S. Smolen, D. Aletaha, A. Barton, G.R. Burmester, P. Emery, G.S. Firestein, A. Kavanaugh, I.B. McInnes, D.H. Solomon, V. Strand, K. Yamamoto, Rheumatoid arthritis, Nat. Rev. Dis. Prim. 4 (2018) 18001.
[296] U.H. Alamgeer, A.M. Hasan, S. Uttra, J. Qasim, M. Ikram, Z.R. Saleem, Niazi, Phytochemicals targeting matrix metalloproteinases regulating tissue degradation in inflammation and rheumatoid arthritis, Phytomed. Int. J. Phytother. Phytopharmacol. 66 (2020), 153134.
[297] C. La Porta, S.A. Bura, J. Llorente-Onaindia, A. Pastor, F. Navarrete, M.S. García-Gutiérrez, R. De la Torre, J. Manzanares, J. Monfort, R. Maldonado, Role of the endocannabinoid system in the emotional manifestations of osteoarthritis pain, Pain 156 (10) (2015) 2001–2012.
[298] A.P. Ames-Sibin, C.L. Barizão, C.V. Castro-Ghizoni, F.M.S. Silva, A.B. Sá-Nakanishi, L. Bracht, C.A. Bersani-Amado, M.R. Marçal-Natali, A. Bracht, J. F. Comar, β-Caryophyllene, the major constituent of copaiba oil, reduces systemic inflammation and oxidative stress in arthritic rats, J. Cell. Biochem. 119 (12) (2018) 10262–10277.
[299] Y.J. Zhang, R.Y. Gan, S. Li, Y. Zhou, A.N. Li, D.P. Xu, H.B. Li, Antioxidant phytochemicals for the prevention and treatment of chronic diseases, Molecules 20 (12) (2015) 21138–21156.
[300] G. Dingeo, A. Brito, H. Samouda, M. Iddir, M.R. La Frano, T. Bohn, Phytochemicals as modifiers of gut microbial communities, Food Funct. 11 (10) (2020) 8444–8471.
[301] J. Gupta, S. Sharma, N.R. Sharma, D. Kabra, Phytochemicals enriched in spices: a source of natural epigenetic therapy, Arch. Pharm. Res. 43 (2) (2020) 171–186.
[302] Y. Li, J.J. Zhang, D.P. Xu, T. Zhou, Y. Zhou, S. Li, H.B. Li, Bioactivities and health benefits of wild fruits, Int. J. Mol. Sci. 17 (8) (2016).

[303] J. Gertsch, Cannabimimetic phytochemicals in the diet – an evolutionary link to food selection and metabolic stress adaptation? Br. J. Pharmacol. 174 (11) (2017) 1464–1483.
[304] S.V. Luca, M. Minceva, J. Gertsch, K. Skalicka-Woźniak, LC-HRMS/MS-based phytochemical profiling of piper spices: global association of piperamides with endocannabinoid system modulation, Food Res. Int. 141 (2021), 110123 (Ottawa, Ont.).
[305] A. Kumar, M. Premoli, F. Aria, S.A. Bonini, G. Maccarinelli, A. Gianoncelli, M. Memo, A. Mastinu, Cannabimimetic plants: are they new cannabinoidergic modulators? Planta 249 (6) (2019) 1681–1694.
[306] H.M. Hashiesh, M.F.N. Meeran, C. Sharma, B. Sadek, J.A. Kaabi, S.K. Ojha, Therapeutic potential of β-caryophyllene: a dietary cannabinoid in diabetes and associated complications, Nutrients 12 (10) (2020).
[307] G. Korte, A. Dreiseitel, P. Schreier, A. Oehme, S. Locher, S. Geiger, J. Heilmann, P. G. Sand, Tea catechins' affinity for human cannabinoid receptors, Phytomed. Int. J. Phytother. Phytopharmacol. 17 (1) (2010) 19–22.
[308] J. Gertsch, Cannabimimetic phytochemicals in the diet – an evolutionary link to food selection and metabolic stress adaptation? Br. J. Pharmacol. 174 (11) (2017) 1464–1483.
[309] R. Scandiffio, F. Geddo, E. Cottone, G. Querio, S. Antoniotti, M.P. Gallo, M. E. Maffei, P. Bovolin, Protective effects of (*E*)-β-caryophyllene (BCP) in chronic inflammation, Nutrients 12 (11) (2020).
[310] M.E. Maffei, Plant natural sources of the endocannabinoid (*E*)-β-caryophyllene: a systematic quantitative analysis of published literature, Int. J. Mol. Sci. 21 (18) (2020).
[311] S. Singh, S.Z. Haider, N.K. Chauhan, H. Lohani, S. Sah, R.K. Yadav, Effect of time of harvesting on yield and quality of Melissa officinalis L. in doon valley, India, Indian J. Pharm. Sci. 76 (5) (2014) 449–452.
[312] R.K. Joshi, Leucas aspera (Willd.) link essential oil from India: β-caryophyllene and 1-octen-3-ol chemotypes, J. Chromatogr. Sci. 54 (3) (2016) 295–298.
[313] S.A. Salami, F. Martinelli, A. Giovino, A. Bachari, N. Arad, N. Mantri, It is our turn to get cannabis high: put cannabinoids in food and health baskets, Molecules 25 (18) (2020).
[314] J. Gertsch, Anti-inflammatory cannabinoids in diet: towards a better understanding of CB(2) receptor action? Commun. Integr. Biol. 1 (1) (2008) 26–28.
[315] K. Sirichaiwetchakoon, G.M. Lowe, S. Kupittayanant, S. Churproong, G. Eumkeb, Pluchea indica (L.) Less. tea ameliorates hyperglycemia, dyslipidemia, and obesity in high fat diet-fed mice, Evid. Based Complement. Altern. Med. eCAM 2020 (2020), 8746137.
[316] B. Farinon, R. Molinari, L. Costantini, N. Merendino, The seed of industrial hemp (Cannabis sativa L.): nutritional quality and potential functionality for human health and nutrition, Nutrients 12 (7) (2020).
[317] H.P.V. Rupasinghe, A. Davis, S.K. Kumar, B. Murray, V.D. Zheljazkov, Industrial hemp (Cannabis sativa subsp. sativa) as an emerging source for value-added functional food ingredients and nutraceuticals, Molecules 25 (18) (2020).
[318] S. Frassinetti, E. Moccia, L. Caltavuturo, M. Gabriele, V. Longo, L. Bellani, G. Giorgi, L. Giorgetti, Nutraceutical potential of hemp (Cannabis sativa L.) seeds and sprouts, Food Chem. 262 (2018) 56–66.
[319] S. Ben-Shabat, E. Fride, T. Sheskin, T. Tamiri, M.H. Rhee, Z. Vogel, T. Bisogno, L. De Petrocellis, V. Di Marzo, R. Mechoulam, An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity, Eur. J. Pharmacol. 353 (1) (1998) 23–31.
[320] E.B. Russo, Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects, Br. J. Pharmacol. 163 (7) (2011) 1344–1364.
[321] M. Santiago, S. Sachdev, J.C. Arnold, I.S. McGregor, M. Connor, Absence of entourage: terpenoids commonly found in Cannabis sativa do not modulate the functional activity of Δ(9)-THC at human CB(1) and CB(2) receptors, Cannabis Cannabinoid Res. 4 (3) (2019) 165–176.
[322] D.B. Finlay, K.J. Sircombe, M. Nimick, C. Jones, M. Glass, Terpenoids from cannabis do not mediate an entourage effect by acting at cannabinoid receptors, Front. Pharmacol. 11 (2020), 359-359.
[323] K. Solymosi, A. Köfalvi, Cannabis: a treasure trove or Pandora's box? Mini Rev. Med. Chem. 17 (13) (2017) 1223–1291.
[324] G.I. Borge, E. Sandberg, J. Øyaas, R.K. Abrahamsen, Variation of terpenes in milk and cultured cream from Norwegian alpine rangeland-fed and in-door fed cows, Food Chem. 199 (2016) 195–202.
[325] G. Tornambé, A. Cornu, P. Pradel, N. Kondjoyan, A.P. Carnat, M. Petit, B. Martin, Changes in terpene content in milk from pasture-fed cows, J. Dairy Sci. 89 (6) (2006) 2309–2319.
[326] S. Nicolussi, J.M. Viveros-Paredes, M.S. Gachet, M. Rau, M.E. Flores-Soto, M. Blunder, J. Gertsch, Guineensine is a novel inhibitor of endocannabinoid uptake showing cannabimimetic behavioral effects in BALB/c mice, Pharmacol. Res. 80 (2014) 52–65.