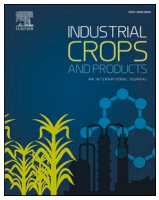
Industrial Crops & Products 213 (2024) 118359

Contents lists available at ScienceDirect

Industrial Crops & Products

journal homepage: www.elsevier.com/locate/indcrop



Health benefits, pharmacological properties, and metabolism of cannabinol: A comprehensive review

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ARTICLE INFO

Keywords:
Cannabinoid receptors
Inflammation
Neuroprotection
Health Benefits
Medicine
Phytocannabinoids

ABSTRACT

Cannabinol (CBN) is a non-psychoactive phytocannabinoid found in *Cannabis sativa*. Although overshadowed by its more well-known counterparts, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), CBN has been gaining attention due to its potential therapeutic properties. This review aims to provide insight into the molecular mechanisms underlying the pharmacological actions of CBN. CBN interacts with the endocannabinoid system (ECS), primarily targeting the CB2 and CB1 cannabinoid receptors. It acts as a partial agonist for both receptors, modulating their activity and downstream signaling pathways. Through these interactions, CBN exhibits diverse effects on various physiological processes, including pain perception, inflammation, immune response, and neuroprotection. Moreover, CBN has been shown to affect non-cannabinoid receptors, including transient receptor potential (TRP) channels, peroxisome proliferator-activated receptors (PPARs), and serotonin receptors. These interactions contribute to the modulation of pain, inflammation, and mood regulation. The molecular mechanisms of CBN also involve its antioxidant and anti-inflammatory properties. CBN has been found to reduce oxidative stress by scavenging reactive oxygen species (ROS) and inhibiting inflammatory mediators. This antioxidant activity potentially contributes to its neuroprotective effects and may have implications for the treatment of neurodegenerative disorders. Furthermore, CBN exhibits potential antimicrobial activity, acting

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https://doi.org/10.1016/j.indcrop.2024.118359
Received 10 November 2023; Received in revised form 16 February 2024; Accepted 4 March 2024
Available online 19 March 2024

against various bacteria, fungi, and methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The underlying mechanisms of this antimicrobial effect are still being elucidated, but may involve disruption of microbial cell membranes and interference with microbial biofilm formation. The molecular mechanisms underlying CBN's pharmacological actions involve its interactions with the ECS, modulation of non-cannabinoid receptors, antioxidant and anti-inflammatory properties, and potential antimicrobial activity. Further research is needed to fully understand the therapeutic potential of CBN and its role in various disease states, paving the way for the development of novel therapeutic interventions. Due to its multiple interests, the isolation and synthesis of CBN has been investigated by several approaches. CBN synthesis involves various approaches, including oxidative conversions, isomerization reactions, enzymatic transformations, and biotransformation techniques. Advancements in synthetic methodologies and innovative strategies continue to contribute to the efficient production of CBN. Further research and optimization are necessary to enhance yields, purity, and scalability of the synthesis processes.

1. Introduction

Medicinal plants provide rich sources of bioactive compounds crucial for drug discovery. Utilized for centuries in traditional medicine, these plants offer a diverse array of potential therapeutic agents. Modern research validates traditional uses and uncovers new bioactive compounds, paving the way for innovative treatments derived from nature's pharmacopeia (Bagri et al., 2009; Sultana et al., 2012, 2024).

Cannabis (*Cannabis sativa* L.) is a plant of the *Cannabaceae* family characterized by the presence of a high content of phytocannabinoids in addition to terpenes, flavonoids, polyphenols, alkaloids, and carbohydrates (Clarke and Merlin, 2013). Over 150 cannabinoids are known, including tetrahydrocannabinol (THC), cannabinol (CBN), and cannabidiol (CBD) (Schwope et al., 2011; Zhong et al., 2023; Zubcevic et al., 2023). These terpenophenolic metabolites are molecules composed of twenty-one carbon atoms associated with carboxylic acids (Saingam and Sakunpak, 2018). CBN, a major constituent of cannabis, is a non-psychotropic cannabinoid and a natural constituent identified in *C. sativa* formed by a non-enzymatic oxidation by-product of Δ^9-THC, following an extended period of storage, essentially under elevated temperatures (Huestis, 2005; Murphy et al., 1990). CBN was the initial cannabinoid isolated and identified from ''charas'', the resin exuded from Indian hemp (Wood, 1899). In 1931, Cahn (Cahn, 1933), elucidated the structure of CBN as $C_{21}H_{26}O_2$ (Cahn, 1933; Work et al., 1939). CBN, also known as 1-hydroxy-3-n-amyl-6,6,9-trimethyl-6-dibenzopyran, is similar to THC, with a variation in cyclohexene (Fig. 1) (Tian et al., 2023). This cycle contains two additional unsaturations upon oxidation and becomes a toluene. Therefore, the fusion of heterocyclic pyran and benzene ring results in the formation of benzopyran (United Nations Office on Drugs and Crime, 2009).

CBN has shown several health benefits, such as neuroprotective effect by reducing increased intraocular pressure, inhibiting synaptic membrane ATPases, partially inhibiting adenylate cyclase activity, inhibiting amidase, delaying the onset of symptoms in SOD1 transgenic mice (Olmsted, 1976; Howlett, 1987; Watanabe et al., 1996; Weydt et al., 2005; Somvanshi et al., 2022), and modulating immune function through several mechanisms, including lymphocyte proliferation inhibition, NF-κB/Rel and IL-2 production by inhibition of IL-2 gene transcription (Herring et al., 1998; Herring and Kaminski, 1999; Jan and Kaminski, 2001). CBN exhibits a variety of pharmacological properties, including anticancer, antimicrobial, analgesic, and anti-inflammatory activities (Shammas, 2006; Wong and Cairns, 2019; Kolar et al., 2023; Mahadeo et al., 2023; Zaiachuk et al., 2023). The objective of this review is to highlight an in-depth knowledge of the pharmacological properties of CBN, showing the mechanism of action through preclinical (*in vivo* and *in vitro*) and clinical tests and providing an insight into its future applications in the pharmaceutical industries.

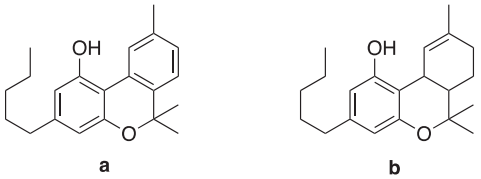

Fig. 1. Molecular structure of CBN (a), and THC (b).

2. Search strategy

This comprehensive review was carried out using pertinent electronic resources, such as Embase, Sciencedirect, SciFinder, Medline PubMed, Google Scholar, and using appropriate search phrases for these particular databases. The search strategy applied binary logical Boolean operators (AND and OR) and the following keywords: cannabinol coumaroltyramine, natural sources, biosynthesis, chemistry, antioxidant, inflammation, cancer, obesity, neurodegenerative disorders, microbial infections, and other diseases. We reviewed and assessed all original research involving identification and/or quantification, as well as research into biological activities through *in vivo*, *in vitro* and *in silico* testing. These studies were published in English in peer-reviewed journals. Editorials, comments, abstracts, reviews, letters, opinions, and redundant research were excluded. ChemDraw Professional 20.0 was used to draw chemical structures.

3. CBN sources

Over the years, various phytocannabinoids were obtained from the cannabis plant, namely Δ^9-THC that is implicated in plant psychoactive effects (Atakan, 2012; Filipiuc et al., 2021). Other phytocannabinoids such as CBD, tetrahydrocannabinolic acid (THCA), CBN, and cannabidiolic acid (CBDA) have also been identified (ElSohly et al., 2017; Filipiuc et al., 2021). CBN was the initial natural cannabinoid extracted by Wood et al. (Wood, 1899) in its pure form. It was derived from cannabis red oil through acetylation, which produced a crystalline acetate CBN derivative with a relatively high concentration. The CBN acetate derivative was subsequently converted into a resinous phenol by hydrolysis (Wood, 1899). Later, many studies reported detecting CBN as a minor compound in fresh cannabis, and they concluded that CBN is a natural thermo-catalytic oxidative product of Δ^9-THC (Appendino, 2020). For years, several groups unsuccessfully attempted to reproduce and expand upon Wood's findings, which suggested that Wood et al. may have been working with old weathered hashish samples, where a significant portion of the active compound Δ^9-THC had oxidized to cannabinol. CBN has only been identified in cannabis despite the discovery of several phytocannabinoids in other plants and fungi (Maioli et al., 2022). In addition to the low concentration in fresh cannabis, CBN's polarity, solubility, and boiling temperature are similar to those of other major cannabinoids, making it difficult to isolate (Appendino, 2020; Maioli et al., 2022). Consequently, synthesis methods were developed and refined to address the challenge of obtaining CBN by extraction from the plant.

To confirm the chemical structure of the naturally isolated CBN, Adams et al. (Adams et al., 1940) first synthesized CBN in 1940 by the

condensation of dihydroolivetol with 4-methyl-2-bromobenzoic acid to obtain the corresponding pyrone (Fig. 2). Subsequently, they aromatized the C ring in the presence of sulfur at 250°C, resulting in the formation of a lactone. Finally, the lactone was converted to CBN in the presence of methylmagnesium iodide.

Novák and Salemink (Novák and Salemink, 1982) synthesised a biphenyl precursor of cannabinol by condensing Grignard's reagent with an oxazoline derivative in tetrahydrofuran, following the method described by Meyers et al. (Meyers et al., 1978), Fig. 3. The process consisted of hydrolyzing the oxazoline group, then cleaving both methoxy groups and catalyzing lactonization through an acid-mediated mechanism, all performed in a one-pot reaction using a mixture of hydrogen iodide and acetic anhydride. The resulting lactone derivative was then methylated to produce CBN using methylmagnesium iodide. Similarly, Hattori et al. (Hattori et al., 1991) synthesized CBN using 2, 6-dialkylphenolic benzoate ester analogs instead of the oxazoline derivative (Fig. 3).

Nüllen and Göttlich (Nüellen and Göttlich, 2013) synthesized the biphenyl precursor by coupling Gilman cuprate with 2-iodobenzamide, according to a modified Ullmann–Ziegler approach (Fig. 4). The obtained biphenyl was then demethylated in the presence of boron tribromide and lactonized in the presence of trifluoroacetic acid. The resulting lactone was gem-methylated to obtain CBN in two steps. First, methyllithium was used to produce the corresponding tertiary benzylic alcohol that was cyclized to CBN, in the presence of trifluoroacetic acid. CBN was synthesized using a Pd(II)/Pd(IV)-catalyzed carboxyl-directed C-H activation/C-O cyclization strategy to form biaryl lactone (Fig. 4) (Li et al., 2013). Subsequently, the protective group on the lactone was removed, and gem-methylation was carried out following the Nüllen protocol (Nüellen and Göttlich, 2013).

Guo et al. (Guo et al., 2017) investigated the reactivity of simple arenes in generating benzo[*c*]chromenes *via* an intramolecular aromatic C−H/C−H coupling reaction catalyzed by palladium (Fig. 5). The subsequent oxidation of the resultant ether in the presence of pyridinium chlorochromate led to a lactone, which was gem-methylated using methyl Lithium. Kloss et al. (Kloss et al., 2018) recorded a comprehensive synthesis of CBN utilizing a photochemical aryl coupling reaction (Fig. 5). The initial step involved the photochemical coupling of aryl compounds to form a biphenyl intermediate. This intermediate underwent demethylation, hydrolysis, and cyclization in a single reaction, yielding the corresponding benzochromenone. Subsequently, the derived lactone was subjected to treatment with methyllithium, resulting in the production of CBN.

Teske and Deiters (Teske and Deiters, 2008) investigated the cyclization of a substituted diyne derived from a salicylaldehyde derivative (Fig. 6). The cyclotrimerization reaction, following a [2+2+2] mechanism, was catalyzed by transition metals and carried out under microwave-mediated conditions. The resulting pyran product was subsequently subjected to oxidation and gem-methylation steps to yield CBN. Nandaluru and Bodwell (Nandaluru and Bodwell, 2012) described the synthesis of CBN by a series of multicomponent domino reactions (Fig. 6). The process involved the reaction of a salicylaldehyde derivative with dimethyl glutaconate in the presence of piperidine. Subsequently, the obtained lactone was reacted with an enamine through an inverse electron demand Diels–Alder reaction, resulting in the creation of a tricyclic product. Afterward, a 1,2-elimination reaction occurred, followed by a dehydrogenation step, resulting in the formation of a 6 H-dibenzo[*b*,*d*] pyranone. To obtain the corresponding acid, the hydrolysis of the 6 H-dibenzo[*b*,*d*] pyranone was performed in the presence of KOH/MeOH. Subsequently, acid treatment with MeLi and p-TsOH led to the final product, CBN.

Minuti et al. (Minuti et al., 2012) investigated the reactivity of an olivetolic derivative with methyl propiolate in ethanol (EtOH) under high pressure (9 Kbar). The resulting phenylcyclohexadiene was then subjected to aromatization in the presence of 2,3-dichloro-5, 6-dicyano-1,4-benzoquinone. Following this, the resultant compound was subsequently converted to CBN through methylation in the presence of methylmagnesium iodide, followed by treatment with *p*-TsOH (Fig. 7). Fan et al. (Fan et al., 2014) synthesized CBN using an intramolecular pyranone Diels–Alder cycloaddition method. Initially, regioselective acylation of olivetol dimethyl ether produced an α,β-unsaturated ketone (Fig. 7). This ketone was then subjected to a Michael addition with diethyl malonate. The resulting product underwent hydrolysis, decarboxylation, and cyclization to form a pyranone. Subsequently, the pyranone was oxidized to the corresponding pyranone using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The resulting pyranone was reacted with propargyl bromide and then cyclized *via* an intramolecular Diels–Alder cycloaddition, leading to the formation of the corresponding pyran, which was oxidized to pyranone. Finally, treatment with methyllithium and trifluoroacetic acid resulted in CBN synthesis.

Mou et al. (Mou et al., 2016) developed a novel approach to synthesize CBN through a formal [4+2] Diels-Alder process. First, a salicylaldehyde derivative and methyl acetoacetate were reacted in the presence of EtOH and piperidine to give 3-acetylcoumarin by Knoevenagel condensation. The resulting product was then reacted with 3, 3-dimethylacrolein, leading to the formation of a benzocoumarin product in one step. This reaction was performed in the presence of 1, 8-diazabicyclo[5.4.0]undec-7-ene and under air. The resulting product was subsequently converted to CBN using previously described protocols (Teske and Deiters, 2008).

Only a limited number of studies have documented the synthesis of CBN without relying on a lactone intermediate. Norseeda et al. (Norseeda et al., 2016) presented a comprehensive CBN synthesis through a Suzuki coupling between a bromide and a boronic acid, followed by gem-dimethylation (Fig. 8). The obtained benzo[*c*]-chromene derivative was treated with phosphorus tribromide and then lithium iodide, resulting in the corresponding tricyclic product, which was

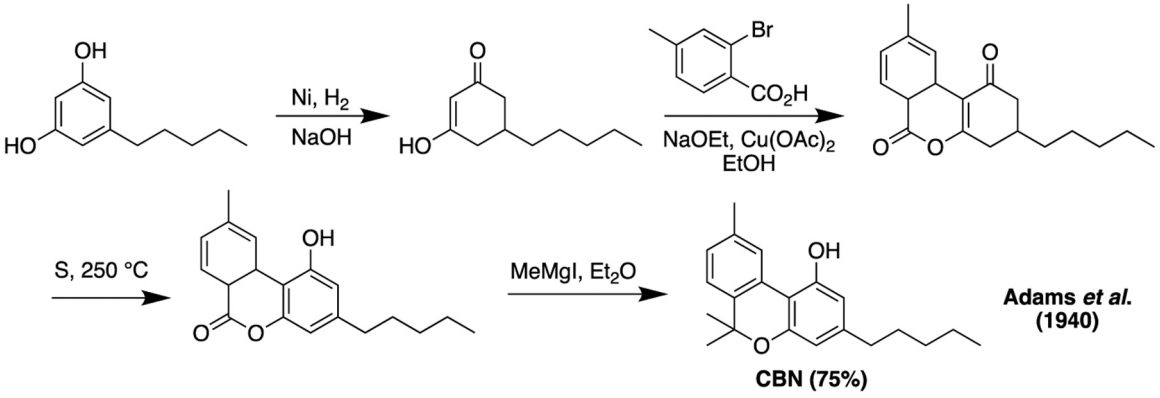

Fig. 2. Synthesis of CBN by condensation of dihydroolivetol with 4-methyl-2-bromobenzoic acid.

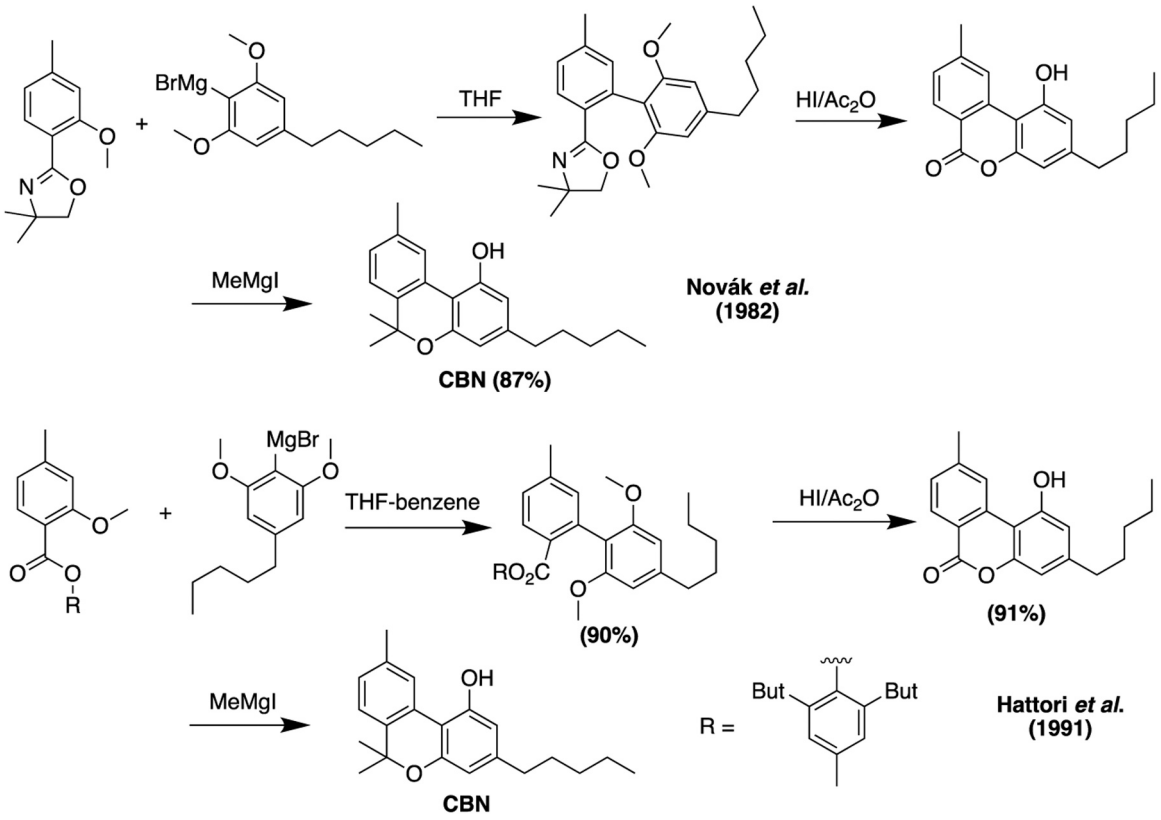

Fig. 3. Synthesis of CBN *via* oxazoline derivative and 2,6-dialkylphenolic benzoate ester.

transformed to CBN *via* demethylation in the presence of hydrogen iodide and acetic anhydride. Recently, Caprioglio et al. (Caprioglio et al., 2019) created the inaugural one-pot complete CBN synthesis from olivetol and citral under basic conditions.

Aromatization of Δ^9-THC was deemed as one of the most straightforward and efficient methods to achieve CBN synthesis. Recent studies by Pollastro et al. (Pollastro et al., 2017) revealed that iodine treatment can convert Δ^9-THC and THCA to CBN (Fig. 9). Additionally, Mechoulam et al. (Mechoulam et al., 1968) and Bastola et al. (Bastola et al., 2007) reported that chloranil or selenium dioxide, and trimethylsilyl polyphosphate, respectively, can selectively convert Δ^9-THC to CBN (Fig. 9).

4. Metabolic effect of CBN

The study conducted by Yamamoto et al. (Yamamoto et al., 1987) demonstrated that the pharmacological effects of 11-OH-CBN, a major metabolite of CBN, were stronger than CBN. From this study, the authors suggested that 11-OH-CBN has the potential to function as an active metabolite derived from CBN that can be used in the pharmacological effects of marihuana (Yamamoto et al., 1987). In 1993, Watanabe et al. (Watanabe et al., 1993) reported that CYP2C29 were the main CYP enzymes involved in THC hepatic metabolism in mice. Research conducted by Yamaori et al. (Yamaori et al., 2010) investigated the inhibitory effects on the catalytic properties of human cytochrome P450 (CYP) 1 enzymes and reported that CBN reduced the activity of CYP1A2 (K_i = 0.0790 mM) and CYP1B1 (K_i = 0.148 mM) compared to CYP1A1 (K_i = 0.541 mM) (Yamaori et al., 2010). Additionally, Yamaori et al. determined the inhibition effect of CBN diltiazem *N*-demethylase activity of human CYP3A enzymes and indicated that CYP3A4, CYP3A5, and HLMs have an IC_{50} greater than 50 μM, while CYP3A7 have an IC_{50} = 23.8 μM (Yamaori et al., 2011). In another study, Yamaori et al. (Yamaori et al., 2012) indicated that CBN potently inhibited CYP2C9 activity with a K_i value of 0.882–1.29 μM.

5. Pharmacological properties of CBN

5.1. Neuroprotective effect of CBN

The pharmacological efficacy of CBN has been reported in numerous studies, several authors have described the neuroprotective potential of this molecule. Work et al. (Work et al., 1939) studied the corneal areflexia test in rabbits to compare the biological effect between CBN and non-crystalline *p*-nitrobenzoates isolated from the resinous exudate of *Cannabis indica* (Indian origin) female flowers. They showed that hydrolysis product was more active and less toxic than CBN, giving a more interesting positive correlation. Recently, Liang et al. (Liang et al., 2022) assessed the neuroprotective effect of CBN towards oxytosis/ferroptosis via the mitochondrial pathway by analyzing the interaction between Ca^{2+} uptake, biogenesis, oxidative stress, bioenergetics, membrane potential, and fusion/fission dynamics. The results showed that CBN effectively preserves the cited functions of mitochondrial keys. In the same year, Somvanshi et al. (Somvanshi et al., 2022) examined the neuroprotective ability of CBN, but against glaucoma. They have demonstrated that CBN was able to reduce the increased intraocular pressure, attenuate trabecular meshwork remodeling, and mediate retinal ganglion cell protection *in vivo* and *in vitro*.

The effectiveness of CBN neuroprotective effects has been confirmed in different ways. Indeed, the analysis of the neurochemical effects of CBN has focused mainly on rat brains by studying different pathways and the involved mechanisms. Domino (Domino, 1976) has compared the impact of 6,9-THC and CBN on rat brain acetylcholine (ACh). The results of this study have shown that CBN was less active than THC in modifying ACh production, even with a high dose of up to 100 mg/kg. In addition, the combined injection of CBN and THC was antagonistic, showing less efficacy than both phytocannabinoids injected alone. In another investigation, Olmsted (Olmsted, 1976) was interested in analyzing the impact of cannabinoids on synaptic membrane enzymes isolated from rat brains using electron micrographic analysis. The

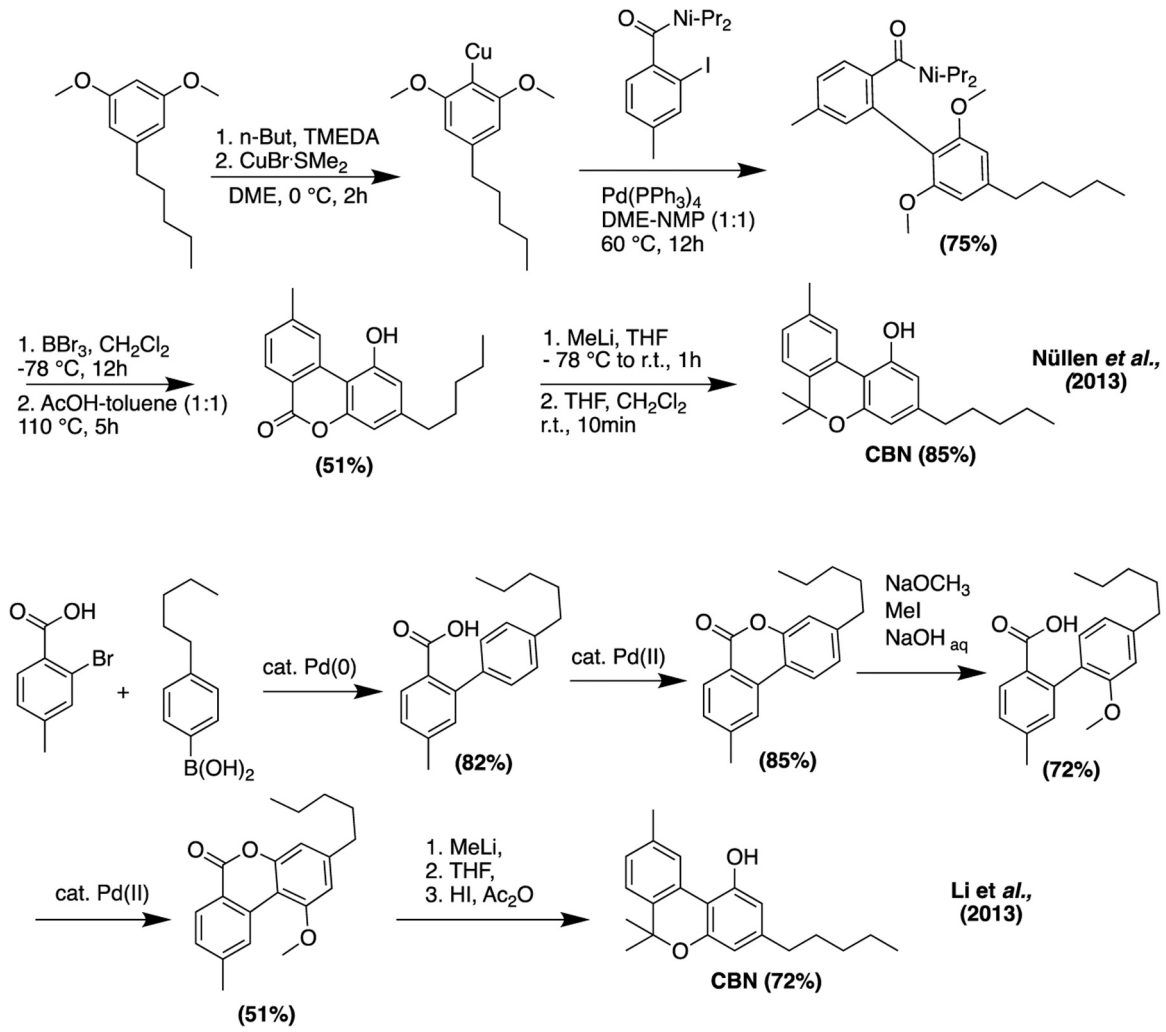

Fig. 4. Synthesis of CBN by coupling with Gilman cuprate and using Pd(II)/Pd(IV)-catalyzed.

findings obtained indicated that only Δ^9-THC displayed an inhibitory effect on the activity of the synaptic membrane Na^+, K^+-ATPase, while CBN exhibited a comparable efficacy to Δ^9-THC in terms of inhibiting both synaptic membrane ATPases. The mechanism by which these cannabinoids act on the brain was examined by Alozie et al. (Alozie et al., 1980), focusing on studying the penetration and regional distribution of ^{3}H-CBN, ^{3}H-CBD, and ^{3}H-Δ^9-THC in rat brain. Hence, the radioactivity levels in plasma remained comparable among the three tested cannabinoids. Nevertheless, ^{3}H-CBD radioactivity exhibited a higher degree of penetration into the brain compared to ^{3}H-Δ^9-THC. However, these cannabinoids entered the brain and displayed analogous distribution across various brain regions.

Enzymes are a specific target of cannabinoids mode of action, Δ^9-THC was described as a promising inhibitor of adenylate cyclase activity of murine neuroblastoma cells, while CBN was partially active. This study has been extended to analyze structure features and their involvement in the inhibitory effects. Carbon hydroxylation was a determinant of activity (Howlett, 1987). Watanabe et al. (Watanabe et al., 1996) have reported that cannabinoids inhibited anandamide amidase activity in mouse brain microsomes, showing that CBD displayed greater amidase inhibition potency than CBN and Δ^9-THC and that mouse brain microsomes exhibited hydrolytic activity for anandamide. Two years later, the same team demonstrated that the enzymatic potential exhibited a greater magnitude in the liver, succeeded by the brain and the testis, where the main activity was localized in the microsomal fraction. Interestingly, this activity was inhibited by Δ^9-THC, CBN, and CBD in the brain but not in the liver (Watanabe et al., 1998). This finding was encouraging to analyze how brain microsomes are able to metabolize THC and CBN. Using human brain microsomes, the findings acquired indicated the metabolic conversion of CBN into 8-hydroxy- and 11-hydroxy-CBN compounds (Watanabe et al., 2013).

Cannabinoids have been reported to cure numerous diseases. Recently, Thornton et al. (Thornton et al., 2020) have shown that these constituents have decreased seizure activity in chemically-induced and snc1a-mutant zebrafish, which constitutes a promising trend in complicated epilepsy disease. In another study, CBN exhibited the ability to postpone the initiation of symptoms in SOD1 transgenic mice, which is a key factor in amyotrophic lateral sclerosis. The results also showed that CBN administration did not affect survival (Weydt et al., 2005). However, CBN administrated to cats caused a significant decrease in ocular tension, while administrated to rats, CBN caused conjunctival and erythema and hyperemia, leading authors to conclude that CBN produced both ocular and neural toxicity (Colasanti et al., 1984). Thus, knowing the concentration and the administrated dose plays an important role.

5.2. *Cannabinol immune effect*

The endocannabinoid system is present within both the innate and adaptive immune systems, where several phytocannabinoids have demonstrated significant effects on immune functions. These compounds play a substantial role in controlling inflammation, modulating

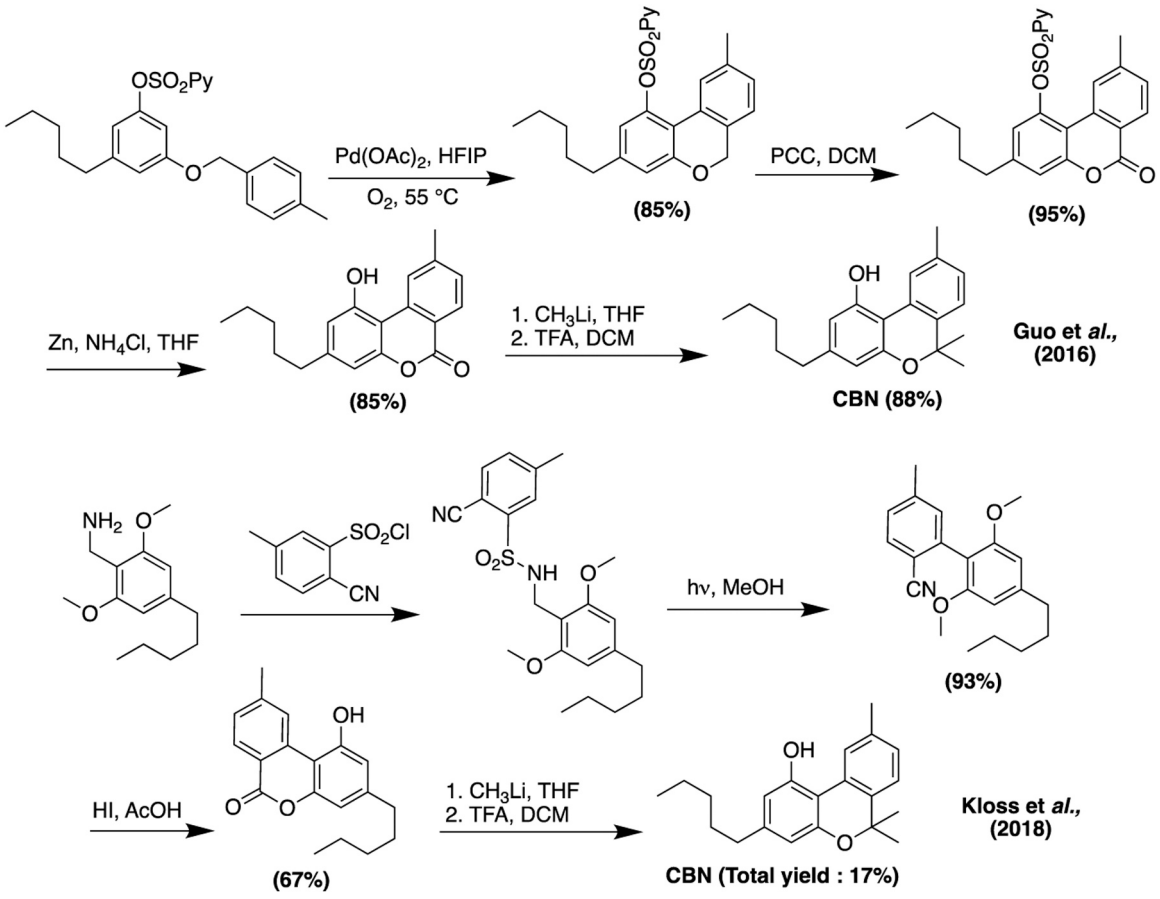

Fig. 5. Synthesis of CBN by intramolecular aromatic C−H/C−H coupling and photochemical aryl coupling.

autoimmunity, and preemptively averting the emergence of detrimental immune reactions (Acharya et al., 2017; Cabral et al., 2015a, 2015b; Chiurchiù et al., 2015a; 2015b; McCoy, 2016).

Levy and Heppner (Levy and Heppner, 1978) investigated the ability of CBN to influence the delayed-type hypersensitivity (DTH) in mice induced by sheep red blood cells (SPEC) derived from a single sheep. The authors of this study indicated that CBN exhibited mild to moderate effectiveness in suppressing DTH (Levy and Heppner, 1978). Herring et al. (Herring et al., 1998) examined the effect of CBN on the modulation of immune function and cAMP signal transduction in lymphoid cells of mice. The findings from this research revealed that CBN exhibits immunomodulatory properties by engaging CB2 receptors in the process of cannabinoid-mediated immune suppression. In addition, CBN modulated cAMP-mediated signal transduction, displayed greater binding affinity for CB2 receptors, and influenced immune responses in mouse lymphoid cells. Furthermore, using CBN, a dose-dependent inhibition (*in vitro*) of anti-sheep red blood cell IgM antibody was noted. CBN exerted its influence on immune function by hindering lymphocyte proliferation and suppressing T-cell-dependent humoral immune reactions. In 1999, Herring and Kaminski (Herring and Kaminski, 1999) explored in deep the mechanism by with CBN influences NF-κB DNA binding activity, cAMP response element (CRE) functioning, and interleukin-2 (IL-2) secretion within phorbol ester (phorbol-12-myristate-13-acetate, PMA) in addition to calcium ionophore (PMA/Io)-activated thymocytes. From this research, they found that CBN inhibited both CRE complexes (CREB-1/activating transcription factor (ATF)-2 complex, and CREB-1 homodimer) by decreasing phosphorylation of CREB/ATF nuclear proteins in PMA/Io-activated thymocytes. Furthermore, NF-kB/Rel and IL-2 production were inhibited after CBN treatment in thymocytes (Herring and Kaminski, 1999). In addition, according to Yea et al. (Yea et al., 2000), CBN inhibited the secretion of IL-2 by the inhibition of IL-2 gene transcription through the inhibition of DNA binding affinity of nuclear factor of activated T-cells (NF-AT) in EL4 cells and activator protein-1 (AP-1). One year later, Herring et al. (Herring et al., 2001) studied the involvement of protein kinase A (PKA) and cAMP in the inhibition exerted by CBN on NF-κB, IL-2, and cAMP response element binding protein (CREB). From this study, CBN inhibited IL-2 expression and activation of CREB, and nuclear factor for the chain k of immunoglobulin (Ig) in B cells (NF-κB). Surprisingly, it has been reported that CBN can negatively and positively modulate IL-2 expression. In 2001, Jan and Kaminski (Jan and Kaminski, 2001) examined the mechanism of action in charge of cannabinol-mediated IL-2 modulation. Their study demonstrated that CBN-induced IL-2 enhancement or inhibition depends on the extent of T cell activation. Indeed, IL-2 inhibition by CBN is obtained when the T lymphocytes are activated to achieve maximal IL-2 production. In contrast, CBN enhances IL-2 production when T cells are stimulated with a suboptimal IL-2 activator. They also reported that the activating and suppressive impacts of CBN on IL-2 seemed to exhibit a strong association with the decrease and elevation of extracellular regulated kinase (ERK), which is a member of the mitogen-activated protein (MAP) family. The same collaborators studied the mechanism of action by which IL-2 gene expression enhanced by CBN. They demonstrated that the elevation in IL-2 secretion induced by CBN was facilitated through the augmentation of IL-2 gene transcription by activating NF-AT in a CB1/CB2-independent manner (Jan et al., 2002). The application of phytocannabinoids promises to be beneficial when it is necessary to quell potentially harmful immune reactions (for example, in autoimmune diseases or organ transplantation). Additionally, the use of CBN can be a potential therapeutic use in immune modulation by selectively engaging the CB2 receptors on lymphoid cells. However, it is necessary to verify the use of CBN against pathogens and tumor cells and verify

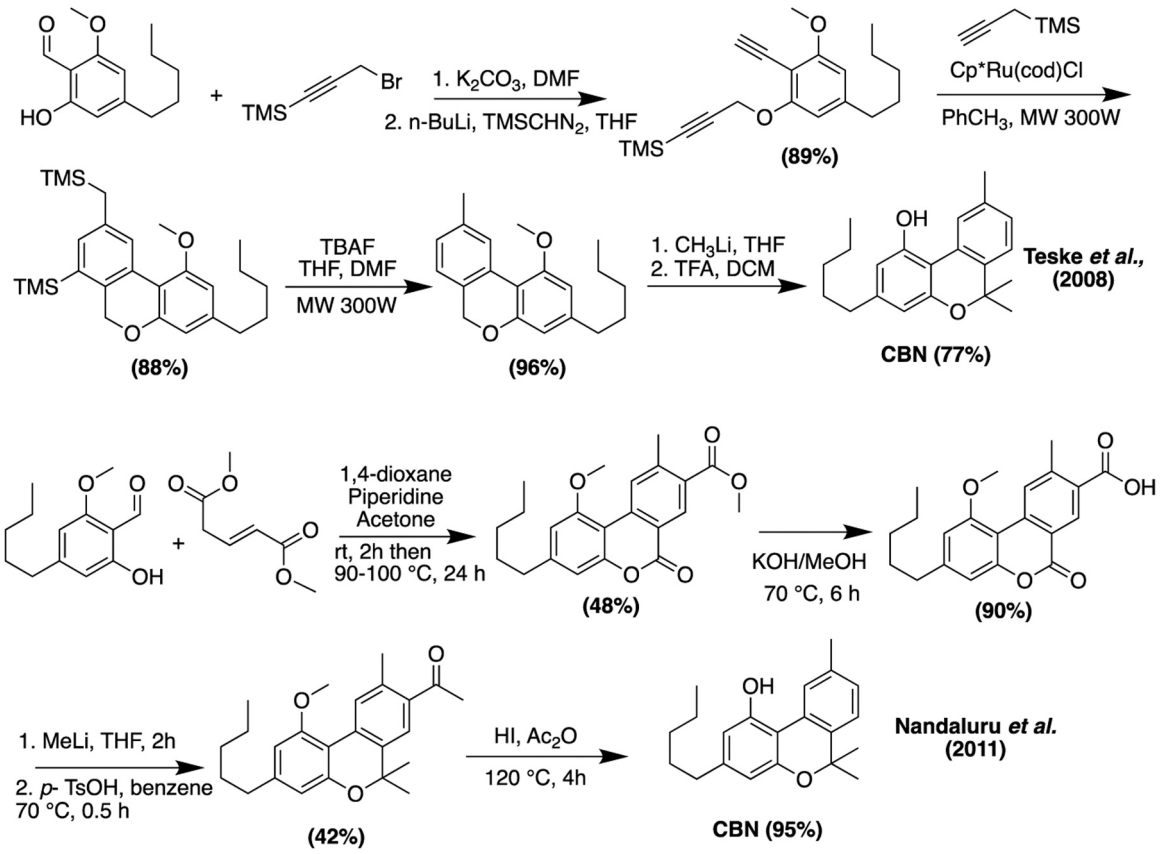

Fig. 6. Synthesis of CBN by cyclization of a salicylaldehyde derivative.

their effect on immunological responses.

5.3. Anticancer effect of CBN

Over the past few years, cannabis and its derivatives have been utilized for various purposes, such as alleviating chemotherapy-induced nausea and vomiting, managing epilepsy, addressing multiple sclerosis, and addressing other medical conditions (Kleckner et al., 2019). Increasingly, a growing body of *in vivo* data started to provide indications of the potential of cannabis to influence the signaling pathways responsible for cancer cell growth, autophagy regulation, programmed cell death, inhibition of blood vessel formation, and the spread of cancer cells to distant sites (Velasco et al., 2016). CBN has only 10% of the psychoactive properties of THC, which makes it interesting from a medical point of view. There are few data that studied the role of CBN in tumor generation and progression.

Munson et al. (Munson et al., 1975) investigated *in vivo* and *in vitro* the potential of CBN against cancer cells. In *in vitro* tests, CBN was evaluated against Lewis lung tumor, bone marrow, and L1210 leukemia cells. At 2.5 10^{-5} M, CBN inhibited the radiolabel uptake of tritiated thymidine (^{3}H-TDR) in the three cell types. In *in vivo* tests, the effect of CBN was evaluated on Lewis lung carcinoma, B-tropic Friend leukemia virus, and murine leukemia L1210 maintained into mice. At 50 mg/kg, CBN decreased the size of tumor (from 875 g during 14 days of treatment to 5.7 g during 24 days of treatment) and increased the mean survival time (27%). Turner and Elsohly (Turner and Elsohly, 1981) studied *in vivo* the effect of CBN on their ability to reduce intraocular pressure on albino rabbits. Using CBN at 10 mg/kg intravenously, the result indicated that this molecule has an equal intraocular pressure lowering effect than 1.5 mg/kg using THC. Shammas et al. (Shammas et al., 2006) evaluated the effect of CBN on hsRAD51 promoter activity transfected into multiple myeloma cell lines (ARP, OPM1, and U266). CBN reduced by 8-fold the activity of the HsRAD51 promoter, a main target in the treatment of multiple myeloma cancer. In 2019, Grijó and coworkers (2019) evaluated the anticancer effect of bioactive compounds of cannabis flowers using supercritical carbon dioxide (scCO2). Using MTT assay, the extract containing CBD (2.7%), 9-THC (68.3%), CBN (3.0%), and (Others 26%) showed a greater anticancer potential against Caco-2, PC3, Hela, SiHa, and C33 tumor cells with a CC50 value of inhibition of cells at a concentration of 22 mg/mL, 2.7 mg/mL, 3.1 mg/mL, and 2.8 mg/mL, respectively (Grijó et al., 2019). In their research, Wang et al. (Wang et al., 2022) provided evidence of how CBN can suppress neuroblastoma tumorigenesis by revealing a previously unknown tumor suppressor network involving miR-34a, which contributes to the anti-neuroblastoma effects of CBN. Similarly, Leelawat et al. (Leelawat et al., 2022) showed that CBN can induce apoptosis in CCA by inhibiting the AKT and MAPK pathways. This led to a reduction in cellular proliferation (*in vitro*) and a decrease in tumor volume (*in vivo*).

All of the studies that have been cited in this discussion express very encouraging results on the anti-cancer effect of CBN, one of the very important compounds of cannabinoids Table 1.

5.4. Antimicrobial effect of CBN

Given the appearance of resistance of microorganisms to drugs and the serious threat to human healthcare globally, the search for alternative substances and methods has included medicinal plants traditionally used for treating many diseases and no sign of drug resistance has been reported till now (AlSheikh et al., 2020; Khare et al., 2021). Cannabis, an herbaceous plant that has been employed for an extended period for medicinal intentions owing to its cannabinoid content (Karas et al., 2020), possesses good antimicrobial activities against many bacteria (including acid-fast bacteria), filamentous fungi, yeast, and

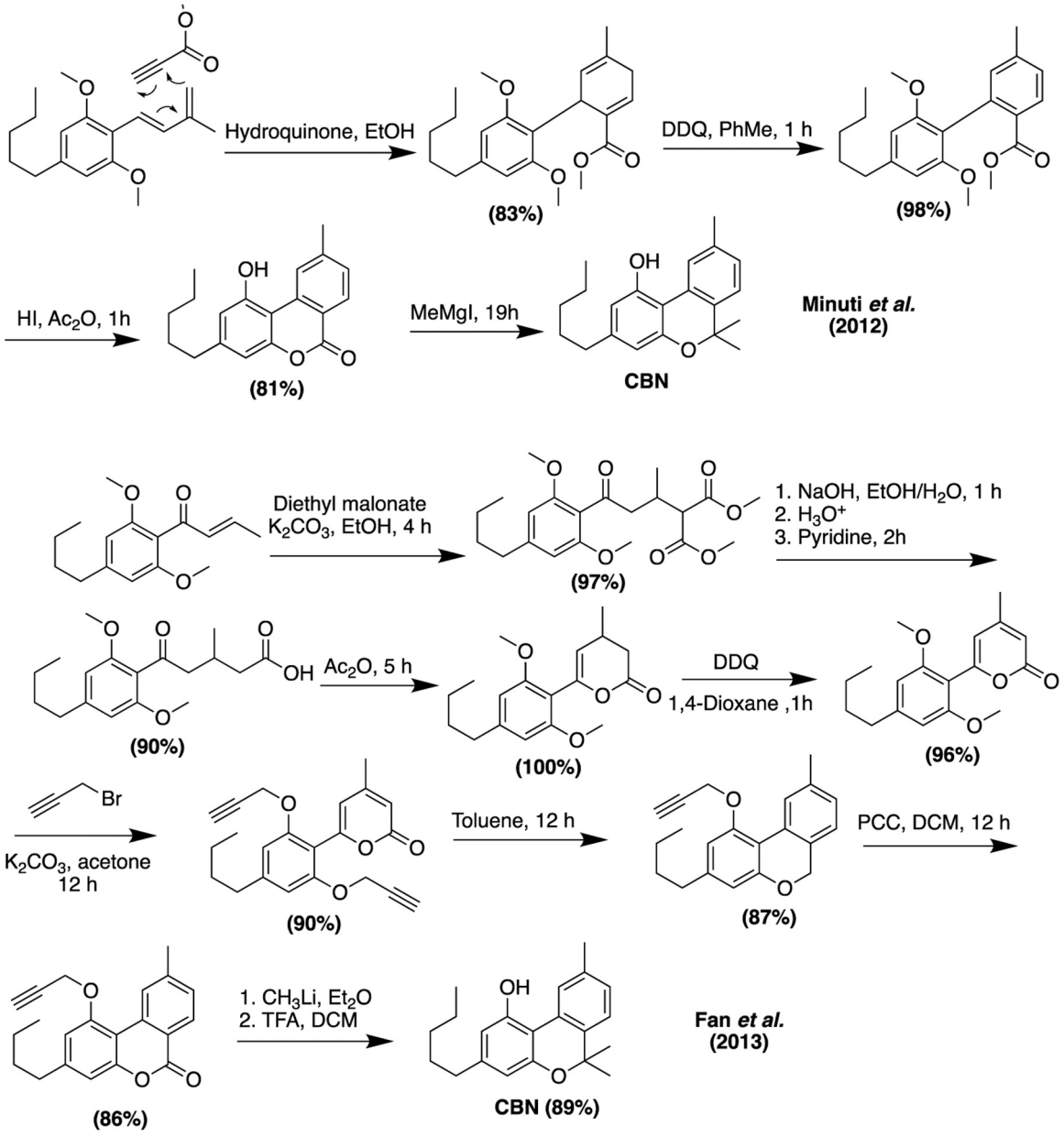

Fig. 7. CBN synthesis through Diels–Alder approach.

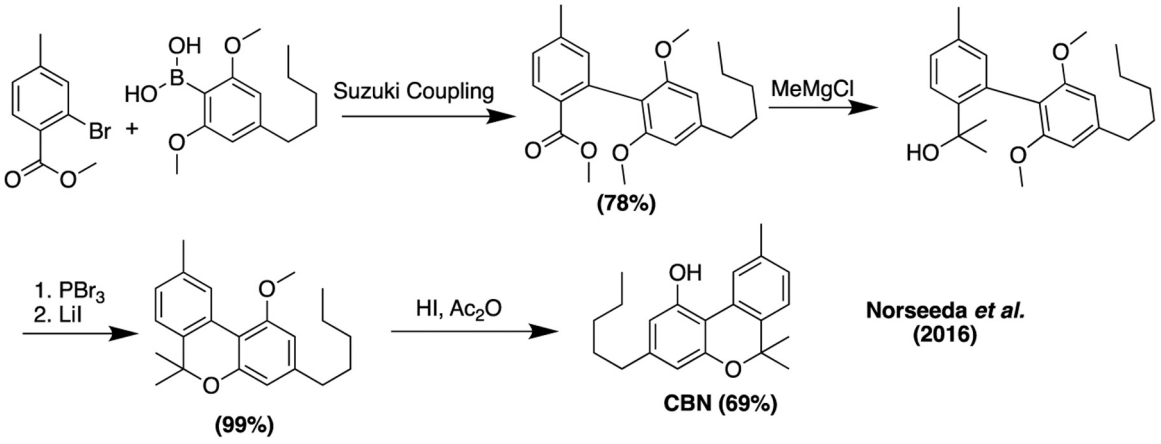

Fig. 8. CBN synthesis through Suzuki coupling.

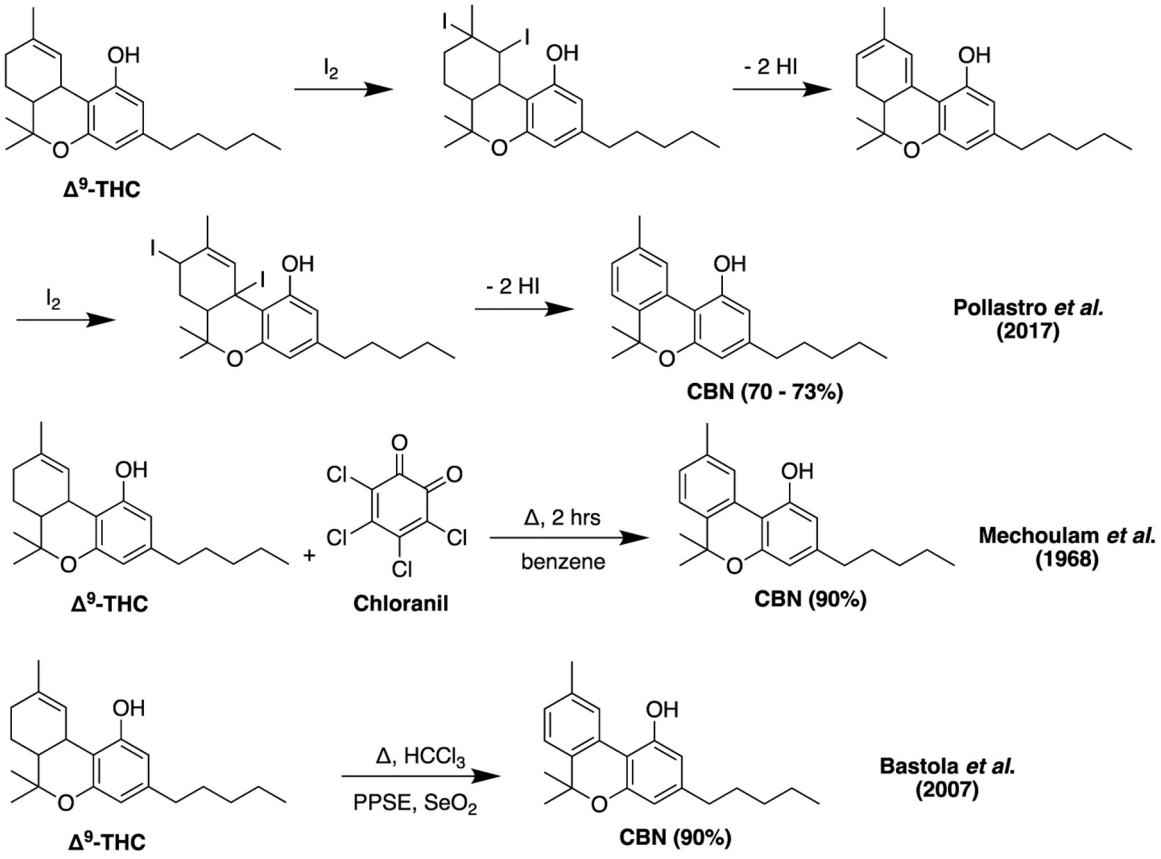

Fig. 9. The semisynthesis of CBN through Δ^9-THC aromatization.

dermatophyte (Turner and Elsohly, 1981). According to a detailed study carried out on 5 types of cannabinoids, CBN showed promising effect towards a variety of resistant bacterial strains, including methicillin-resistant *Staphylococcus aureus* (MRSA) strains EMRSA-15 (methicillin-resistant), XU212 (tetracycline-resistant), RN4220 (macrolide-resistant strain), SA-1199B (multidrug-resistant strain), and a standard laboratory strain (ATCC25923). The minimum inhibitory concentration (MIC) was around 1 μg/mL (Appendino et al., 2008).

5.5. Analgesic and anti-inflammatory effects of CBN

Numerous research described the pharmacological activities of cannabis (Paton and Pertwee, 1973) but its use as an analgesic is still under discussion due to its psychoactive effects (Maione et al., 2013). Besides the major psychoactive constituent of cannabis (Burstein, 1973; Ulugöl, 2014), CBN showed analgesic and anti-inflammatory effects. The analgesic effectiveness was tested *in vivo* compared to aspirin and morphine using the Randall-Selitto paw pressure test, hot plate (heat) test, and the acetic-induced writhing test. CBN showed differences in effectiveness depending on the test. It was found that, like aspirin, CBN exhibited efficacy only in decreasing the frequency of writhing and in particular increasing the pain threshold of the non-injected paw. The magnitude of the analgesic activity in both tests was linear, dose-related and stable at some dose. In the case of acetic-induced writhing test, CBN was effective at a dose ranging from 12.5 to 50.0 mg/kg. In the same context, the extent of analgesic efficacy in the paw pressure test remained unaffected even when the dosage of CBN was raised beyond 160.0 mg/kg. In addition, the CBN was ineffective against thermally-induced pain (Sofia et al., 1975). Another study evaluated the effect of CBN and their combinations with other cannabinoids on nerve growth factor (NGF)-induced masticatory muscle sensitization and on masseter muscle mechanoreceptors. At a concentration of 1 mg/mL, CBN proved effective in alleviating the mechanical sensitization prompted by NGF. However, the combination of CBD/CBN resulted in a prolonged and sustained reduction in sensitivity (Wong and Cairns, 2019). The authors of this study suggested that CBD and CBN could be used as analgesics for chronic muscle pain disorders without central side effects. Although the impact of CBN effect was less potent than that of THC, its potential benefits lie in its minimal psychotropic effects (Amar, 2006; Pertwee, 2005).

The anti-inflammatory effect of CBN has been investigated *in vitro* on human U937 cells (Zaiachuk et al., 2023). The inhibitory effects of cannabinoids on TNF-α inhibition were studied in LPS-stimulated U937 cell lines. CBN show highly significant inhibition of IL-6, IL-10 and MCP-1 cytokines at the concentration ranging between 50–100 pg/mL despite it is less responsive to IL-1β, IL-8 and TNF-α (Zaiachuk et al., 2023). Besides that, CBN has been investigated for its anticonvulsant and anti-inflammatory properties (Evans, 1991; Turner et al., 1980). Since CBN showed a high affinity with CB2 receptors, the effect can be more than just on the central nervous system. The correlation between analgesic and anti-inflammatory properties within cannabinoids has been established to be associated with their peripheral actions, which are separate from THC central effects.

5.6. Concentration of CBN in the blood and capillary

Due to its low concentration, there are very few publications describing the distribution of CBN in the blood and hair. According to the study of McCallum (McCallum, 1974), blood tests, performed on individuals 25 minutes after smoking cannabis, showed abnormally high levels of the detected CBN (about 100 ng/mL). However, smoked CBN cannot reach this level in the blood. Therefore, it appears that CBN may result from further metabolism of 11-hydroxy-Δ^9-THC (Fig. 2). Furthermore, analyses discovered 2 g of CBN in the blood of rats, even

Table 1
Anticancer activity of CBN.

Types of cell lines used	Tests used	Major results	References
Occular cell in glaucomatous	*In vivo* study in two-sex albino rabbits weighing 2–4 kg based on intra-ocular pressure measurement	CBN is slightly active in reducing intraocular pressure	(Elsohly et al., 1981)
Lewis lung tumor, bone marrow, and L1210 leukemia cells	*In vitro* effects of cannabinoids on 3 H-TDR	CBN inhibited the radiolabel uptake of tritiated thymidine (^{3}H-TDR) in the three cell types	(Munson et al., 1975)
Lewis lung carcinoma, B-tropic Friend leukemia virus, and murine leukemia L1210 cells	*In vivo* mice hosting cells	- CBN decreased the size of tumor (from 875 g to 5.7 g) - CBN increased the mean survival time (27%)	
Multiple myeloma cell lines (ARP, OPM1, U266)	*In vitro* hsRAD51 promoter activity	CBN reduced by 8-fold the activity of the HsRAD51 promoter in multiple myeloma cells	(Shammas et al., 2006)
Neuroblastoma cell lines (IMR-5 and SK-N-AS)	Anti-neuroblastoma effect of CBN via inhibition of AKT pathway and transactivation of miR-34a	Demonstration of CBN's suppressive role in neuroblastoma tumorigenesis, highlighting a novel and crucial miR-34a tumor suppressor network in the anti-neuroblastoma actions of CBN	(Wang et al., 2022)
Cholangiocarcinoma cell line	*In vivo* antitumor effect of cannabinol on CCA cells and xenograft mice	CBN induced apoptosis in CCA by inhibiting AKT and MAPK pathways	(Leelawat et al., 2022)

though CBN was administrated in doses that did not surpass 1 g. This increase in the quantity of CBN is due to its formation from Δ^1-THC and Δ^6-THC (Fig. 10).

The primary objective of a single study was to examine CBN distribution in hair samples taken from 7 males and females respectively. Using GC/GC-MS method, these samples were examined. Analysis revealed that THC was detected only in one sample at a concentration below the cut-off value, while CBN was not detected in all hair samples (Rodrigues et al., 2018). The study suggested that there is no linear correlation between CBD levels in hair and the daily consumption dosage of CBD (Rodrigues et al., 2018).

5.7. Other activities of CBN

In addition to their pharmacological activities, researchers reported other biological effects of CBN as antinociceptive effects. Chesher et al. (Chesher et al., 1973) investigated the antinociceptive effects of CBN acetate extract. This was accomplished through a hot-plate test to assess reaction times and by gauging intestinal motility *via* the pace of a charcoal meal in mice. The authors showed that administering CBN acetate orally at varying doses (10, 20, 40, and 60 mg/kg) led to a proportional escalation in reaction time during the hot-plate test, while also resulting in corresponding dose-dependent reductions in the movement of the charcoal meal. Levy and Heppner (Levy and Heppner, 1978) studied the ability of CBN component to alter DTH response to sheep red blood cells (SPBC) in mice. The results of this study demonstrated that four daily postimmunization treatments with 100 mg/kg CBN beginning 1 hour after immunization reduced 60% peak response in day 4. In another study, administering CBN to mice prior to swimming, at concentrations of 5.0 and 40.0 mg/kg, displayed a significant decrease in the post-swim grooming behavior observed (Chesher and Jackson, 1980). This effect might be due to generalized suppression of responding and to the efficacy of CBN in blocking other dopamine (DA) receptor antagonists mediated behaviors. The antitussive activity of CBN were explored through methodologies involving electrical stimulation of the superior laryngeal nerve or mechanical stimulation of the tracheal mucosa on pentobarbital-anesthetized cats. Even at dosages as high as 10.0 mg/kg, CBN showed antitussive properties (Gordon et al., 1976). Furthermore, when administered concurrently, CBN and Δ^9-THC exhibited a combined effect. This was evidenced by CBN enhancing the cue-related effects of Δ^9-THC, leading to an elevation in the percentage of appropriate responses to the drug. However, the duration of this effect remained unchanged, as indicated by the results obtained (Järbe and Hiltunen, 1987). McLaughlin et al. found that cannabinoids stimulate hunger in humans (McLaughlin et al., 1979). Furthermore, Farrimond et al. concluded for the first time that CBN increased feeding by inducing a CB1R-mediated increase in appetite behavior (Farrimond et al., 2012). Faubert and Kaminski conducted an *in vivo* investigation into the impact of CBN on the activity of AP-1 in primary mouse splenocytes (Faubert and Kaminski, 2000). They reported that cannabinoid components exhibited immunosuppressive effects, likely orchestrated *via* Gi-protein coupled receptors that exerted a downregulatory influence on adenylate cyclase. They determined that this effect was attributable to a reduction in the nuclear expression of c-fos and c-jun, alongside posttranslational alterations of these phosphoproteins, as well as the suppression of ERK MAP kinase activation. Moreover, Stinchcomb et al. (Stinchcomb et al., 2004) evaluated the *in vitro* cutaneous transdermal flux of CBN by measuring the permeability, flux, lag times, and tissue concentration. Based on the results of this study, the researchers observed that both CBD and CBN exhibited permeabilities that were ten times greater than that of Δ^8-THC. Additionally, CBD demonstrated notably shorter lag times compared to CBN. Furthermore, the tissue concentrations of Δ^8-THC were markedly elevated in comparison to those of CBN (Stinchcomb et al., 2004). Despite the results obtained, more controlled human studies are required to determine the ultimate role of these products in human skin permeation. The antioxidant activity of CBN has been studied by Dawidowicz and co-workers *in vitro* using spectrophotometric methods: DPPH, ABTS, β-carotene CUPRAC, ORAC, and FRAP (Dawidowicz et al., 2021). The outcomes demonstrated that CBN possesses antioxidant capabilities, which were evident in its capacity to diminish metal ions, halt the oxidation process, and scavenge free radicals. Additionally, the antioxidant potential of CBN was assessed through *in vitro* experimentation involving H_2O_2-induced oxidative stress in differentiated neuronal SH-SY5Y cells. The findings from this investigation highlighted the significant antioxidant efficacy of CBN, indicating its potential for the development of novel pharmaceuticals targeted at oxidative stress therapy (Raja et al., 2020). Moreover, the CBN showed narcotic detoxification as evidenced by its significant suppression of certain manifestations of the morphine abstinence syndrome in morphine-dependent mice. These included behaviors such as rearing, defecation, and withdrawal-induced jumping upon naloxone administration (Bhargava, 1976). Karler and Turkanis (Karler and Turkanis, 1981) assessed the anticonvulsant effects of CBN through oral administration in mice utilizing an electroshock test. The results indicate that CBN is an effective anticonvulsant with an anticonvulsant dose (ED_{50} values) of 230 mg/kg and a peak effect of about 2 hr. From this study, the authors showed that CBN blocked the hippocampal seizure discharges induced by direct electrical stimulation, which allowed it to have strong anticonvulsant activity. The same effect was reported by Chesher and Jackson (Chesher and Jackson, 1974), which investigated

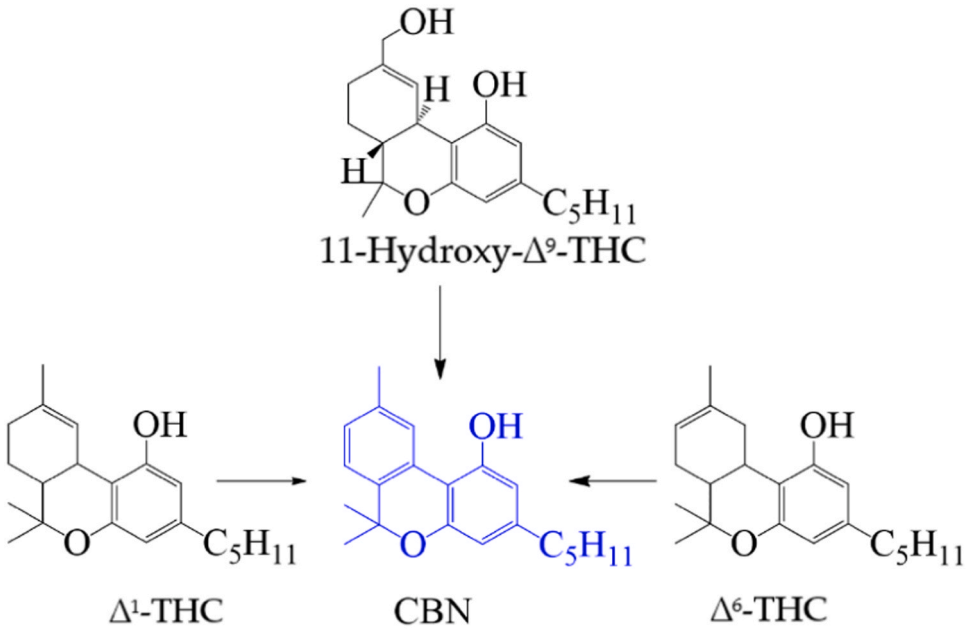

Fig. 10. Structure of cannabinol and its derivatives.

the anticonvulsant activity of orally administered CBN in mice utilizing chemoshock (Phenobarbitone induced convulsions) methods and revealed that oral administration of CBN was effective in protecting mice against PTZ induced convulsions. Using cultured rat granulosa cells, Adashi et al. (Adashi et al., 1983) studied the immediate impacts of cannabinoids on ovarian activities. The study revealed that cannabinoids, specifically those related to THC but without psychoactive properties (such as CBN), exerted direct inhibitory influences on various granulosa cell functions that are dependent on FSH Table 2.

6. Clinical trials

CBN human tests are limited, and few studies on humans have discussed its pharmacokinetic properties and their effects (Agurell et al., 1981; Hollister, 1973; Johansson et al., 1987; Perez-Reyes et al., 1973). Karniol et al. (Karniol et al., 2008) studied the interaction of 50 mg CBN, 25 mg CBN + 25 mg Δ^9-THC, and 50 mg CBN + 25 mg Δ^9-THC orally. From this research, CBN tended to increase the effects of THC on certain aspects of psychological and physiological processes. Hollister (Hollister, 1973) tested the effect of administration of 100 mg of CBN orally and 30 mg of CBN by injection. They reported that CBN did not contribute to the pharmacological effect and had no cannabis-like effect. In addition, CBN is excreted partially unchanged in the urine. In the same year, Perez-Reyes et al. (Perez-Reyes et al., 1973) studied the pharmacological effect of infused 10 mg of CBN in humans. They reported that CBN is capable of producing a marijuana-like 'high' although the doses required for it are several larger than those of Δ^9-THC. The interaction between CBN and THC has also been studied. According to Hollister and Gillespie (Hollister and Gillespie, 1975), THC combined with CBN (20 mg and 40 mg, respectively) produced no detectable modification in the intensity, quality, or duration of the effects observed with THC alone. In a study conducted by Agurell et al. (Agurell et al., 1981), the oral ingestion of CBN (40 mg) resulted in plasma levels comparable to those achieved with THC (20 mg), suggesting that CBN might possess a shorter half-life than THC. In another study, Johansson et al. (Johansson et al., 1987) indicated that CBN had a high clearance, a substantial volume of distribution, and notably slow elimination from the body. This assessment of deuterium labeled CBN's pharmacokinetics provided insights into CBN's dynamics. Furthermore, this study demonstrated that the kinetics of CBN, THC, and CBD are similar excluding the terminal half-life and the volume of distribution.

7. Concluding remark and perspectives

Here we have reported the chemical and biological properties of CBN. It has been pointed out that CBN is generated as a result of the degradation of THC when the plant is exposed to heat and oxygen. While CBN is present in small amounts in fresh cannabis, its concentration increases as the plant ages or undergoes oxidation. CBN interacts with the ECS in the human body, weakly binding to cannabinoid receptors (CB2 and CB1). Its primary effects are associated with sedation and relaxation, making it a potential natural sleep aid. CBN analgesic properties suggest that it may have a role in pain management, particularly for neuropathic and inflammatory pain.

In addition to its potential as a remedy for sleep issues and pain relief, CBN shows promise in other areas. Some studies provided that it has neuroprotective properties, offering potential benefits in addressing neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. It may also stimulate appetite, making it useful for people with reduced appetite due to medical conditions or treatments. Preliminary research indicates that CBN might possess antibacterial activities, which may be helpful in fighting certain bacterial infections.

Although these insights highlight the potential applications of CBN, further research is necessary to understand its mechanisms of action, potential side effects, and optimal clinical use. It is important to note that regulations regarding cannabinoids can vary by region. It is therefore essential to consult healthcare professionals or experts in your jurisdiction for accurate and up-to-date information.

In summary, CBN, derived from cannabis, exhibits sedative, analgesic, potential neuroprotective, appetite-stimulating, and antibacterial properties. Thus, CBN is a promising candidate for sleep disorders, pain management, neurodegenerative conditions, appetite stimulation, and potential antimicrobial applications. However, continued research is essential to establish its effectiveness, safety, and appropriate clinical use.

Funding

This study was funded by the Deputyship for Research and Innovation, Ministry of Education in Saudi Arabia (Project number ISP23-81)

Table 2
Other activities of cannabinol.

Activities	Experimental approaches	Key results	References
Antinociceptive effects	Hot-plate method Oral administration of cannabinol acetate at doses of 10,20, 40, 60 mg/kg	Showed dose-dependent antinociceptive effect Induced a rise in reaction time proportional to the administered dose	(Chesher et al., 1973)
Hypersensitivity (DTH) responses	Injected intradermally was a volume of 0.02 mL containing 1 ×10^8 SRBCs using a 30-gauge needle in mice DTH reaction was quantified by determining the disparity in footpad enlargement between the injected left hind paw and the non-injected right hind paw	Reduced the Day 4 peak response by 60%	(Levy and Heppner, 1978)
Suppressed post-swim grooming behavior in mice	Grooming behaviour induced by swimming	CBN elicited a dosage-dependent reduction in swim-induced grooming behavior in mice	(Chesher and Jackson, 1980)
Antitussive activity	Cats under pentobarbital anesthesia were subjected to either electrical stimulation of the superior laryngeal nerve	Induced antitussive effects even at doses as elevated as 10.0 mg/kg	(Gordon et al., 1976)
Cannabimimetic activity	Drug discrimination learning techniques, open-field and temperature measurements, along with a procedure involving palpation-induced vocalization in rats	Increased the percentage of responding appropriately to the drug,	(Järbe and Hiltunen, 1987)
Immunosuppressive actions	Primary mouse splenocytes *in vitro*	Diminished the nuclear presence of c-jun and c-fos Inhibited the activation of ERK MAP kinases.	(Faubert and Kaminski, 2000)
Antioxidant activity	DPPH, ABTS, ORAC, FRAP, β-carotene, and CUPRAC	Antioxidant activity greater than that of Trolox in all tests	(Dawidowicz et al., 2021)
	An *in vitro* model utilizing specialized human neuronal SY-SH5Y cells that have undergone differentiation Oxidative damage induced by hydrogen peroxide	Exhibited a significant antioxidant activity	(Raja et al., 2020)
Narcotic detoxification	Naloxone-Precipitated Abstinence in Morphine-Dependent Mice	Suppressed the morphine abstinence precipitated by naloxone, as indicated by an elevation in the naloxone ED_{50} value Suppressed defecation and rearing behavior	(Bhargava, 1976)
Anticonvulsant activity	Chemoshock (Phenobarbitone induced convulsions) methods in mice. Electroshock test in mice	Significant anticonvulsant activity ED_{50} values of 230 mg/kg Peak effect about 2 hr	(Chesher and Jackson, 1974) (Karler and Turkanis, 1981)
Anti-gonadal activity	*In vitro* ovarian functions using cultured rat granulosa cells	Direct inhibitory effects on a variety of FSH-dependent granulosa cell functions	(Adashi et al., 1983)
Human skin effect	*In vitro* human cutaneous transdermal flux of CBN, CBD, and Δ^8-THC	CBD and CBN exhibited permeabilities 10 times greater than Δ^8-THC Lag times for CBD were notably briefer compared to CBN Δ^8-THC amassed considerably higher tissue concentrations compared to CBN	(Stinchcomb et al., 2004)

CRediT authorship contribution statement

Yatinesh Kumari: Writing – review & editing. **Ikram Zaouekd:** Writing – review & editing. **Bey Hing Goh:** Conceptualization, Writing – review & editing. **Ahmed Hajib:** Writing – original draft. **Abdelhakim Bouyahya:** Conceptualization, Project administration, Supervision. **Soukaina Msairi:** Writing – original draft, Writing – review & editing. **Sang Loon Tan:** Writing – review & editing. **Smail Amalich:** Writing – original draft, Writing – review & editing. **Naoual El Meniyiy:** Writing – original draft, Writing – review & editing. **Manal Lahyaoui:** Writing – original draft, Writing – review & editing. **Chaimae Rais:** Writing – original draft, Writing – review & editing. **Ashraf N. Abdalla:** Writing – original draft, Writing – review & editing. **Asaad Khalid:** Writing – original draft, Writing – review & editing. **Nasreddine El Omari:** Writing – original draft, Writing – review & editing. **Sara Khouri:** Writing – original draft. **Salma E. Ibrahim:** Writing – original draft, Writing – review & editing. **Aya Khouchlaa:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors extend their appreciation to the Deputyship for Research and Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project with number: ISP23–81.

References

Acharya, N., Penukonda, S., Shcheglova, T., Hagymasi, A.T., Basu, S., Srivastava, P.K., 2017. Endocannabinoid system acts as a regulator of immune homeostasis in the gut. Proc. Natl. Acad. Sci. 114, 5005–5010. https://doi.org/10.1073/pnas.1612177114.

Adams, R., Baker, B.R., Wearn, R.B., 1940. Structure of cannabinol. III. Synthesis of cannabinol, 1-hydroxy-3-n-amyl-6, 6, 9-trimethyl-6-dibenzopyran1. J. Am. Chem. Soc. 62, 2204–2207. https://doi.org/10.1021/ja01865a083.

Adashi, E.Y., Jones, P.B., Hsueh, A.J., 1983. Direct antigonadal activity of cannabinoids: suppression of rat granulosa cell functions. Am. J. Physiol. 244, E177–E185. https://doi.org/10.1152/ajpendo.1983.244.2.E177.

Agurell, S., Carlsson, S., Lindgren, J.E., Ohlsson, A., Gillespie, H., Hollister, L., 1981. Interactions of Δ11-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography with cannabinol and cannabidiol following oral administration in man. Experientia 37, 1090–1092. https://doi.org/10.1007/BF02085029.

Alozie, S.O., Martin, B.R., Harris, L.S., Dewey, W.L., 1980. 3H-Δ9-tetrahydrocannabinol, 3H-cannabinol and 3H-cannabidiol: penetration and regional distribution in rat brain. Pharmacol. Biochem. Behav. 12, 217–221. https://doi.org/10.1016/0091-3057(80)90359-7.

AlSheikh, H.M.A., Sultan, I., Kumar, V., Rather, I.A., Al-Sheikh, H., Jan, A.T., Haq, Q.M. R., 2020. Plant-based phytochemicals as possible alternative to antibiotics in combating bacterial drug resistance. Antibiotics 9, 480. https://doi.org/10.3390/antibiotics9080480.

Amar, M.B., 2006. Cannabinoids in medicine: a review of their therapeutic potential. J. Ethnopharmacol. 105, 1–25. https://doi.org/10.1016/j.jep.2006.02.001.

Appendino, G., 2020. The early history of cannabinoid research. Rend. Lince. Sci. Fis. 31, 919–929. https://doi.org/10.1007/s12210-020-00956-0.

Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., Smith, E., Rahman, M.M., 2008. Antibacterial cannabinoids from *Cannabis sativa*: a structure−activity study. J. Nat. Prod. 71, 1427–1430. https://doi.org/10.1021/np8002673.

Atakan, Z., 2012. Cannabis, a complex plant: different compounds and different effects on individuals. Ther. Adv. Psychopharmacol. 2, 241–254. https://doi.org/10.1177/2045125312457586.

Bagri, P., Ali, M., Aeri, V., Bhowmik, M., Sultana, S., 2009. Antidiabetic effect of *Punica granatum* flowers: effect on hyperlipidemia, pancreatic cells lipid peroxidation and antioxidant enzymes in experimental diabetes. Food Chem. Toxicol. 47 (1), 50–54.

Bastola, K.P., Hazekamp, A., Verpoorte, R., 2007. Synthesis and spectroscopic characterization of cannabinolic acid. Planta Med. 73, 273–275. https://doi.org/10.1055/s-2007-967129.

Bhargava, H., 1976. Effect of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice. Psychopharmacology 49, 267–270. https://doi.org/10.1007/BF00426828.

Burstein, S.H., 1973. Labeling and metabolism of the tetrahydrocannabinols. In: Mechoulam, R., Burstein, S. (Eds.), Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects. Academic Press, Massachusetts, pp. 167–190.

Cabral, G.A., Ferreira, G.A., Jamerson, M.J., 2015. Endocannabinoids and the immune system in health and disease, Handbook of Experimental PharmacologyEndocannabinoids. Springer Link, New York, pp. 185–211R.G. Pertwee.

Cabral, G.A., Rogers, T.J., Lichtman, A.H., 2015b. Turning over a new leaf: cannabinoid and endocannabinoid modulation of immune function. J. Neuroimmune Pharmacol. 10, 193–203. https://doi.org/10.1007/s11481-015-9615-z.

Cahn, R.S., 1933. 326. Cannabis indica resin. Part IV. The synthesis of some 2: 2-dimethyldibenzopyrans, and confirmation of the structure of cannabinol. J. Chem. Soc. 1933, 1400–1405. https://doi.org/10.1039/JR9330001400.

Caprioglio, D., Mattoteia, D., Minassi, A., Pollastro, F., Lopatriello, A., Muñoz, E., Taglialatela-Scafati, O., Appendino, G., 2019. One-pot total synthesis of cannabinol *via* iodine-mediated deconstructive annulation. Org. Lett. 21, 6122–6125. https://doi.org/10.1021/acs.orglett.9b02258.

Chesher, G.B., Jackson, D.M., 1974. Anticonvulsant effects of cannabinoids in mice: Drug interactions within cannabinoids and cannabinoid interactions with phenytoin. Psychopharmacologia 37, 255–264. https://doi.org/10.1007/BF00421539.

Chesher, G.B., Jackson, D.M., 1980. Post-swim grooming in mice inhibited by dopamine receptor antagonists and by cannabinoids. Pharmacol. Biochem. Behav. 13, 479–481. https://doi.org/10.1016/0091-3057(80)90260-9.

Chesher, G.B., Dahl, C.J., Everingham, M., Jackson, D.M., Marchant-Williams, H., Starmer, G.A., 1973. The effect of cannabinoids on intestinal motility and their antinociceptive effect in mice. Br. J. Pharmacol. 49, 588–594. https://doi.org/10.1111/j.1476-5381.1973.tb08534.x.

Chiurchiù, V., Battistini, L., Maccarrone, M., 2015a. Endocannabinoid signalling in innate and adaptive immunity. Immunology 144, 352–364. https://doi.org/10.1111/imm.12441.

Chiurchiù, V., Leuti, A., Maccarrone, M., 2015b. Cannabinoid signaling and neuroinflammatory diseases: a melting pot for the regulation of brain immune responses. J. Neuroimmune Pharmacol. 10, 268–280. https://doi.org/10.1007/s11481-015-9584-2.

Clarke, R., Merlin, M., 2013. Cannabis: evolution and ethnobotany. 1st ed. Berkeley: University of California Press.

Colasanti, B.K., Craig, C.R., Allara, R.D., 1984. Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. Exp. Eye Res. 39, 251–259. https://doi.org/10.1016/0014-4835(84)90013-7.

Dawidowicz, A.L., Olszowy-Tomczyk, M., Typek, R., 2021. CBG, CBD, Δ9-THC, CBN, CBGA, CBDA and Δ9-THCA as antioxidant agents and their intervention abilities in antioxidant action. Fitoterapia 152, 104915. https://doi.org/10.1016/j.fitote.2021.104915.

Domino, E.F., 1976. Effects of Δ9-tetrahydrocannabinol and cannabinol on rat brain acetylcholine. In: Nahas, G.G., Paton, W.D.M., Idänpään-Heikkilä, J.E. (Eds.), Marihuana. Springer Link, New York, pp. 407–413.

Elsohly, M.A., Harland, E., Murphy, J.C., Wirth, P., Waller, C.W., 1981. Cannabinoids in glaucoma: a primary screening procedure, 472S-478S J. Clin. Pharmacol. 21. https://doi.org/10.1002/j.1552-4604.1981.tb02627.x.

ElSohly, M.A., Radwan, M.M., Gul, W., Chandra, S., Galal, A., 2017. Phytochemistry of Cannabis sativa L, unraveling the complex chemistry and pharmacology of Cannabis sativa, New YorkPhytocannabinoids. Springer Link, pp. 1–36A.D.KinghornH.FalkS. GibbonsJ.Kobayashi.

Evans, F.J., 1991. Cannabinoids: the separation of central from peripheral effects on a structural basis. Planta Med. 57, S60–S67.

Fan, F., Dong, J., Wang, J., Song, L., Song, C., Chang, J., 2014. An intramolecular pyranone diels—alder cycloaddition approach to cannabinol. Adv. Synth. Catal. 356, 1337–1342. https://doi.org/10.1002/adsc.201301037.

Farrimond, J.A., Whalley, B.J., Williams, C.M., 2012. Non-Δ9tetrahydrocannabinol phytocannabinoids stimulate feeding in rats. Behav. Pharmacol. 23, 113–117. https://doi.org/10.1097/FBP.0b013e32834ed832.

Faubert, B.L., Kaminski, N.E., 2000. AP-1 activity is negatively regulated by cannabinol through inhibition of its protein components, c-fos and c-jun. J. Leukoc. Biol. 67, 259–266. https://doi.org/10.1002/jlb.67.2.259.

Filipiuc, L.E., Ababei, D.C., Alexa-Stratulat, T., Pricope, C.V., Bild, V., Stefanescu, R., Stanciu, G.D., Tamba, B.-I., 2021. Major phytocannabinoids and their related compounds: should we only search for drugs that act on cannabinoid receptors? Pharmaceutics 13, 1823. https://doi.org/10.3390/pharmaceutics13111823.

Gordon, R., Gordon, R.J., Sofia, D., 1976. Antitussive activity of some naturally occurring cannabinoids in anesthetized cats. Eur. J. Pharmacol. 35, 309–313. https://doi.org/10.1016/0014-2999(76)90233-8.

Guo, D.-D., Li, B., Wang, D.-Y., Gao, Y.-R., Guo, S.-H., Pan, G.-F., Wang, Y.-Q., 2017. Synthesis of 6H-benzo [c] chromenes *via* palladium-catalyzed intramolecular dehydrogenative coupling of two aryl C–H bonds. Org. Lett. 19, 798–801. https://doi.org/10.1021/acs.orglett.6b03763.

Hattori, T., Suzuki, T., Miyano, S., 1991. A practical and efficient method for the construction of the biphenyl framework; nucleophilic aromatic substitution on 2-methoxybenzoates with aryl grignard reagents. J. Chem. Soc. Chem. Commun. 1991, 1375–1376. https://doi.org/10.1039/C39910001375.

Herring, A.C., Kaminski, N.E., 1999. Cannabinol-mediated inhibition of nuclear factor-κB, cAMP response element-binding protein, and interleukin-2 secretion by activated thymocytes. J. Pharmacol. Exp. Ther. 291, 1156–1163.

Herring, A.C., Koh, W.S., Kaminski, N.E., 1998. Inhibition of the cyclic AMP signaling cascade and nuclear factor binding to CRE and κB elements by cannabinol, a minimally CNS-active cannabinoid. Biochem. Pharmacol. 55, 1013–1023. https://doi.org/10.1016/S0006-2952(97)00630-8.

Herring, A.C., Faubert Kaplan, B.L., Kaminski, N.E., 2001. Modulation of CREB and NF-κB signal transduction by cannabinol in activated thymocytes. Cell. Signal. 13, 241–250. https://doi.org/10.1016/S0898-6568(01)00145-0.

Hollister, L.E., 1973. Cannabidiol and cannabinol in man. Experientia 29, 825–826. https://doi.org/10.1007/BF01946311.

Hollister, L.E., Gillespie, H., 1975. Interactions in man of delta-9-tetrahydrocannabinol; II. Cannabinol and cannabidiol. Clin. Pharmacol. Ther. 18, 80–83. https://doi.org/10.1002/cpt197518180.

Howlett, A.C., 1987. Cannabinoid inhibition of adenylate cyclase: relative activity of constituents and metabolites of marihuana. Neuropharmacology 26, 507–512. https://doi.org/10.1016/0028-3908(87)90035-9.

Huestis, M.A., 2005. Pharmacokinetics and metabolism of the plant cannabinoids, Δ 9-tetrahydrocannibinol, cannabidiol and cannabinol. In: Pertwee, R.G. (Ed.), Cannabinoids. Springer Link, New York, pp. 657–690.

Jan, T.-R., Kaminski, N.E., 2001. Role of mitogen-activated protein kinases in the differential regulation of interleukin-2 by cannabinol. J. Leukoc. Biol. 69, 841–849. https://doi.org/10.1189/jlb.69.5.841.

Jan, T.-R., Rao, G.K., Kaminski, N.E., 2002. Cannabinol enhancement of interleukin-2 (IL-2) expression by T cells is associated with an increase in IL-2 distal nuclear factor of activated T cell activity. Mol. Pharmacol. 61, 446–454. https://doi.org/10.1124/mol.61.2.446.

Järbe, T.U., Hiltunen, A.J., 1987. Cannabimimetic activity of cannabinol in rats and pigeons. Neuropharmacology 26, 219–228. https://doi.org/10.1016/0028-3908(87)90212-7.

Johansson, E., Ohlsson, A., Lindgren, J.-E., Agurell, S., Gillespie, H., Hollister, L.E., 1987. Single-dose kinetics of deuterium-labelled cannabinol in man after intravenous administration and smoking. Biomed. Environ. Mass Spectrom. 14, 495–499. https://doi.org/10.1002/bms.1200140904.

Karas, J.A., Wong, L.J., Paulin, O.K., Mazeh, A.C., Hussein, M.H., Li, J., Velkov, T., 2020. The antimicrobial activity of cannabinoids. Antibiotics 9, 406. https://doi.org/10.3390/antibiotics9070406.

Karler, R., Turkanis, S.A., 1981. The cannabinoids as potential antiepileptics, 437S-448S J. Clin. Pharmacol. 21. https://doi.org/10.1002/j.1552-4604.1981.tb02624.x.

Karniol, I.G., Shirakawa, I., Takahashi, R.N., Knobel, E., Musty, R.E., 2008. Effects of Δ9-Tetrahydrocannabinol and Cannabinol in Man. Pharmacology 13, 502–512. https://doi.org/10.1159/000136944.
Khare, T., Anand, U., Dey, A., Assaraf, Y.G., Chen, Z.-S., Liu, Z., Kumar, V., 2021. Exploring phytochemicals for combating antibiotic resistance in microbial pathogens. Front. Pharmacol. 12, 720726 https://doi.org/10.3389/fphar.2021.720726.
Kleckner, A.S., Kleckner, I.R., Kamen, C.S., Tejani, M.A., Janelsins, M.C., Morrow, G.R., Peppone, L.J., 2019. Opportunities for *Cannabis* in supportive care in cancer, 1758835919866362 Ther. Adv. Med. Oncol. 11. https://doi.org/10.1177/1758835919866362.
Kloss, F., Neuwirth, T., Haensch, V.G., Hertweck, C., 2018. Metal-free synthesis of pharmaceutically important biaryls by photosplicing. Angew. Chem. Int. Ed. 57, 14476–14481. https://doi.org/10.1002/anie.201805961.
Kolar, N., Bankoglu, E.E., Stopper, H., 2023. Cellular effects of cannabinoids from *Cannabis sativa in vitro*. Span. J. Environ. Mutagen. Genom. 27, 98.
Leelawat, S., Leelawat, K., Yimsoo, T., Wunnakup, T., Monton, C., Khamthong, N., Madaka, F., Maha, A., Songsak, T., 2022. Antitumor effects of delta (9)-tetrahydrocannabinol and cannabinol on cholangiocarcinoma cells and xenograft mouse models. Evid. Based Complement. Altern. Med. 2022, 1–14. https://doi.org/10.1155/2022/6477132.
Levy, Jeffrey A., Heppner, G.H., 1978. Alterations in murine delayed type hypersensitivity responses by delta-8-THC and cannabinol. J. Immunopharmacol. 1, 105–114. https://doi.org/10.3109/08923977809027332.
Li, Y., Ding, Y.J., Wang, J.Y., Su, Y.M., Wang, X.S., 2013. Pd-catalyzed C–H lactonization for expedient synthesis of biaryl lactones and total synthesis of cannabinol. Org. Lett. 15 (11), 2574–2577.
Liang, Z., Soriano-Castell, D., Kepchia, D., Duggan, B.M., Currais, A., Schubert, D., Maher, P., 2022. Cannabinol inhibits oxytosis/ferroptosis by directly targeting mitochondria independently of cannabinoid receptors. Free. Radic. Biol. Med. 180, 33–51. https://doi.org/10.1016/j.freeradbiomed.2022.01.001.
Mahadeo, M.N., Lee, E., Bains, J., Ruben, P.C., Thewalt, J.L., 2023. Cannabidiol and cannabinol have distinct effects on membrane structure. Biophys. J. 122, 83a. https://doi.org/10.1016/j.bpj.2022.11.653.
Maioli, C., Mattoteia, D., Amin, H.I.M., Minassi, A., Caprioglio, D., 2022. Cannabinol: history, syntheses, and biological profile of thAS e greatest "minor" cannabinoid. Plants 11, 2896. https://doi.org/10.3390/plants11212896.
Maione, S., Costa, B., Di Marzo, V., 2013. Endocannabinoids: a unique opportunity to develop multitarget analgesics. Pain 154, S87–S93. https://doi.org/10.1016/j.pain.2013.03.023.
McCallum, N.K., 1974. The determination of cannabinol levels in the blood and interpretation of their significance. In: McQueen, E.G., Dunedin (Eds.), Newer concepts of cannabis action and opiate dependence. Basel: Karger Publishers, pp. 33–37.
McCoy, K.L., 2016. Interaction between cannabinoid system and toll-like receptors controls inflammation. Mediat. Inflamm. 2016, e5831315 https://doi.org/10.1155/2016/5831315.
McLaughlin, C.L., Baile, C.A., Bender, P.E., 1979. Cannabinols and feeding in sheep. Psychopharmacology 64, 321–323. https://doi.org/10.1007/BF00427517.
Mechoulam, R., Yagnitinsky, B., Gaoni, Y., 1968. XII. Stereoelectronic factor in the chloranil dehydrogenation of cannabinoids. Total synthesis of dl-cannabichromene. J. Am. Chem. Soc. 90, 2418–2420. https://doi.org/10.1021/ja01011a037.
Meyers, A.I., Gabel, R., Mihelich, E.D., 1978. Nucleophilic aromatic substitution on (o-methoxyaryl) oxazolines. A convenient synthesis of o-alkyl-, o-alkenyl-, and o-arylbenzoic acids. J. Org. Chem. 43, 1372–1379. https://doi.org/10.1021/jo00401a018.
Minuti, L., Temperini, A., Ballerini, E., 2012. High-pressure-promoted diels–alder approach to biaryls: application to the synthesis of the cannabinols family. J. Org. Chem. 77, 7923–7931. https://doi.org/10.1021/jo301203k.
Mou, C., Zhu, T., Zheng, P., Yang, S., Song, B.-A., Chi, Y.R., 2016. Green and rapid access to benzocoumarins *via* direct benzene construction through base-mediated formal [4+2] reaction and air oxidation. Adv. Synth. Catal. 358, 707–712. https://doi.org/10.1002/adsc.201500771.
Munson, A.E., Harris, L.S., Friedman, M.A., Dewey, W.L., Carchman, R.A., 1975. Antineoplastic activity of cannabinoids. J. Natl. Cancer Inst 55, 597–602. https://doi.org/10.1093/jnci/55.3.597.
Murphy, L.L., Steger, R.W., Smith, S., Bartke, A., 1990. Effects of delta-9-tetrahydrocannabinol, cannabinol and cannabidiol, alone and in combinations, on luteinizing hormone and prolactin release and on hypothalamic neurotransmitters in the male rat. Neuroendocrinology 52, 316–321. https://doi.org/10.1159/000125604.
Nandaluru, P.R., Bodwell, G.J., 2012. Multicomponent synthesis of 6h-dibenzo [b,d] pyran-6-ones and a total synthesis of cannabinol. Org. Lett. 14, 310–313. https://doi.org/10.1021/ol2030636.
Norseeda, K., Tummatorn, J., Krajangsri, S., Thongsornkleeb, C., Ruchirawat, S., 2016. Synthesis of 6-alkyl-6h-benzo [c] chromene derivatives by cyclization/selective ether cleavage in one pot: total synthesis of cannabinol. Asian J. Org. Chem. 5, 792–800. https://doi.org/10.1002/ajoc.201600095.
Novák, J., Salemink, C.A., 1982. Cannabis xxiv. A new convenient synthesis of cannabinol. Tetrahedron Lett. 23, 253–254. https://doi.org/10.1016/S0040-4039(00)86800-8.
Nüellen, M.P., Göttlich, R., 2013. Synthesis of cannabinol by a modified Ullmann–Ziegler cross-coupling. Synlett 24, 1109–1112. https://doi.org/10.1055/s-0033-1338428.
Olmsted, C.A., 1976. Effects of cannabinoids on synaptic membrane Enzymes. I. In vitro studies on synaptic membranes isolated from rat brain. Am. J. Drug Alcohol Abus. 3, 485–505. https://doi.org/10.3109/00952997609014289.
Paton, W.D., Pertwee, R.G., 1973. The pharmacology of cannabis in animals. In: Mechoulam, R., Burstein, S. (Eds.), Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects. Academic Press, Massachusetts, pp. 191–285.
Perez-Reyes, M., Timmons, M.C., Davis, K.H., Wall, E.M., 1973. A comparison of the pharmacological activity in man of intravenously administered delta9-tetrahydrocannabinol, cannabinol, and cannabidiol. Experientia 29, 1368–1369. https://doi.org/10.1007/BF01922823.
Pertwee, R.G., 2005. Pharmacological actions of cannabinoids. In: Pertwee, R.G. (Ed.), Cannabinoids. New York: Springer Link, pp. 1–51.
Pollastro, F., Caprioglio, D., Marotta, P., Moriello, A.S., De Petrocellis, L., Taglialatela-Scafati, O., Appendino, G., 2017. Iodine-promoted aromatization of p-menthane-type phytocannabinoids. J. Nat. Prod. 81, 630–633. https://doi.org/10.1021/acs.jnatprod.7b00946.
Raja, A., Ahmadi, S., de Costa, F., Li, N., Kerman, K., 2020. Attenuation of oxidative stress by cannabinoids and cannabis extracts in differentiated neuronal cells. E328 Pharmaceuticals 13. https://doi.org/10.3390/ph13110328.
Rodrigues, A., Yegles, M., Van Elsué, N., Schneider, S., 2018. Determination of cannabinoids in hair of CBD rich extracts consumers using gas chromatography with tandem mass spectrometry (GC/MS-MS). Forensic Sci. Int. 292, 163–166. https://doi.org/10.1016/j.forsciint.2018.09.015.
Saingam, W., Sakunpak, A., 2018. Development and validation of reverse phase high performance liquid chromatography method for the determination of delta-9-tetrahydrocannabinol and cannabidiol in oromucosal spray from cannabis extract. Rev. Bras. Farmacogn. 28, 669–672. https://doi.org/10.1016/j.bjp.2018.08.001.
Schwope, D.M., Karschner, E.L., Gorelick, D.A., Huestis, M.A., 2011. Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. Clin. Chem. 57, 1406–1414. https://doi.org/10.1373/clinchem.2011.171777.
Shammas, M.A., Bertheau, R.C., Munshi, V., Patel, L., Prabhala, R., Desarnaud, F., Driscoll, J., Munshi, N.C., 2006. Critical role of recombinase (HsRAD51) in genetic instability in multiple myeloma. Blood 108, 2078. https://doi.org/10.1182/blood.V108.11.2078.2078.
Sofia, R.D., Vassar, H.B., Knobloch, L.C., 1975. Comparative analgesic activity of various naturally occurring cannabinoids in mice and rats. Psychopharmacologia 40, 285–295. https://doi.org/10.1007/BF00421466.
Somvanshi, R.K., Zou, S., Kadhim, S., Padania, S., Hsu, E., Kumar, U., 2022. Cannabinol modulates neuroprotection and intraocular pressure: A potential multi-target therapeutic intervention for glaucoma. Biochim. Biophys. Acta Mol. Basis Dis. 1868, 166325 https://doi.org/10.1016/j.bbadis.2021.166325.
Stinchcomb, A.L., Valiveti, S., Hammell, D.C., Ramsey, D.R., 2004. Human skin permeation of Δ8-tetrahydrocannabinol, cannabidiol and cannabinol. J. Pharm. Pharmacol. 56, 291–297. https://doi.org/10.1211/0022357022791.
Sultana, H.S., Ali, M., Panda, B.P., 2012. Influence of volatile constituents of fruit peels of *Citrus reticulata* Blanco on clinically isolated pathogenic microorganisms under *In–vitro*. Asian Pacific J. Trop. Biomed. *2* (3), S1299–S1302.
Sultana, S., SN, M.N.U., Zafar, A., 2024. Novel products as promising therapeutic agents for angiogenesis inhibition. Curr. Drug Deliv. 38204254 https://doi.org/10.2174/0115672018277869231217165048.
Teske, J.A., Deiters, A., 2008. A cyclotrimerization route to cannabinoids. Org. Lett. 10, 2195–2198. https://doi.org/10.1021/ol800589e.
Thornton, C., Dickson, K.E., Carty, D.R., Ashpole, N.M., Willett, K.L., 2020. *Cannabis* constituents reduce seizure behavior in chemically-induced and scn1a-mutant zebrafish. Epilepsy Behav. 110, 107152 https://doi.org/10.1016/j.yebeh.2020.107152.
Tian, M., Xie, D., Yang, Y., Tian, Y., Jia, X., Wang, Q., Deng, G., Zhou, Y., 2023. Hedychium flavum flower essential oil: chemical composition, anti-inflammatory activities and related mechanisms *in vitro* and *in vivo*. J. Ethnopharmacol. 301, 115846 https://doi.org/10.1016/j.jep.2022.115846.
Turner, C.E., Elsohly, M.A., 1981. Biological activity of cannabichromene, its homologs and isomers, 283S-291S J. Clin. Pharmacol. 21. https://doi.org/10.1002/j.1552-4604.1981.tb02606.x.
Turner, C.E., Elsohly, M.A., Boeren, E.G., 1980. Constituents of Cannabis sativa L. XVII. A review of the natural constituents. J. Nat. Prod. 43, 169–234. https://doi.org/10.1021/np50008a001.
Ulugöl, A., 2014. The endocannabinoid system as a potential therapeutic target for pain modulation. Balk. Med. J. 31, 115–120. https://doi.org/10.5152/balkanmedj.2014.13103.
United Nations Office on Drugs and Crime. Recommended methods for the identification and analysis of cannabis and cannabis products: manual for use by national drug testing laboratories, ⟨https://www.unodc.org/documents/scientific/ST-NAR-40-Ebook_1.pdf⟩; 2009 [accessed 13 March 2023].
Velasco, C., Woods, A.T., Petit, O., Cheok, A.D., Spence, C., 2016. Crossmodal correspondences between taste and shape, and their implications for product packaging: a review. Food Qual. Prefer. 52, 17–26. https://doi.org/10.1016/j.foodqual.2016.03.005.
Wang, B., Li, D., Cherkasova, V., Gerasymchuk, M., Narendran, A., Kovalchuk, I., Kovalchuk, O., 2022. Cannabinol inhibits cellular proliferation, invasion, and angiogenesis of neuroblastoma via novel miR-34a/tRiMetF31/PFKFB3 Axis. Cancers 14, 1908. https://doi.org/10.3390/cancers14081908.
Watanabe, K., Narimatsu, S., Matsunaga, T., Yamamoto, I., Yoshimura, H., 1993. A cytochrome P450 isozyme having aldehyde oxygenase activity plays a major role in metabolizing cannabinoids by mouse hepatic microsomes. Biochem. Pharmacol. 46, 405–411. https://doi.org/10.1016/0006-2952(93)90516-Y.
Watanabe, K., Kayano, Y., Matsunaga, T., Yamamoto, I., Yoshimura, H., 1996. Inhibition of anandamide amidase activity in mouse brain microsomes by cannabinoids. Biol. Pharm. Bull. 19, 1109–1111. https://doi.org/10.1248/bpb.19.1109.

Watanabe, K., Ogi, H., Nakamura, S., Kayano, Y., Matsunaga, T., Yoshimura, H., Yamamoto, I., 1998. Distribution and characterization of anandamide amidohydrolase in mouse brain and liver. Life Sci. 62, 1223–1229. https://doi.org/10.1016/s0024-3205(98)00052-6.

Watanabe, Kazuhito, Miyamoto, M., Yamaori, S., Hasegawa, K., Watanabe, Kanako, Suzuki, O., 2013. Human brain microsomes: their abilities to metabolize tetrahydrocannabinols and cannabinol. Forensic Toxicol. 31, 307–311. https://doi.org/10.1007/s11419-013-0181-x.

Weydt, P., Hong, S., Witting, A., Möller, T., Stella, N., Kliot, M., 2005. Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival. Amyotroph. Lateral Scler. 6, 182–184. https://doi.org/10.1080/14660820510030149.

Wong, H., Cairns, B.E., 2019. Cannabidiol, cannabinol and their combinations act as peripheral analgesics in a rat model of myofascial pain. Arch. Oral. Biol. 104, 33–39. https://doi.org/10.1016/j.archoralbio.2019.05.028.

Wood, B., Spivey, W.T.N., Easterfield, T.H., 1899. III.–Cannabinol. Part 1. J. Chem. Soc. Trans. 75, 20–36. https://doi.org/10.1039/CT8997500020.

Work, T.S., Bergel, F., Todd, A.R., 1939. The active principles of cannabis indica resin. I. Biochem. J. 33, 123–127. https://doi.org/10.1042/bj0330123.

Yamamoto, I., Watanabe, K., Kuzuoka, K., Narimatsu, S., Yoshimura, H., 1987. The pharmacological activity of cannabinol and its major metabolite, 11-hydroxycannabinol. Chem. Pharm. Bull. 35, 2144–2147. https://doi.org/10.1248/cpb.35.2144.

Yamaori, S., Kushihara, M., Yamamoto, I., Watanabe, K., 2010. Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. Biochem. Pharmacol. 79, 1691–1698. https://doi.org/10.1016/j.bcp.2010.01.028.

Yamaori, S., Ebisawa, J., Okushima, Y., Yamamoto, I., Watanabe, K., 2011. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: Role of phenolic hydroxyl groups in the resorcinol moiety. Life Sci. 88, 730–736. https://doi.org/10.1016/j.lfs.2011.02.017.

Yamaori, S., Koeda, K., Kushihara, M., Hada, Y., Yamamoto, I., Watanabe, K., 2012. Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. Drug Metab. Pharmacokinet. 27, 294–300. https://doi.org/10.2133/dmpk.DMPK-11-RG-107.

Yea, S.S., Yang, K.-H., Kaminski, N.E., 2000. Role of nuclear factor of activated t-cells and activator protein-1 in the inhibition of interleukin-2 gene transcription by cannabinol in EL4 T-cells. J. Pharmacol. Exp. Ther. 292, 597–605.

Zaiachuk, M., Suryavanshi, S.V., Pryimak, N., Kovalchuk, I., Kovalchuk, O., 2023. The anti-inflammatory effects of *Cannabis sativa* extracts on LPS-induced cytokines release in human macrophages. Molecules 28, 4991. https://doi.org/10.3390/molecules28134991.

Zhong, N., Li, D., Wang, B., Kovalchuk, O., Kovalchuk, I., 2023. Cannabinol inhibits cell growth and triggers cell cycle arrest and apoptosis in cancer cells. Biocatal. Agric. Biotechnol. 48, 02627. https://doi.org/10.1016/j.bcab.2023.102627.

Zubcevic, K., Petersen, M., Bach, F.W., Heinesen, A., Enggaard, T.P., Almdal, T.P., Holbech, J.V., Vase, L., Jensen, T.S., Hansen, C.S., 2023. Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment. Eur. J. Pain. 27, 492–506. https://doi.org/10.1002/ejp.2072.