The impact of phyto- and endo-cannabinoids on central nervous system diseases : A review

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ABSTRACT

Background and aim: *Cannabis sativa* L. is a medicinal plant with a long history. Phyto-cannabinoids are a class of compounds from *C. sativa* L. with varieties of structures. Endocannabinoids exist in the human body. This article provides an overview of natural cannabinoids (phyto-cannabinoids and endocannabinoids) with an emphasis on their pharmacology activities.
Experimental procedure: The keywords "*Cannabis sativa* L″, "cannabinoids", and "central nervous system (CNS) diseases" were used for searching and collecting pieces of literature from PubMed, ScienceDirect, Web of Science, and Google Scholar. The data were extracted and analyzed to explore the effects of cannabinoids on CNS diseases.
Result and conclusion: In this paper, schematic diagrams are used to intuitively show the phyto-cannabinoids skeletons' mutual conversion and pharmacological activities, with special emphasis on their relevant pharmacological activities on central nervous system (CNS) diseases. It was found that the endocannabinoid system and microglia play a crucial role in the treatment of CNS diseases. In the past few years, pharmacological studies focused on Δ^9-THC, CBD, and the endocannabinoids system. It is expected to encourage new studies on a more deep exploration of other types of cannabinoids and the mechanism of their pharmacological activities in the future.

1. Introduction

As one of the oldest plants in the world, *Cannabis sativa* L. has been used in textiles and medicinals for thousands of years.[1] The Chinese invented hemp paper in about 2000 BC, which is the earliest record of the application of hemp.[2] Cannabinoids are a class of compounds naturally exist in *C. sativa* L. and animal's central nervous and immune systems with multiple pharmacological activities. Cannabinoids exhibit a terpenophenolic skeleton, and they can be divided by sources as the endocannabinoids, the synthetic cannabinoids, and the phyto-cannabinoids.[3] The phyto-cannabinoids are isolated from *C. sativa* L. They are the main active ingredients of *C. sativa* L., and work by imitating endo-cannabinoids to activate specific receptors in human.[4] The main phyto-cannabinoids are Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD). In addition to *C. sativa* L. a series of cannabinoid analogs were also discovered in *Echinacea* species, *Helichrysum umbraculigerum*, and *Radula* species.[5]

Endocannabinoids play an immunoregulatory role in the immune system and modulate the excitability of the central nervous system. AEA (anandamide, *N*-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol) are the two major endocannabinoids.[6] To date, hundreds of cannabinoids have been isolated and identified. The cannabinoid receptors are a class of G protein-coupled receptor proteins, and the recognized cannabinoid receptors are cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2).[7] CB1 is mainly distributed in the nervous system and expressed in brain

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List of abbreviations		Aβ	Amyloid β-peptide
		LRP-1	Lipoprotein receptor-related protein 1
CBN	Cannabinol	LPS	lipopolysaccharide
THC	Tetrahydrocannabinol	ERK	Extra-cellular signal-regulated kinase
CBD	Cannabidiol	iNOS	Inducible nitric oxide synthase
AEA	Anandamide	IL-1β	Interleukin 1β
2-AG	2-arachidonoylglycerol	PD	Parkinson's disease
CB	Cannabinoid receptor	MAGL	Monoacylglycerol lipase
CNS	Central nervous system	FAAH	Fatty acid amide hydrolase
CBC	Cannabichromene	TNF-α	Tumor necrosis factor-α
CBG	Cannabigerol	PGE2	Prostaglandin E2
CBL	Cannabicyclol	NO	Nitric oxide
CBE	Cannabielsoin	ENT-1	Equilibrate nucleoside transporter 1
CBT	Cannabitriol	TRPV1	Transient receptor potential vanilloid 1 receptor
ECS	Endocannabinoid system	MS	Multiple sclerosis
AD	Alzheimer's disease	EAE	Experimental autoimmune encephalomyelitis
GSH-Px	Glutathione peroxidase	TLR4	Toll Like Receptor 4
HD	Huntington's disease		

tissue, which plays a role in regulating neurotransmitter transmission. The CB1 pathway is involved in metabolic syndrome and related symptoms, such as atherosclerosis, type 2 diabetes, and others.[8] CB2 primarily distributes in immune tissues and cells, and plays an immunomodulatory role. Cannabinoids can act on the immune system through CB2, while CB2 is only active in specific cell populations.[9] Numerous studies showed that cannabinoids have multiple pharmacological activities, such as reducing inflammation, pain modulation, treating sleep disorders, depressants, anti-epilepsy and other central nervous system (CNS) disorders.[10–13]

Neuroinflammation is considered a critical process in the development of the central nervous system. The CNS diseases include neurodegenerative diseases, depression, sleep disorders, epilepsy, stroke, multiple sclerosis, and pain.[14] The CNS disease was associated with inflammation, especially neuroinflammation. Therefore, the prevention of neuroinflammation seems to be one of the most effective treatments for these disorders.

This review will cover studies in the field up to 2022 focusing on chemical structure diversities and pharmacological activities of natural cannabinoids. It will provide a comprehensive inventory of cannabinoids of different origins and outline the pharmacological activities on CNS diseases.

2. Chemical structures of cannabinoids

2.1. Phyto-cannabinoids

The phyto-cannabinoids are classified according to three-part skeletal structure differences, which are the isoprenyl residue, the resorcinyl core, and the side chain.[15] Δ^9-tetrahydrocannabinol (THC)-type compounds are the largest number of phyto-cannabinoids. Δ^9-THC-type compounds are sensitive to air and temperature and are prone to oxidation and degradation. Oxidative degradation of Δ^9-THC caused by heating, light exposure, or aging will lead to CBN, and acid isomerization will generate Δ^8-tetrahydrocannabinol (Δ^8-THC) (Fig. 1). Both Δ^9-THC-type and Δ^8-THC-type belong to tetrahydrocannabinol-type (THC-type) compounds. Δ^9-THC is the main active ingredient of *Cannabis*, used for anti-emetic and analgesic for cancer patients, anti-anxiety, anti-in-flammatory, and other medical purposes.[1]

Other major phyto-cannabinoids in *Cannabis* are CBD-type compounds. Although the structures of CBD and Δ^9-THC show certain similarities, the two compounds have different biological properties. Other phyto-cannabinoids type contains Cannabicyclol (CBL)-type, Cannabielsoin (CBE)-type, Cannabinol (CBN)-type, and Cannabitriol (CBT)-type are also shown here.[15] Δ^9-THC, Cannabidiol (CBD), Cannabichromene (CBC), Cannabigerol (CBG), and Cannabinol (CBN) are the main phyto-cannabinoids. Cannabichromene (CBC) is also one of the most abundant phyto-cannabinoids in Cannabis spp. Cannabigeroids are one of the most diverse types of phyto-cannabinoids in chemical structure and are isomers with some structural changes based on isoprenyl.[16] The structure of Cannabigerol (CBG)-type compounds are linear isoprenyl skeleton. Also, there are some cannabinoids with monocyclic (CBC and CBD) or bicyclic (CBE, CBL, and CBN) structures (Fig. 1). The chemical structures of phyto-cannabinoids were listed in the Supplementary files.

2.2. Endocannabinoids

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are two major endocannabinoids. *N*-arachidonoyldopamine (NADA), *O*-arachidonoylethanolamide (VA), and 2-arachidonoylglycerol ether (2-AGE) derived from n-3 polyunsaturated fatty acids are also considered endocannabinoids.[17] Endocannabinoids, receptors, and enzymes (synthesize and degrade endocannabinoids) constitute the endocannabinoid system (ECS, Fig. 2). The ECS is a neuro-modulation network that participates in the development of the central nervous system and plays an important role in the homeostasis maintenance of cognition, behavior, emotion, development, and various physiological processes. Studies have shown that the endocannabinoid system is the foundation of emotional homeostasis and cognitive function.[18]

3. Pharmacological activities

Many studies have shown that cannabinoids have a variety of pharmacological activities. These have aroused the interest of the scientific community to find therapeutic effects in different aspects. The central nervous system (CNS) is huge and complex. In the past few decades, pieces of evidence have shown that a series of CNS diseases are related to neuroinflammation, including neurodegen-erative diseases, depression, sleep disorders, and epilepsy.[14] The endocannabinoid system is widespread in the CNS and participates in the control of many neurophysiological processes such as pain,
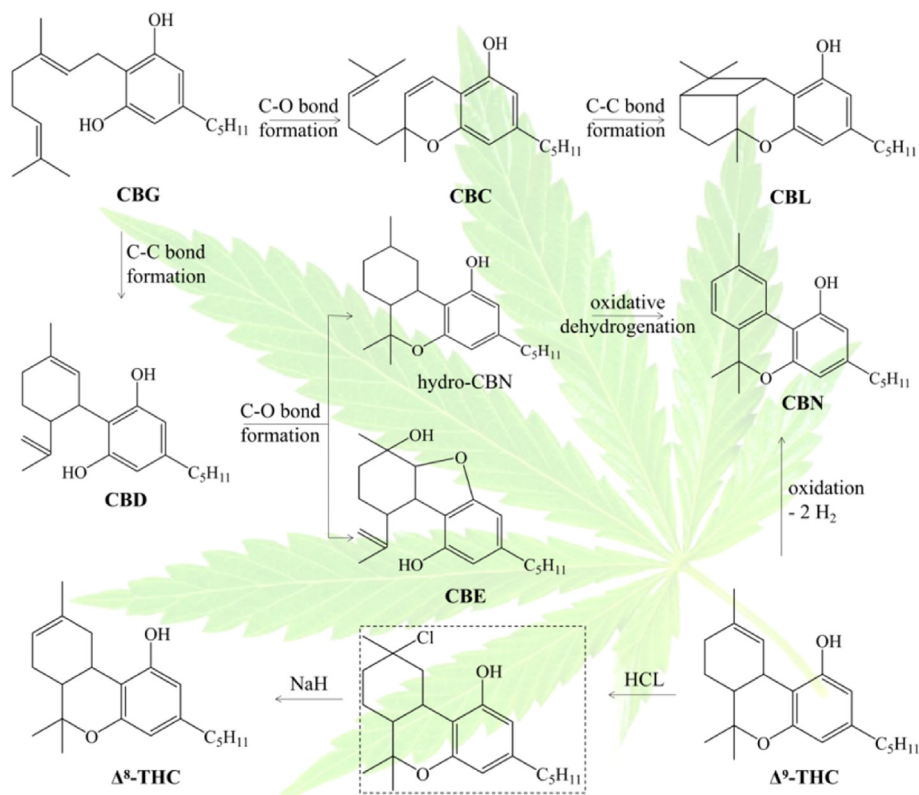
Fig. 1. The reciprocal transformation of the skeletal structure of the major cannabinoids.
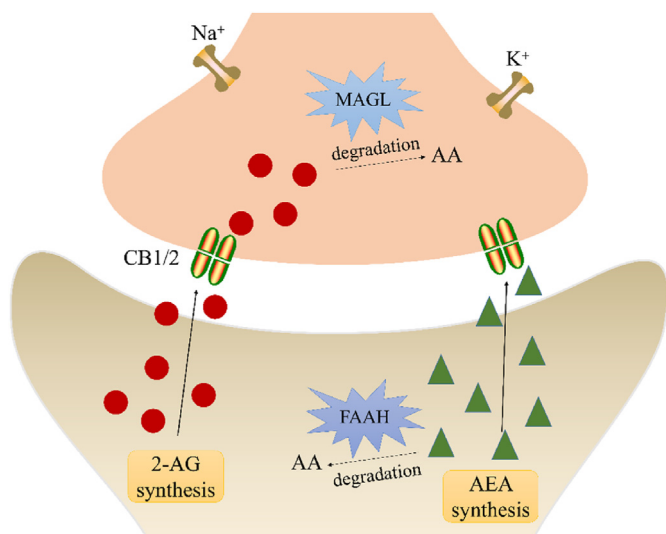

Fig. 2. Schematic of the endocannabinoid system. The main endocannabinoids AEA and 2-AG are synthesized after postsynaptic cell stimulation. 2-AG is degraded by monoacylglycerol lipase (MAGL) which is expressed in the presynaptic terminal. While fatty acid amide hydrolase (FAAH) is localized to postsynaptic cells, which predominantly degrades AEA. AEA and 2-AG are transported across the membrane and respectively act on cannabinoid receptors (CB1 and CB2) which are expressed on presynaptic terminals, to exhibit the corresponding therapeutic effects.

motor function, depression and cognition.[19]

3.1. Neurodegenerative diseases

Neuroinflammation involves the activation of microglia and astrocytes, resulting in the secretion of proinflammatory cytokines, which can activate a series of pathways. Neuroinflammation is a critical process in the development of CNS diseases.[14] Therefore, the prevention of neuroinflammation remains one of the effective methods in the treatment of these diseases. Many research have been devoted to study the neuroprotective properties of cannabinoids. They found that cannabinoids can provide neuroprotection for various neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).[20] This protective effect is thought to inhibit the release of glutamate at synapses because the addition of extracellular glutamate can damage neurons.[20] The endocannabinoid system expressed in basal neural stem cells is an effective target for motor dysfunction treatment, which can regulate the release of neurotransmitters and motor activity.[21,22] As the course of AD and PD progresses, the ECS may be permanently over-activated, which could even contribute to the suppression of motor activity and loss of memory (Fig. 3).[23]

3.1.1. Alzheimer's disease (AD)

The ECS has an important neuroprotection role in neurodegenerative diseases. Alzheimer's disease (AD) is a neurodegenerative disease associated with Aβ accumulation, oxidation, neuroinflammatory, and age.[24] High levels of AEA could exhibit neuroprotective effects. In the kainic acid-induced seizures mice model, it was shown that as age increased, AEA levels decreased and 2-AG levels increased.[11] It was shown that the treatment of THC (0.75 mg/kg·bw, i.p.), CBD (0.75 mg/kg·bw, i.p.), or a mix of △9-THC and CBD (0.75 mg/kg·bw each botanical extract, i.p.) could reduce cognitive impairment in AD model mice.[25] A combination of △9-THC and CBD could significantly decrease microgliosis and the expression of several cytokines, thereby reducing the pro-inflammatory response of ERK 1/2 (extra-cellular signal-regulated
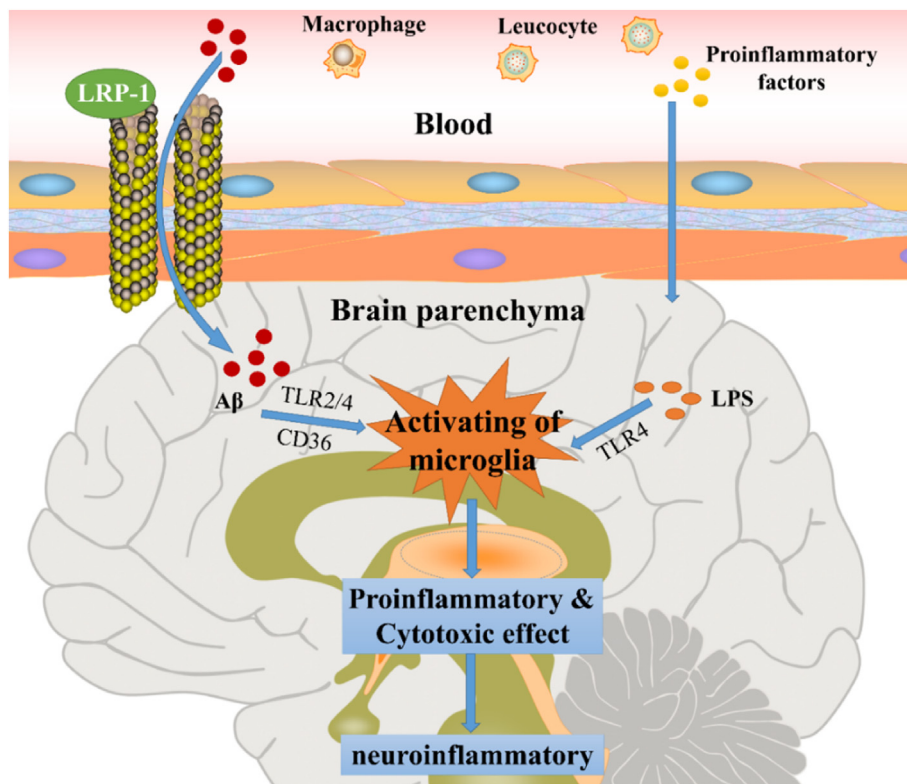
Fig. 3. Schematic representation of mechanisms of neuroinflammation in CNS diseases. Neuroinflammatory is caused by proinflammatory cytokines, pathogenic molecules (e.g. LPS), Aβ and other infections, injury, etc. Amyloid β-peptide (Aβ) is produced by aging or senescence, which can be transported from blood to the brain via the low density lipoprotein receptor-related protein 1 (LRP-1). Lipopolysaccharide (LPS) works through toll Like Receptor 4 (TLR4). The activation of microglia leads to proinflammatory cytokines (IL-1β, IL-4, TNF-α, NO, ROS) synthesis and cytotoxic effect, which causes neuroinflammatory related to CNS diseases.

kinase) to Aβ.[25] $\triangle^9$-THC and CBD have a therapeutic effect on AD. It was reported that $\triangle^9$-THC directly interacted with Aβ inhibiting its aggregation, whereas CBD reduced Aβ production by activating PPARγ. The aggregation of Aβ in the brain is one of the triggers of AD.[26] Limited clinical evidence showed that cannabinoids had beneficial effects on AD patients, and almost no other side effects were observed during treatment with $\triangle^9$-THC (1.5 mg twice daily), except for euphoria, drowsiness, or fatigue.[27] It was reported that Aβ$_{42}$ accumulation and plaque deposition induced the expression of CB2. Though CB2 receptor activation played an important role in controlling the microglia responses to Aβ accumulation that the mechanism remains to be elucidated.[28] Despite the limited clinical evidence clarifying the therapeutic effect of cannabinoids in AD, assessment of cognitive profiles and neurodegenerative markers is still lacking, which will encourage additional clinical trials to clarify the potential therapeutic effect of cannabinoids in AD.

3.1.2. Parkinson's disease (PD)

Parkinson's disease (PD) is the most common neurodegenerative disease after Alzheimer's disease. The symptoms of PD include muscle rigidity, movement disorder, tremor, psychological symptoms, cognitive impairment, sleep disorder, somatoform autonomic dysfunction, and others.[29] In PD models, CB2 receptor expression increased and microglia activation indicated the dysregulation of the cannabinoid system. The CB2 receptor expression increased while the CB1 receptor remained in PD patients. Substantial evidence suggests that CB2 receptors play an important role more than CB1 receptors in the regulation of neuroinflammation associated with PD.[30] It is reported that cannabinoids show a reduction of L-dopa-induced dyskinesia via CB1 receptor activation.[31] Increased

expression of CB1 and CB2 receptors was observed in MPTP-induced macaques, but a low expression in dyskinetic animals was indicated due to the prolonged use of L-dopa.[32] Intrastriatal injection of LPS in mice led to microglia activation and the expression of CD68, which induced an inflammatory response. Furthermore, the activation of the CB2 receptor impaired LPS-induced CD68 expression in the striatum, while decreasing the regulation of tyrosine hydroxylase and striatal iNOS. On the contrary, exacerbated functional deficits and increased microglial activation were developed after LPS injection in CB2-deficient mice.[33] THC was proven to relieve LPS-induced neuroinflammation in mice and have a potential neuroprotective effect via PPARγ activation. L-dopa will increase dynorphin and ERK phosphorylation. In PD mice study, it was found that $\triangle^9$-THC (3 mg/kg·bw, i.p.) and CBD (3 mg/kg·bw, i.p.) had neuroprotective action.[34] THC activating PPARγ will decrease dynorphin and ERK phosphorylation. And the activation of PPARα by oleoylethanolamide could down-regulate the expression of FosB and pAcH3, which could also relieve L-dopa dyskinesia.[32] The CB1-CB2 heteromer levels were increased in 6-OHDA model mice, which recovered in L-dopa treatment mice. This might be due to the cannabinoids' compensatory neuroprotective mechanism, or the overexpression of the CB1-CB2 heteromer contributes to movement disorder.[35] Together, the modulation of cannabinoid receptors on microglia may provide an effective treatment target for PD, further study of the mechanism of cannabinoid receptors for treating PD is needed, which will contribute to the development of potential new therapies of cannabinoid for treating PD.

3.1.3. Huntington's disease (HD)

Huntington's disease (HD) is a neurodegenerative disease caused by the accumulation of mutant huntingtin protein in neurons and glial cells. Mutant huntingtin protein will cause inflammatory responses in glial cells, which will increase the levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF-α).[14] It was reported that the increasing level of IL-6 can be detected in HD gene carriers' plasma which can predict onset more than a decade ahead of time. The microglial activation associated with cognitive function was also related to the HD onset.[36] It was reported that the activation of the CB2 receptor could alleviate inflammation response and neuron injury.[21] The downregulation of the CB1 receptor has been detected in early HD patients. CB1 could inhibit the release of glutamate. The downregulation of the CB1 receptor will lead to a high level of glutamate and aggravate its damage to nerve cells. Multiple studies have shown that the downregulation of CB1 may also aggravate cytotoxicity like oxidative stress.[37] The neuroprotective effect of CBG has also been evaluated in R6/2 and 3 - nitropropionate-lesioned mice, and the neuroprotective effect of CBG might not be mediated by CB1/2, it might be mediated by other targets like PPARs.[26] The inflammation, brain edema, movement disorder, and neuronal loss in HD model mice were reduced after the administration of CB2 receptor select agonists.[21] Based on previous studies, cannabinoids can bind to CB1/2 receptors to alleviate neurotoxicity, oxidation injury, and inflammation, such as $\triangle^9$-THC (10 mg/kg·bw) and CBD (10 mg/kg·bw), which were considered a new therapeutic way for HD.[38] A clinical evaluation is still required before cannabinoids be used as a treatment for HD, and Sativex® ($\triangle^9$-THC + CBD) might be a good choice.

3.2. Pain

According to the length of duration, pain can be divided into acute pain and chronic pain. In the light of the cause of the pain, it can be divided into nociceptive, inflammatory, neuropathic, and oncological. Compared to nociceptive pain, short-term acute pain is easier to treat. Inflammatory and neuropathic pain may shift into a lasting chronic pain that is difficult to treat.[39] For centuries, preparations of cannabis have been used as analgesics. Studies have found that the analgesic components in cannabis are mainly two active cannabinoids: $\triangle^9$-THC and CBD. In the past two decades, many drugs affecting the ECS have been developed for pain relief. There are currently three drugs that can activate cannabinoid receptors as commercial products: Cesamet® (nabilone), Marinol® ($\triangle^9$-THC + dronabinol), and Sativex® ($\triangle^9$-THC + CBD), they can be used for the analgesic treatment of cancer, neuropathic and spasticity associated with multiple sclerosis.[39] However, phyto-cannabinoids have some side effects and should be carefully considered before use. Of particular concern is that patients with a history of mental illness should refrain from phyto-cannabinoids drugs like Sativex® ($\triangle^9$-THC + CBD),[40] which might lead to transient mental illness episode onset or recurrence.[41] The endocannabinoid system is largely involved in the regulation of pain and inflammation. Endocannabinoids are generated on demand and mainly produce short-term anti-nociceptive effects through binding to CB1 receptors in nociceptive neurons.[39] The inhibitory effect of MAGL on acute pain appears to be predominantly CB1-mediated, whereas CB2-mediated has been found in models of inflammatory and neuropathic pain.[42] The current findings indicate that cannabis analgesics have a therapeutic effect on chronic pain especially neuropathic pain, and further mechanistic research is necessary.

3.3. Epilepsy

Epilepsy is a chronic neurological disease characterized by recurrent and spontaneous seizures. Cannabis has a long history of anti-epileptic effects. In recent years, people have studied the anti-epileptic effects of cannabinoid compounds and found that the phyto-cannabinoids $\triangle^9$-THC, $\triangle^9$-THCV, CBD, CBDV, endocannabinoids, and synthetic cannabinoids all have anti-epileptic effects in animal models.[43] Currently, cannabinoids used clinically to treat epilepsy in mice models include THC ($\triangle^9$-THC, 1–100 mg/kg·bw, i.p.) and CBD (5–400 mg/kg·bw, i.p.), and mainly CBD.[24] $\triangle^9$-THC depends on the activation of CB1 and CB2 receptors, and the anti-epileptic mechanism of CBD is still unclear. Some studies believe that CBD has a low affinity for CB1 and CB2 receptors and may interfere with other targets in the brain including TRPV1, voltage-gated potassium, sodium channels, GPR55, etc.[43] In the past few years, the use of CBD to treat epilepsy has increased dramatically. Cases have shown that treatment with a high CBD/THC ratio can effectively reduce the frequency of seizures.[44] Scientific evidence suggested that CBD had a significant effect on reducing seizures. CBD was an agonist on TRP channels, especially in TRPV1, which was responsible for regulating the Ca^{2+} channel.[43] However, current evidence is insufficient to explain the mechanism of the antiepileptic action of CBD. More data are needed to explain the antiepileptic mechanism of cannabinoids.

3.4. Depression

Depression is one of the most common neuropsychiatric diseases. Studies have found that the ECS is partially involved in the control of emotional behavior and emotions through the functional coupling of the monoamine system in the brain.[45] Studies have shown that the endocannabinoid system plays a key role in the pathogenesis of depression and the regulation of the effects of antidepressants. The level of serum endocannabinoids in patients with major depression will also change.[46] Some studies have found that patients with depression have lower levels of endocannabinoid AEA and 2-AG. Besides, 2-AG levels are lower in patients with longer depressive episodes, while patients with mild depression have higher levels.[47] Therefore, depression can be improved by increasing the content of endocannabinoid 2-AG. Studies have found that aerobic exercise can increase the content of 2-AG in the body.[47,48] In addition to adjusting the ECS, the use of phyto-cannabinoids to treat depression is also considered. Studies have pointed out that when CBC is used in combination with other cannabinoids such as CBD (0.2 ng/nL, intracranial infusions) and THC (0.2 ng/nL, intracranial infusions), it has an effect on improving insomnia and antidepressants.[49,50] However, some research pointed out that cannabis has two opposite effects on depression. On the one hand, the heavy use of cannabis is associated with a higher incidence of depression. On the other hand, the main active ingredient of cannabis $\triangle^9$-THC as an agonist of CB1 and CB2 can reduce depressive behavior.[46] Increased CB1 levels could be detected in the dorsolateral prefrontal cortex of depressed patients, whereas did not affect CB1 immune response in the dorsolateral prefrontal cortex. However, the changes in CB2 levels were not been detected in the dorsolateral prefrontal cortex.[18] The increased CB1 expression and a lack of CB1-induced Gi/o proteins activation could be detected in anti-depression treated studies.[46] Pieces of evidence have shown that CBD had anti-depression and anxiolytic properties which were not related to the action of CBD on CB1 and CB2,[51] while the mechanism of CBD acting on anti-depression was not clear.

3.5. Sleep disorders

Sleep is regulated by circadian rhythm. Disorders of circadian rhythm cause sleep disorders. The sleep disorder can be primary or can be triggered by brain diseases such as multiple sclerosis, mental diseases, and other conditions.[14] It is reported that about 30–35% of the population is under sleep deprivation. In an animal study, sleep disorder was associated with increased IL-6 level and microglia activation, and injury of hippocampal associated with learning and memory was observed.[52] It is reported that sleep disorder was associated with IL-1β, IL-6, TNF-α, and CRP levels increasing.[53] Another report has shown that sleep disorder was associated with NF-κB activation and the increasing levels of TNF-α and IL-1β in the hippocampus.[54] Sleep disorder will increase the microglia activation and Aβ level, which may promote brain injury.[55,56] Pieces of evidence showed that circadian rhythm and sleep disorder were related to the increasing levels of proinflammatory cytokines. However, the pathophysiology mechanism is unclear.

$\triangle^9$-THC and CBD interact with the endocannabinoid system and other systems to influence mood and sleep, which are increasingly used to regulate sleep disorders. Previous studies have revealed that an endocannabinoid concentration changes the circadian rhythm. The inhibition of MAGL and increasing level of 2-AG were found in mice brains, which had a wake-promoting effect.[57] Preclinical evidence has shown that AEA has a sleep-promoting effect. THC is a partial agonist at CB1receptor to promote sleep like AEA. It is also reported that CBD can inhibit FAAH to increase the level of AEA, which could be a mechanism for CBD's sleep-promoting effect.[58] Evidence has shown that nabiximols® (THC and CBD) have an effective improvement to sleep disorders caused by pain. However, it is not clear whether this improvement is due to improved sleep itself or the improvement in pain.[59] Cannabinoids are increasingly used to treat sleep disorders, but the mechanism is unclear.

3.6. Stroke

Stroke is divided into two types: ischemic and hemorrhagic stroke. The excitotoxicity and inflammatory were considered key factors to ischemic neuron damage. Glutamate release is due to brain ischemic, which would cause NMDA receptors over-activation and Ca^{2+} influx, leading to excitotoxicity-induced cell death.[60] The activated microglia clear dead cells, which causes the production of anti-inflammatory and pro-inflammatory factors and ROS/RNS (reactive oxygen species/reactive nitrogen species).[61] The activated microglia have M1 and M2 two phenotypes, the M1 microglia are pro-inflammatory and could induce neurons cells death, whereas the M2 microglia are associated with the recovery of brain damage.[30] Microglia could synthesize 2-AG and AEA, this could be a source of endocannabinoids under inflammatory conditions. Mecha et al. reported that more synthesis of 2-AG and AEA significantly activated the M2 microglia than resting microglia.[62] The increasing endocannabinoid synthesis has positive feedback on CB1/2 receptors activation and enhances the anti-inflammatory effect and the M2 microglia protection. This will promote the M2 microglia producing neuroprotective factors and reduce pro-inflammatory factors.[30] Studies have shown that the M1 microglia and the M2 microglia were interconvertible under certain circumstances. Microglia is an important modulator of immune response in ischemic stroke. However, the modulation mechanism of microglia activation and proliferation remains unclear.[60] Thus, understanding M1/2 is up- or down-regulation, exploring the mechanism of M1-M2 microglia transformation, and controlling the transformation of M1-M2 microglia might be important directions for treating ischemic stroke (Fig. 4).

3.7. Multiple sclerosis

The onset of multiple sclerosis (MS) was associated with genetic, environmental, and other infectious factors. But the onset mechanism and the specific sequelae responsible for the development of MS were still unclear. Experimental autoimmune encephalomyelitis (EAE) is a common animal model used in MS research and may help in the development of new treatments for MS, but it still has limitations.[30] M1 and M2 microglia have been proved to show different predominate during the EAE model established. M1 microglia might be related to aggravating EAE, whereas increased M2 microglia levels were related to inflammation and disease improvement.[63] It was reported that the inhibition of M1 microglia accumulation in CNS could relieve disease. Also, the activation of M2 microglia could inhibit CD4$^+$ T cells in EAE mice and relieve disease.[64] The CB1 receptor was detected to express in neurons and injured axons, whereas CB2 was absent.[65] Previous studies have shown that the endocannabinoid system is involved in the development of MS, and cannabinoids were used to treat MS.[66] A combination of 27 mg/mL $\triangle^9$-THC and 25 mg/mL CBD (Sativex®) was proven to relieve spastic and pain in MS patients. Sativex® ($\triangle^9$-THC + CBD) might be a potentially effective medicine for treating MS.[13] Exploring the role of cannabinoids in the development of MS will contribute to understanding the mechanism of this disease and developing new therapeutic methods (Fig. 4).

4. Conclusion

The predominant natural component of cannabis-derived drugs is Δ^9-THC followed by CBD and CBN. AEA and 2-AG are the main endocannabinoids.[67] Although cannabinoids have many health benefits, a long-term consumption of cannabinoids can also put patients at risk for mental illnesses such as depression. Exposure to cannabis during development may be particularly harmful to the brain and central nervous system.[68] It is shown that the negative effects of cannabinoids include dependence, delayed response, anxiety, and others, which depend on the administration method and dosage.[69] Cannabis-derived drugs are widely used in the world. However, legalizing and rationalizing these drugs are rapidly changing the research and use of cannabis. Cannabis derivatives are popularly developed for pharmaceutical use, despite the lack of safety and efficacy evidence. Pieces of evidence showed that cannabinoids had beneficial effects on CNS diseases, which tend to encourage further exploration of their biological activities. Cannabinoids have diverse chemical structures and pharmacology activities, which have been used in many fields of modern medicine over the past decades.[70] Table 1 summarizes the effects and recommended doses of cannabinoids on CNS diseases. Even though the use of *C. sativa* L. is prohibited in many countries, its beneficial effect should not be ignored.

This review focused on natural cannabinoids reporting 112 phyto-cannabinoids (divided into eight types) and five endocannabinoids. The diversities of the cannabinoids' chemical structures lead to a variety of pharmacological effects. By activating cannabinoid receptors 1 or 2, cannabinoids exhibit various pharmacological activities. Sometimes cannabinoids can also act on other targets such as GPR55, TRPV1, and others. Currently, cannabinoids are beneficial to the medical and scientific communities. A large amount of scientific literature has shown the therapeutic potential of cannabinoids in pathological conditions. These compounds can be used as potential therapies for CNS diseases. The endocannabinoid system and microglia played an important role in CNS diseases. Microglia as immune cells are involved in the pathological reactions of various diseases of the central nervous system, while the regulating mechanism was not fully clarified. The specific
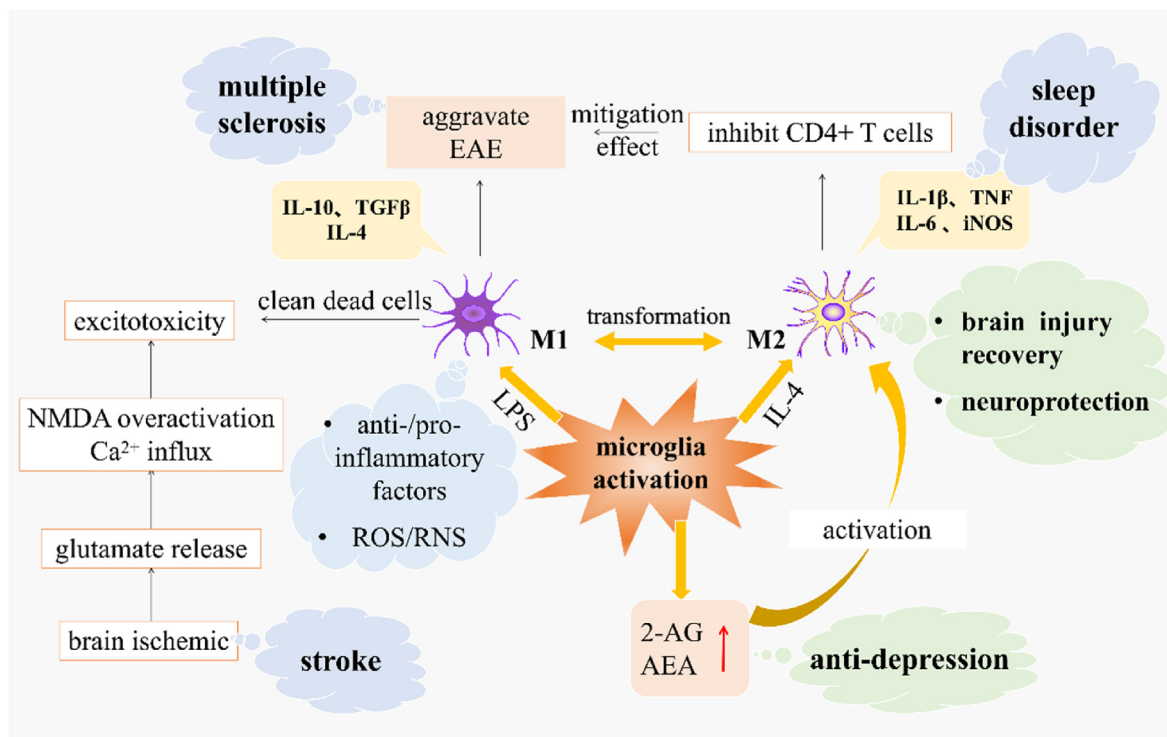
Fig. 4. The effect of activated microglia in several CNS diseases. Microglia has two phenotypes: M1 was activated by LPS which produces IL-1β, TNF, IL-6, and iNOS. M2 was activated by IL-4 and expressed IL-10, IL-4, and TGFβ, which contributes to brain injury recovery. M1 and M2 were interconvertible under certain circumstances.

Table 1
The pharmacological effects of prominent cannabinoids on CNS diseases.

Diseases	Compounds	Effects	Reference
Alzheimer's disease	THC (0.75 mg/kg·bw, i.p.) CBD (0.75 mg/kg·bw, i.p.) a mix of △⁹-THC and CBD (0.75 mg/kg·bw each botanical extract, i.p.) △⁹-THC (1.5 mg twice daily)	reduce cognitive impairment in AD model mice decrease microgliosis and the expression of several cytokines; reduce the pro-inflammatory response of ERK 1/2 (extra-cellular signal-regulated kinase) reduce the aggregation of Aβ; side effects: euphoria, drowsiness, or fatigue	[20] [27]
Parkinson's disease	△⁹-THC (3 mg/kg·bw, i.p.); CBD (3 mg/kg·bw, i.p.) THC	relieve LPS-induced neuroinflammation in mice, have a neuroprotective effect via PPARγ activation activate PPARγ; relieve ʟ-dopa dyskinesia	[34] [32]
Huntington's disease	CBG △⁹-THC (10 mg/kg·bw); CBD (10 mg/kg·bw)	neuroprotective effect in R6/2 and 3 - nitropropionate-lesioned mice bind to CB1/2 receptors to alleviate neurotoxicity	[26] [38]
Pain	Cesamet® (nabilone), Marinol® (△⁹-THC + dronabinol), Sativex® (△⁹-THC + CBD) endocannabinoids (AEA and 2-AG)	analgesic treatment of cancer, neuropathic and spasticity associated with multiple sclerosis regulation of pain and inflammation	[39]
Epilepsy	△⁹-THC (1–100 mg/kg·bw, i.p.); CBD (5–400 mg/kg·bw, i.p.)	CBD had a significant effect on reducing seizures	[24,43]
Depression	CBC used in combination with CBD (0.2 ng/nL, intracranial infusions) or THC (0.2 ng/nL, intracranial infusions) CBD	improve insomnia and antidepressants anti-depression and anxiolytic	[49,50] [51]
Sleep disorders	CBD AEA △⁹-THC	inhibit FAAH to increase the level of AEA to promote sleep sleep-promoting effect activate CB1 receptor to promote sleep	[59]
Stroke	AEA and 2-AG	activate the M2 microglia, anti-inflammatory effect, improve ischemic neuron damage	[30]
Multiple sclerosis	Sativex® (△⁹-THC + CBD)	activate M2 microglia, inhibit CD4⁺ T cells in EAE mice, treat multiple sclerosis	[13,64]

mechanism of the endocannabinoid system and microglia remains to be explored. Up to now, the role and pharmacological mechanism of more cannabinoids besides THC and CBD in CNS diseases remain to be investigated. It is believed that cannabinoids can be efficient and reasonably used in the future.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2022.10.004.

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