Journal of Affective Disorders Reports 12 (2023) 100463

Contents lists available at ScienceDirect

Journal of Affective Disorders Reports

journal homepage: www.sciencedirect.com/journal/journal-of-affective-disorders-reports

Review Article

Cannabinoids and neuroinflammation: Therapeutic implications

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ARTICLE INFO

Keywords:
Phytocannabinoids
THC and CBD
endogenous cannabinoids
anadamide and 2-AG
Microglia
Neuroinflammation
Anti-covid 19
therapeutic potential

ABSTRACT

This review summarizes the pharmacological properties of tetrahydrocannabinol (THC) and cannabidiol (CBD), cannabinoid components of several species of herbal cannabis. The pharmacological effects of the phytocannabinoids have been extensively investigated and the importance of the cannabinoid receptors (CB1 and CB2) on immune cells has provided important information on the intracellular targets for these molecules. In addition to the phytocannabinoids, endogenous cannabinoids also exist in the form of anadramide and 2-srodolylglycerol (2-AG). These, together with their synthesizing and metabolizing enzymes, form the cannabinoid system. Since the discovery of the endocannabinoid system and the role that neuroinflammation plays in neurological and psychiatric illness, the potential therapeutic importance of this system has been of growing interest. In addition, the need to develop drugs which specifically target the CB1 and CB2 receptors has been stimulated by the pharmacological complexity of both THC and CBD. This review briefly summarizes the therapeutic potential of the naturally occurring and the synthetic cannabinoids which will need to be developed, if such drugs are to fulfill the therapeutic promise which the cannabinoids offer.

1. Introduction

Herbal cannabis has a long history both for its psychotropic properties and for its therapeutic uses. Some of the earliest references to its uses were discovered in Egyptian medical papyrus from about 1550 BCE, but an even earlier record was detected from China in 2700 BCE. in which the hallucinogenic effects of cannabis, in addition to its ability to stimulate appetite and reduce pain due to gout, were described (Clarke and Merlin, 2013).

These metabolites differ in their tetrahydrocannabinol (THC) content. Currently approximately 600 metabolites of cannabis have been isolated with over 20% being classed as cannabinoids (Chandra et al., 2017). Of these the psychoactive metabolite THC and the non-psychoactive metabolite cannabidiol (CBD) have received particular attention (Fig. 1). THC was first synthesized by Mechoulan and Gaoni in 1965, and this stimulated an interest in its pharmacological properties. By contrast, CBD has only recently undergone a detailed pharmacological investigation following the discovery of its anti-oxidant, analgesic and anti-inflammatory properties (Morales et al., 2017, Fig. 1).

However, despite the long history of the medicinal use of herbal cannabis, detailed research into its pharmacology and therapeutic potential is fairly recent. This is mainly due to its recreational abuse and the legal restrictions which followed due to its adverse effects on health and its addictive potential.

Besides the phytocannabinoids, endogenous cannabinoids, known as endocannabinoids, have more recently been discovered. These are widely distributed in mammalian tissues. The endocannabinoid system consists of the cannabinoid receptors, CB1 and CB2, the endogenous cannabinoids (anandamide and 2-arachidonyl glycerol (2-AG)) and the key metabolizing enzyme, fatty acid amide hydrolase (FAAH) (Lu and Makie, 2016).

The cannabinoid receptors CB1 AND CB2 were discovered in 1990 and 1993, respectively. The CB1 receptor is a G-protein coupled receptor with 7 transmembrane spanning domains. It is predominately located in the central nervous system, but is also present in the terminals of peripheral nerves, the gastrointestinal tract and the reproductive system (Herkenham et al., 1990; Richardson et al., 1998). CB1 receptors also occur on immune cells where their activation can promote both pro- and anti-inflammatory activity (Howlett, 2002).

The CB2 receptor was initially thought to be restricted to peripheral organs where it is located on the cell membrane of immune cells and immune organs, but it is now evident that CB2 receptors are present in the brain, as well as on sensory terminals in the peripheral nervous system. Both CB1 and CB2 receptors can inhibit the release of pro-inflammatory mediators by a combination of the inhibition of adenyl cyclase, calcium channel deactivation, and the stimulation of the MAPK/ERK pathway (Howlett, 2002; Zou and Kumar, 2018, Fig. 2).

Microglia constitute more than 70% of the total cell population in the

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https://doi.org/10.1016/j.jadr.2023.100463
Received 4 December 2022; Accepted 3 January 2023
Available online 7 January 2023

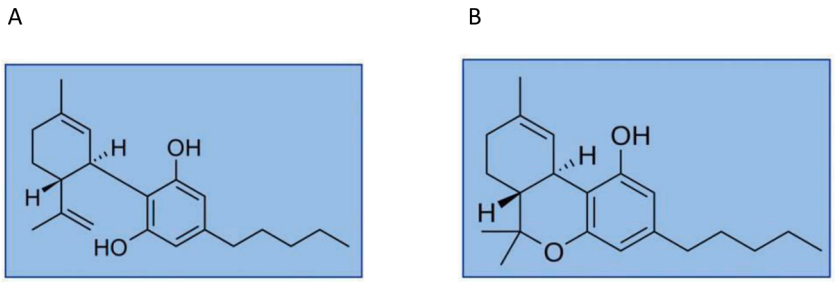

Fig. 1. Chemical structures of (A) tetrahydrocannabinol (THC) and (B) cannabidiol (CBD).

brain and spinal cord, and represent the first line of defense against brain infection (Romero-Sandoval et al., 2008). Under physiological conditions microglia play a key role in the induction and maintenance of synaptic plasticity by modifying the synaptic structure (Nimmerjahn et al., 2005), but can also result in synaptic defects which can cause neurological disorders (Wake et al., 2013). Once activated by an inflammatory challenge, for example a bacterial infection, the structure of microglia changes from the normal static anti-inflammatory phenotype to a reactive pro-inflammatory phenotype. The reactive microglia express CB2 receptors, and in the dorsal horn of the spinal cord they have been shown to be highly expressed in animal models of neuropathic pain and chronic pain (Wotherspoon et al., 2005). CB2 receptors have also been identified in post mortem brain tissue of patients with Alzheimer's disease (Tolon et al., 2009) and there is evidence that CB2 receptors are increased in activity in neuritic plaques associated with microglia (Benito et al., 2003).

Low grade neuro-inflammation is a well-established phenomenon in the pathophysiology of neuropsychiatric disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis (Reddy et al., 2020). Neuro-inflammation is also widely observed in patients with major psychiatric disorders, such as schizophrenia, major depression, bipolar depression and anxiety disorders (Moylan et al., 2013; Berk et al., 2011; Davis et al., 2014). The changes following the onset of the neuroinflammatory challenge have also been implicated in the development of neuro-cognitive impairment, behavioral changes and neuroprogression, which are frequently associated with the chronic outcome of these conditions (Berk et al., 2011; Davis et al., 2014).

There is clinical evidence that there is a reduced expression and a functional reduction in the activity of CB1 receptors in both first episode and chronic schizophrenic patients, changes which are correlated with an increase in the severity of the symptoms (Mihov, 2016, Borgan et al., 2019); this change in CB1 receptor function is correlated with the rise in glutamate (Borgan et al., 2021). Such a change in glutamate could contribute to the neurotoxicity arising from the activation of the tryptophan-kynurenine pathway by pro-inflammatory cytokines. This will be discussed in more detail in a later section of this review. A reduction in the activity of the CB1 receptors has also been reported to occur in patients with anxiety and stress, as well as in those with major depressive disorder (Monteleone et al., 2010).

The reduction in the functional activity of CB1 receptors is reflected in the increase in the concentrations of the endocannabinoids, 2-AG and arachidonic acid, which increase in all brain regions in patients with schizophrenia, and which return to resting levels following remission (Minichino et al., 2019). In Alzheimer's disease and brain trauma the

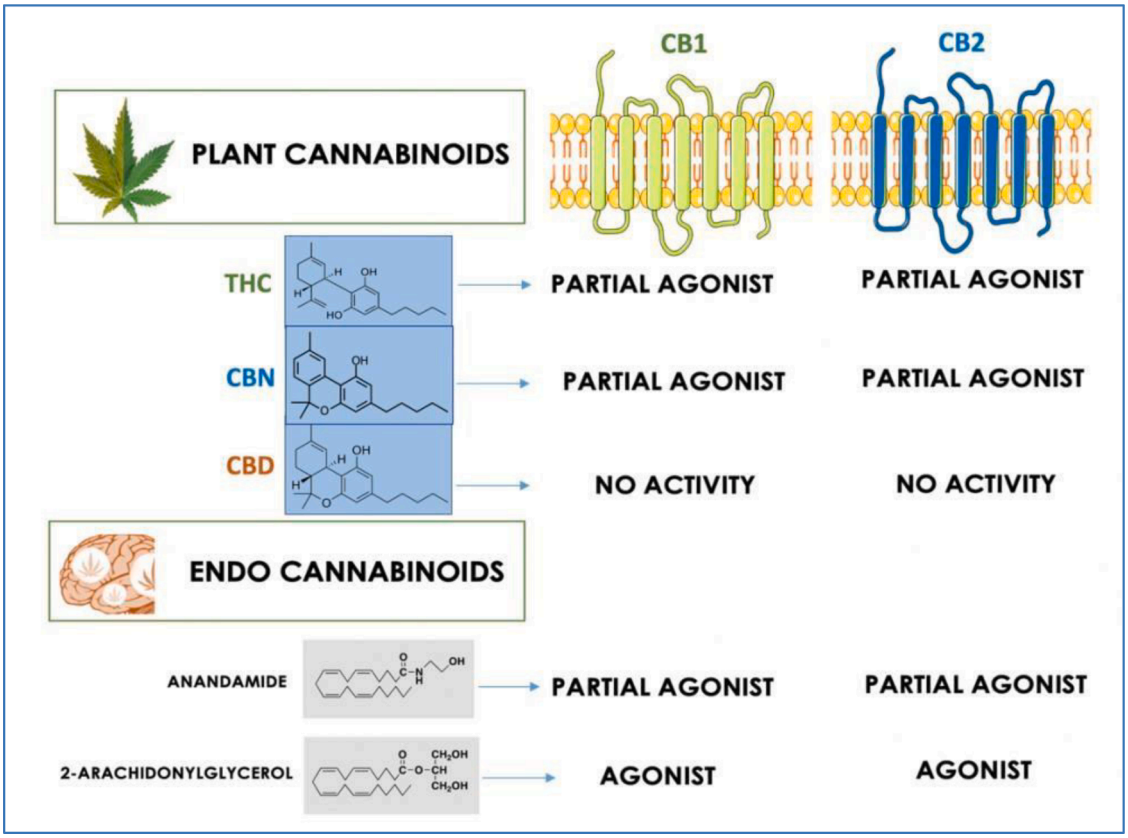

Fig. 2. Activity of cannabinoids on CB receptors. Cannabinoid receptor 1 (CB1) and 2 (CB2), Tetrahydrocannabinol (THC), cannabiol (CBN) and cannabidiol (CBD).

changes in the concentration of the endocannabinoids are associated with a reduction in the activity of fatty acid acyl hydrolase (FAAH), the enzyme which metabolizes the endocannabinoids. However, the changes in the endocannabinoid system in depressed patients appears to be inconsistent and vary with the gender, presence of antidepressants, degree of exercise and a history of smoking (Amatriain-Fernández et al., 2021).

As changes in the activity of the CB1 receptors appear to play a role in the psychophysiology of several neuropsychiatric disorders, it would be anticipated that CB1 antagonists could be of therapeutic benefit to these patients. As will be apparent from a later comment in this review, CB1 inverse agonists, and the agonist rimonabant, have been shown to have beneficial therapeutic effects, but have been withdrawn from clinical use because of their side effects, which include depressive-like and psychotic symptoms and panic attacks (Moreira et al., 2009).

Inflammasomes are a high molecular weight scaffold formed by an assembly of different proteins which consists of three parts; a sensor protein, an adaptor protein ASC, and an effector protein caspase-1. Sensor proteins are six NLRs (NLRP1, NLRP3, NLRP6, NLRP7, NLRP12, and NLRC4). Inflammasomes are cytoplasmic inflammatory signal protein complexes that, when activated, promote caspase-1-mediated maturation and secretion of the proinflammatory cytokines, interleukin (IL)−1b and IL-18, leading to pyroptosis. Recent date also suggests that they participate in the development of chronic inflammatory disorders, in contrast to their role in regulating innate immunity. (Suryavanshi et al., 2021)

Regarding mammalian host resistance, toll like receptors (TLRs) bind pathogen-associated molecular patterns (PAMPs) present within microbial molecules. Important innate immune cells expressing TLRs are monocytes, macrophages, microglial cells, and dendritic cells. Involvement of cannabinoid receptors in suppressing TLR responses has been established by multiple approaches; cannabinoid receptor-selective agonists causing inhibition and cannabinoid receptor-selective antagonists reversing inhibition (Suryavanshi et al., 2021)

When the immune system encounters a pathogen, innate immune cells recognize the pathogen via TLRs and other pattern-recognition receptors to trigger an inflammatory response. Innate immune cells are an important source of endocannabinoids, and these cells synthesize and metabolize endocannabinoids. TLR-mediated activation of the innate immune cells enhances their endocannabinoid levels. In the absence of any infection, but as a result of physical trauma, it produces DAMPs that are detected as distress signals via TLRs. This increases local endocannabinoid production in response to tissue damage during disease progression and infection. Innate immune cells may play a role in regulating endocannabinoid homeostasis. By modulating local inflammation, the endocannabinoid system TLR signals can also alter cannabinoid receptor expression, and thus alter sensitivity to cannabinoids. However, in cases where inflammation is exacerbated, cannabinoids may become resistant to immunosuppression, even if the cells contain high endocannabinoids. Therefore, a better understanding of the relationship between cannabinoid and TLR signaling pathways is needed, and holds promise therapeutically (McCoy, 2016).

The anti-inflammatory potential of cannabinoids, and thus their relationship with chronic inflammatory diseases has been known for some time. However, few studies in recent years have suggested that cannabinoids may also have a role in the modulation of the inflammatory effect. The anti-inflammatory effects of cannabinoids are thought to be due specifically to their potential inhibitory effect on NLRP3. In addition, recent findings suggest that cannabinoids, being CB1 receptor agonists, play a key role in this anti-inflammatory mechanism of action. In addition, cannabinoids play a role in inflammatory cytokine signaling pathways, and while our understanding of the molecular mechanisms whereby cannabinoids modulate inflammatory signals is still limited, there is support for the view that they may be therapeutic targets in the regulation of inflammatory signaling mechanisms (Fig. 3).

Unlike the CB1 receptors, changes in the CB2 receptors in

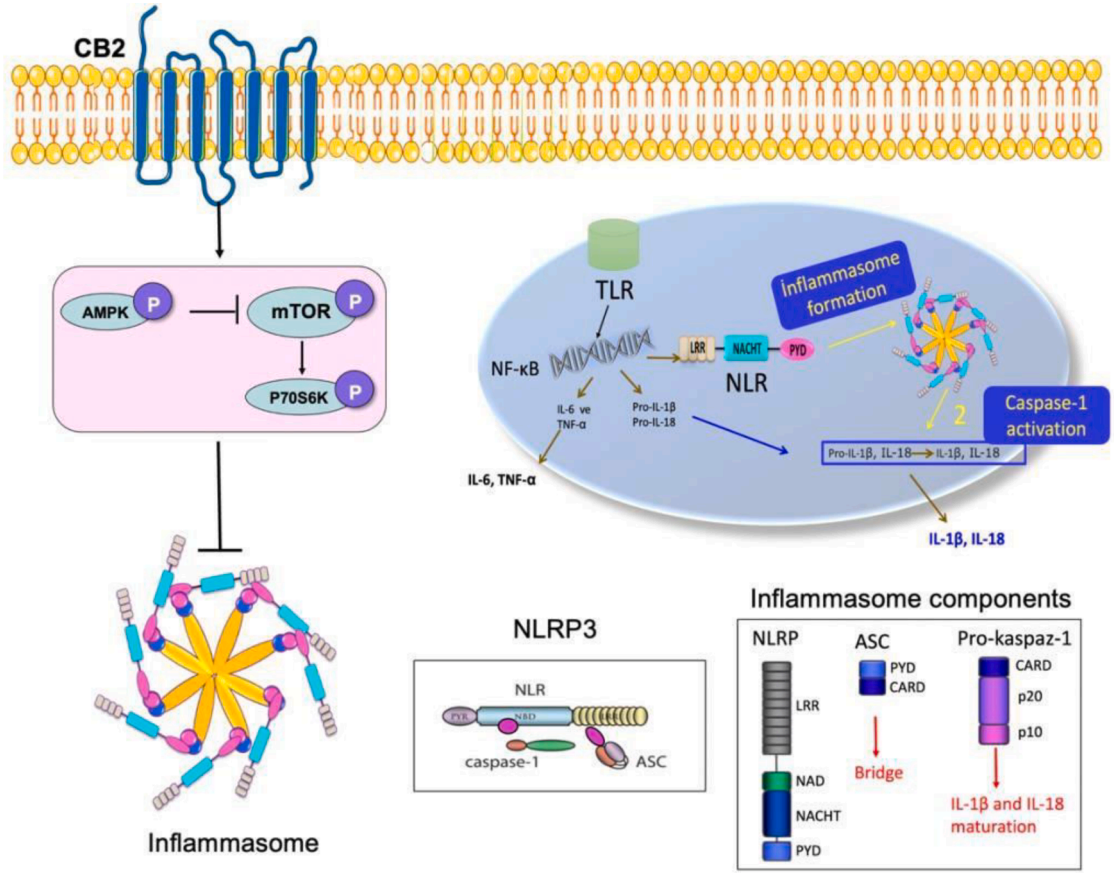

Fig. 3. Schematic illustration of the mechanism of CB2R activation that inhibits NLRP3 inflammasome. CB2R receptor activation phosphorylates the AMPK-mTOR-P70S6K signaling cascades and inhibits NLRP3 inflammasome initiation and activation, which decreases Casp-1 activation and IL-1β mature and alleviates an inflammatory cascade. Adapted from Ke et al., 2016.

neuropsychiatric disorders has not been associated with major changes. An increase in the activity of these post synaptic receptors inhibits neuronal activity and modulates CB1 receptors in the hippocampus. This results in inhibition of GABA receptors, and thereby affects working memory; changes in the pain response also occur (Chen et al., 2017; Sadanandan et al., 2020). Experimental studies have also shown that CB2 receptors modulate glutamate release, but the precise mechanism is unclear (Zhang et al., 2021).

Anecdotal evidence demonstrates that the phytocannabinoids possess anti-inflammatory properties. Phytocannabinoids reduce prostaglandin and cytokine synthesis in immunocytes by inhibiting both cyclooxygenase activity, and the MAPK pathway, respectively. Neurogenic inflammation is also modulated by activation of the endocannabinoid system (Duncan et al., 2004). 2-AG is the most abundant cannabinoid in the brain and is known to be elevated following brain injury and as a result of neuroinflammation. These effects are relatively transient. In addition, 2-AG decreases the permeability of the blood-brain barrier and inhibits the acute effects of the pro-inflammatory cytokines, TNF-alpha, IL-1beta and IL-6 (Panikashvilli et al., 2006). In studies of the effects of intracerebral hemorrhage in rats, CB2 receptor agonists were shown to prevent damage to the blood brain barrier which provides supporting evidence for the clinical observations (Li et al., 2018).

The changes in the integrity of the blood brain barrier caused by neuroinflammation are accompanied by endothelial cell damage, changes in the integrity of the tight junctions, apoptosis, a modulation of astrocyte function and the induction of pro-inflammatory cytokines (Varatharaj and Galea, 2017). Thus, the maintenance of the integrity of the blood brain barrier is important in preventing systemic inflammation from reaching the brain. The endocannabinoids have now been shown to play an important role in this regard, thereby providing a potential target for new drug development in the future.

1.1. The link between cannabinoids and neuroinflammation in depression

Many clinical studies indicate that the recreational use of phytocannabinoids and synthetic cannabinoids can contribute to the development of depression (Seely et al., 2012; Dieker et al., 2018), with synthetic cannabinoids being more likely to do so than phytocannabinoids (Görgülü and Sevindik, 2020). This is due to the greater affinity of the synthetic cannabinoids for the CB1 receptors (Martinotti et al., 2017).

Of the many immune and endocrine factors which contribute to the pathophysiology of major depression, the functional defect in the serotonergic system has been implicated as a major contributor. The link between the neuroinflammatory changes and the serotonergic system has been the subject of serious consideration by Maes, 1995) and further discussed by Myint and Kim (2003, 2014) who studied how pro-inflammatory cytokines activate the tryptophan-kynurenine pathway which then results in a reduction in serotonin synthesis and an increase in neurodegeneration. A summary of the main changes initiated by proinflammatory cytokines in the tryptophan kynurenine pathway is illustrated in Fig. 4.

For over 50 years, tryptophan has been known to be the precursor of serotonin in the enterochromaffin cells of the gastrointestinal tract and also in areas of the brain. Approximately 95% of tryptophan is metabolized through the tryptophan kynurenine pathway leaving about 5% to be converted to serotonin.

The tryptophan kynurenine pathway is controlled by two major enzymes, the widely distributed indoleamine, 2,3-dioxygenase (IDO), which is activated by pro-inflammatory cytokines (IL-1alpha, IL-6, IL-8) and the interferons (IFN alpha and TNF alpha), and tryptophan dioxygenase (TDO) which is activated in the liver by glucocorticoids. This pathway is particularly vulnerable to stress and the effects of the neuroinflammatory changes associated with all major psychiatric disorders (Leonard, 2017). Quinolinic acid is the main neurotoxic end product of the pathway.

Although the cannabinoids have traditionally been associated with an anti-inflammatory action by decreasing the activity of CB1 and increasing CB2 receptor activity (Ranieri et al., 2016) there is now evidence that they also increase neuroinflammation due to proinflammatory cytokines increasing the activity of cannabinoid receptors on immune cells (Jean-Gilles et al., 2015). These effects on neuroinflammation are dependent on the cannabinoid concentration, and experimental studies have shown that the biphasic effects also depend on previous exposure to cannabinoids (Massi et al., 2006). This may help explain the adverse effects of the CB1 antagonist/inverse agonist, rimonabant. This drug was used to aid smoking cessation and obesity, but was withdrawn from clinical use due to its severe side effects (Christensen et al., 2007). These side effects were linked to an increase in IL-6 and TNF alpha (Beyer et al., 2010).

While there is substantial clinical evidence implicating cannabinoids as causative factors in depression, the precise mechanism whereby this occurs is unproven. Nevertheless, the tryptophan kynurenine pathway is a possible target (Zador et al., 2021) as shown in Fig. 4.

1.2. Therapeutic importance of cannabidiol

The isolation and structure of CBD was first described by Adams and Hunt in 1940, but remained largely uninvestigated until recently, because CBD seemed to lack well established behavioral effects as shown by THC. As a cannabinoid, the worldwide legal restrictions further limited studies of the therapeutic potential of CBD. However, anecdotal reports demonstrated that it had anticonvulsant, anxiolytic, analgesic, neuroprotective and sleep promoting properties, and also lacked the dependence effects associated with THC (Crippa et al., 2018). Particular attention has been directed to the effects of CBD on pain syndromes, such as neuropathic pain and arthritic pain.

Unlike THC and related phytocannabinoids, CBD has very weak activity at CB1 and CB2 receptors suggesting that its pharmacological activity is related to its action on neurotransmitter receptors, ion channels and enzymes (Thomas et al., 1998; Tham et al., 2019).

CBD is a nonstimulant phytocannabinoid accounting for nearly 50% of the content of Cannabis sativa and related species. The anti-inflammatory and neuroprotective properties are attributed to its activation of 5HT1A receptors where it acts as an allosteric modulator (Rock et al., 2012). It also interacts with various orphan G-protein coupled receptors, the transient receptor potential cation V 1 channel receptor (TRPV1), thereby contributing to its effects on pain control, the peroxisome proliferator activated receptor gamma (PPAR gamma), and GPCR 55, all effects which are associated with its anti-inflammatory activity. CBD is also a weak antagonist of mu and delta opioid receptors and a partial agonist at dopamine 2 receptors (Mlost et al., 2020). These interactions with numerous different types of molecular processes explain its complex pharmacology (Fig. 5).

CBD is used therapeutically to attenuate pain and spasm in patients with multiple sclerosis, arthritic pain and anxiety. It is likely that such patients are also taking other therapeutic drugs concurrently to treat

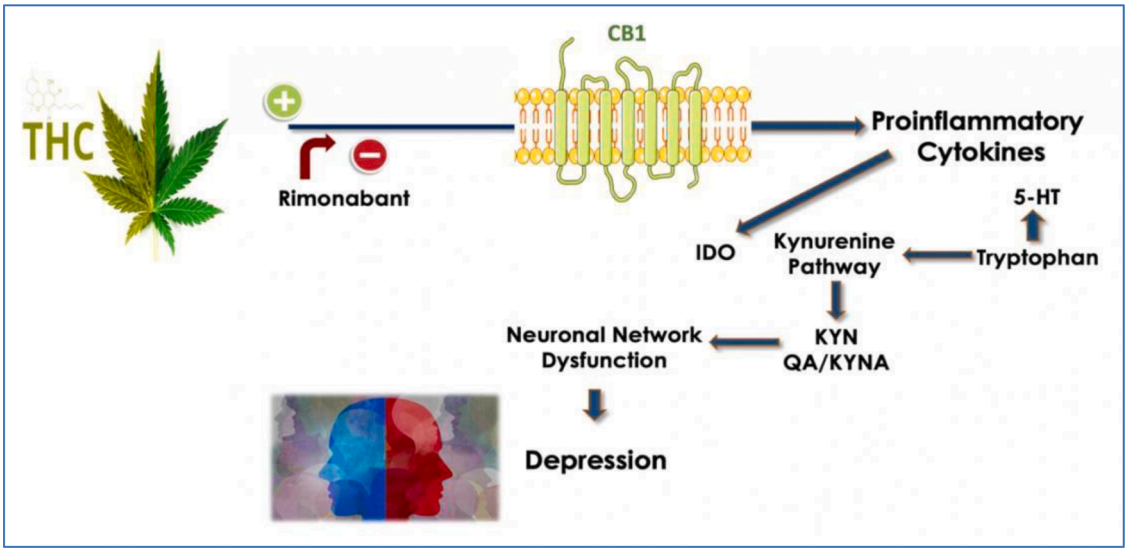

Fig. 4. Link between cannabinoid activity and changes in the tryptophan-kynurenine pathway. Tetrahydrocannabinol (THC), cannabinoid receptor 1 (CB1), serotonin (5-HT), kynurenine (KYN), quinolinic acid (QA) and kynurenic acid (KYNA).

their condition. As CBD has a high affinity for several enzymes in the cytochrome P450 super family (CYP's), possible drug interactions might also occur thereby affecting the therapeutic activity of these drugs. Fig. 6 summarizes the main CYP enzymes inhibited by CBD (Fig. 7).

While it is important to be aware of potential drug interactions in patients taking CBD therapeutically, drugs are eliminated by a number of different routes, and not by renal excretion, therefore, the clinical consequences of a drug interaction cannot be accurately predicted from the in vitro data. It is, however, important to be considered in the event of toxicity or a change in the potency of a drug response.

In addition to its pharmacological complexity, CBD and the other cannabinoids also displace anandamide and 2-AG from CB1 and CB2 receptors. As the half-lives of the endocannabinoids substantially differ (hours verses minutes, respectively) as do their tissue distributions, this further adds to the complexity in the pharmacology of CBD. It may also act as an indirect agonist at cannabinoid receptors by increasing the tone to the endocannabinoid response (Crivelaro do Nascimento et al., 2020), but it can also directly inhibit CB1 receptors (Tham et al., 2019). Furthermore, the partial activity on CB2 receptors is dependent on the receptor expression, density and tonic activity which results in varying effects of CBD in different tissues under different physiological and pathological conditions. This has already been referred to by Mlost et al. 2020).

2. Could cannabinoids provide protection against the covid-19 virus?

The covid-19 pandemic, caused by the Severe Acute Respiratory Syndrome coronavirus (SARS-Cov 2), has so far resulted in over 272 m cases worldwide and 5.3 m deaths, as reported by WHO in 2021. Despite

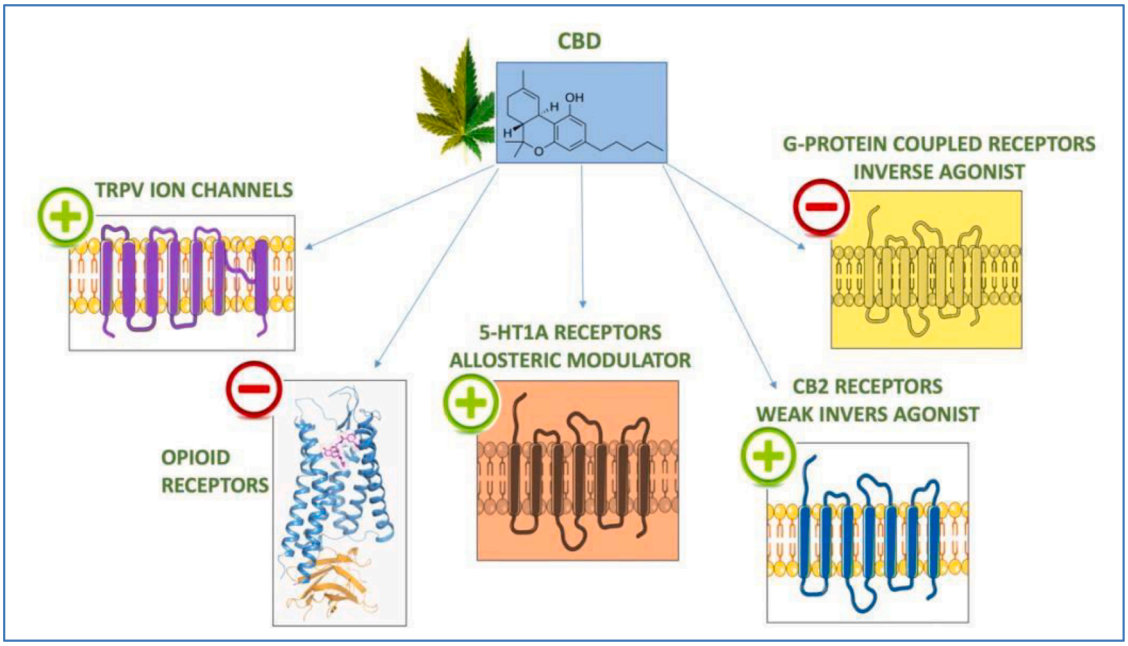

Fig. 5. Summary of the targets leading to the complex pharmacology of cannabidiol (CBD). Transient receptor potential cation V channel receptor (TRPV), Cannabinoid receptor 2 (CB2), serotonin (5-HT)1A receptor.

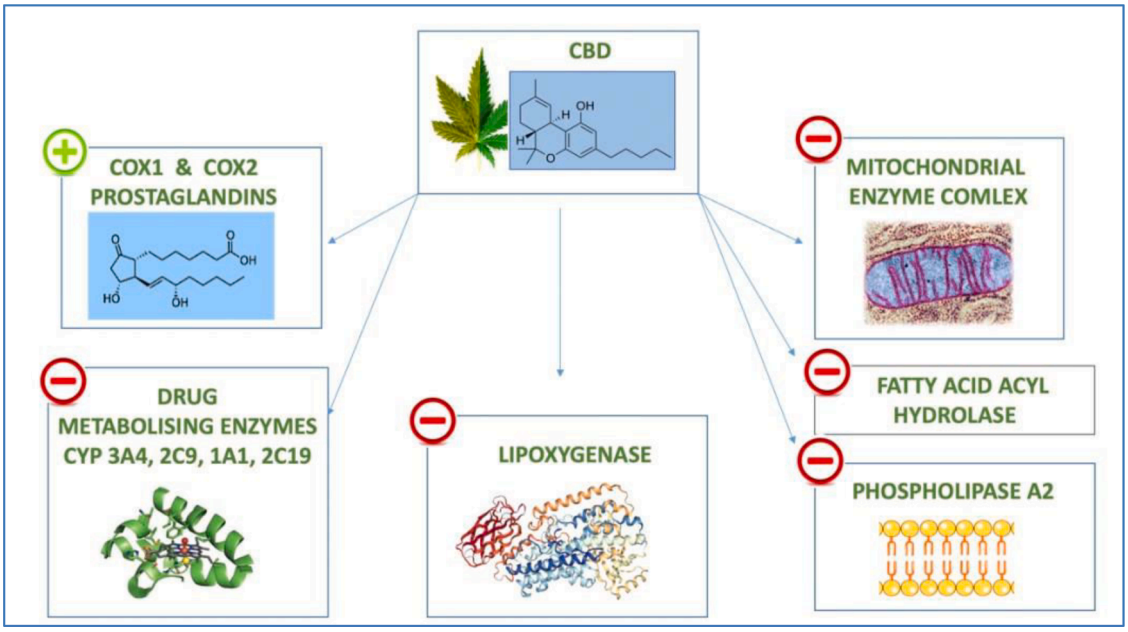

Fig. 6. Interaction of cannabidiol (CBD) with some important metabolic enzyme targets (Adapted from Mlost et al., 2020).

the development of highly effective vaccines against the 3 main variants of covid 19, mutants of the virus arise, which may not be vulnerable to the currently available vaccines. In addition, despite the efficacy of the vaccines, reinfection by the virus frequently occurs.

The molecular structure and mechanisms whereby members of the coronaviridae family enter mammalian cells and cause the pathological changes in heart, lungs, kidney and nervous system, stimulate the synthesis and release of inflammatory mediators, which results in the lethal "cytokine storm", has been extensively covered elsewhere (Shereen et al., 2020; Lai et al., 2020; Raj et al., 2021).

To date, the main studies which demonstrate that the cannabinoids have potent anti-covid 19 properties have been conducted in vitro (for example, by Raj et al. 2021). Virtual screening for the interaction between 32 cannabinoids and the SARS-Cov2M pro enzyme, a protease which plays a major role in the life cycle of the virus, demonstrated that the most potent antiviral properties were shown by THC and CBD, compared to the reference drugs lopinavir, chloroquine and remdesivir. The authors concluded that THC and CBD could be considered in combination, or with other antiviral drugs, to reduce the access and spread of the virus.

In another recent in vitro study, Wang et al. (2022) investigated the potency of CBD on the angiotensin-2 converting enzyme receptor. The ACE-2 receptor is the functional cellular entry target, together with the transmembrane serine protease 2 (TMPRSS2), for the virus. Lung fibroblasts were used as the target cells, and the results showed that CBD potently inhibited both ACE-2 and TMPRSS2 via the AKT pathway (see above for the role of the AKT pathway in inflammation).

Affinity Selection Mass Spectrometry has been used to identify potential drugs that target the Covid-19 spike protein. Cannabinoid acids (cannabigerolic acid, cannabidiolic acid) were found to be allosteric and orthosteric ligands with micromolecular affinity for the spike proteins. These cannabinoid acids were shown to prevent the infection of human epithelial cells by a pseudo virus expressing the SARS-Cov-2 spike protein and were equally effective against the alpha- and beta- SARS Cov-2 variants. This implies that some cannabinoids have the potential to prevent and treat SARS-Cove 2 infections (Breemen et al., 2022).

Research into the application of cannabinoids to the treatment of Covid-19 is in its early stages and based on in vitro studies and mouse in vivo models. Not all of the findings implicate THC with anti-viral potential but, so far, all have identified CBD as of potential importance. For example, in a large study in the USA, CBD and its metabolite 7-hydroxy-CBD, but not THC, potently blocked the replication of SARS-Cov2 in lung epithelial cells by inhibiting viral gene expression. Interestingly, patients from the National Covid Cohort Collaborative CBD study had a significant negative association with the Covid-19 tests for infection (Nguyen et al., 2022).

While these studies emphasize the importance of CBD as a preventative treatment for the early stages of Covid-19 infection, it is essential that detailed clinical studies are undertaken before the therapeutic potential of CBD and its analogues can be realized.

3. Conclusion

While over 100 potentially active phytocannabinoids have been discovered, their detailed pharmacological properties await elucidation. So far, detailed studies and limited therapeutic applications of the two most prominent phytocannabinoids, THC and CBD, have been made. Investigating the properties of phytocannabinoids is further complicated because the clinical activities of these molecules reflect a combination of numerous minor components of the plant extracts (such as cannabivarin, cannabigerol and THC acid) which could interact with THC or CBD in vivo. Clearly more research is warranted before conclusions made regarding the precise cannabinoid targets can be identified due to their actions on multiple cellular targets. The term "endocannabinaidome" has been used to encompass the pharmacological complexity of the cannabinoids (Fig. 7).

So far, the therapeutic targets for phytocannabinoids, particularly THC, have been limited to specific types of childhood epilepsy, such as Dravet's syndrome, spasticity in multiple sclerosis and inflammation and arthritic pain. The anti-inflammatory activity of CBD, together with the activation of the age associated CB2 receptors, could be beneficial for the treatment of Alzheimer's disease, Parkinsonism and Huntington's disease. The management of neuropathic pain, due to the action of CBD on TRPV1, referred to previously, is another potentially important therapeutic area of interest.

A number of synthetic compounds, for example rimonabant, nabilone and orlistat, have already been developed based on their specificity to target aspects of the cannabinoid system. In the future, synthetic cannabinoids will need to be developed to more specifically target aspects of the endocannabinoid system, rather than broadly targeting the

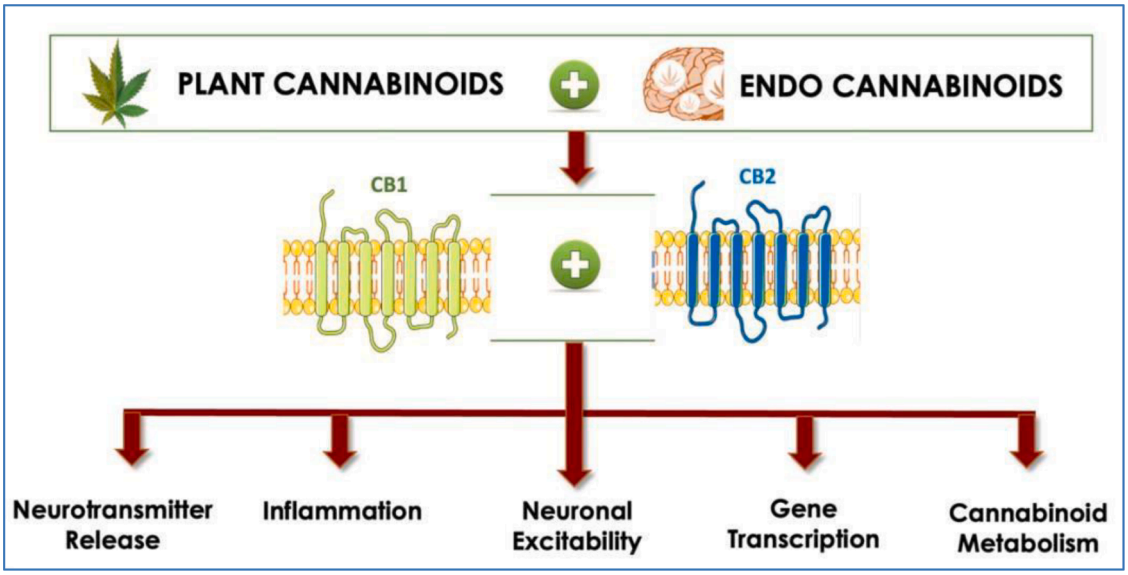

Fig. 7. Multiple cellular targets for the cannabinoids. Cannabinoid receptor 1 (CB1), cannabinoid receptor 2 (CB2).

system which has so far been used to study semi-purified phytocannabinoids. Clearly there is a large potential for novel therapeutic compounds to be discovered in synthetic cannabinoids, but this requires much more research before this potential can be fully realized.

Author statement

The authors confirm that the submitted review article is original work and it has not been published elsewhere not is it being considered for publication in another journal.

Part of this review formed the basis of a lecture to the International Workshop on the Therapeutic Potential of the Cannabinoids held in Brno, Czech Republic. May 2022.

Declaration of Competing Interest

The authors report no conflict of interest.

Acknowledgments

None.

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