Heliyon 8 (2022) e12172

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

The gut microbiota in neurodegenerative diseases: revisiting possible therapeutic targets for cannabidiol

Bruna Stefane Alves de Oliveira [a], Debora Sandrini Milanezi [a], Priscila do Val Gonzaga [a], Fernanda Rabello Detoni [a], Renato Nery Soriano [b,*]

[a] Department of Medicine, Federal University of Juiz de Fora, Governador Valadares, MG, 35032-620, Brazil
[b] Division of Physiology and Biophysics, Department of Basic Life Sciences, Federal University of Juiz de Fora, Governador Valadares, MG, 35020-360, Brazil

ARTICLE INFO

Keywords:
Intestinal dysbiosis
Alzheimer's disease
Blood-brain barrier
Cannabis sativa
Microbiota-gut-brain axis

ABSTRACT

Understanding the pathophysiology of Alzheimer's disease (AD) is essential to improve the efficacy of treatments and, consequently, patients' lives. Unfortunately, traditional therapeutic strategies have not been effective. There is therefore an urgent need to discover or develop alternative treatment strategies. Recently, some pieces of the puzzle appear to emerge: on a hand, the gut microbiota (GM) has gained attention since intestinal dysbiosis aggravates and generates some of the pathological processes of AD; on the other hand, cannabidiol (CBD), a phytocannabinoid, attenuates intestinal inflammation and possesses neuroprotective properties. Intestinal dysbiosis (increased population of proinflammatory bacteria) in AD increases plasma lipopolysaccharide and Aβ peptide levels, both responsible for increasing the permeability of the blood-brain barrier (BBB). A leaky BBB may facilitate the entry of peripheral inflammatory mediators into the central nervous system and ultimately aggravate neuroinflammation and neuronal death due to chronic activation of glial cells. Studies investigating the GM reported a strong relationship between intestinal dysbiosis and AD. In this review we conjecture that the GM is a promising therapeutic target for CBD in the context of AD.

1. Introduction

Advances in understanding the pathological processes in Alzheimer's disease (AD) have led to extensive efforts to find promising targets to develop therapeutic strategies. Currently, the knowledge on the neuro- and enteroendocrine regulations of the enteric nervous system (ENS), and the functions and regulation of both the neuroimmune axis and the microbiota-gut-brain axis support the notion that the gut microbiota (GM) may modulate: (i) factors that maintain the functional integrity of the intestine–especially through regulation of the endocannabinoid system (ECS) (Muccioli et al., 2010; Mestre et al., 2018) –, (ii) immunological status (Jiang et al., 2017), and (iii) brain functions (Spielman et al., 2018).

Thus, more attention should be paid to the findings showing the impact of alterations in the GM composition on the pathogenesis of AD. Intestinal dysbiosis can aggravate the progression or even generate common pathological processes in AD (Figure 1) (Kim et al., 2020; Fox et al., 2019) and other diseases, neurodegenerative (Spiealman et al., 2019; Adamczyk-Sowa et al., 2017) or not (Lynch and Pedersen, 2016; Qin et al., 2012; Yang et al., 2015; Naseribafrouei et al., 2014), even in clinical trials (Szablewski 2018; Jiang et al., 2017).

Current methods and therapeutic strategies for stopping (or at least attenuating) the debilitating and fatal AD progression are not effective (Joe and Ringman, 2019). Regarding the most promising therapeutic candidates for the treatment of AD, there is a growing number of articles providing evidence of the potent effects of cannabidiol (CBD):(i) neuroprotection (Campos et al., 2016; Booz 2011); (ii) negative modulation of inflammatory processes; and (iii) possible control of intestinal bacteria populations by acting together with delta-9-tetrahydrocannabinol (THC) (Al-Ghezi et al., 2019). Moreover, CBD has been shown to exhibit psychoactive characteristics as it acts on anxiety (anxiolytic effect; Shannon et al., 2019; Zuardi et al., 2017) and can block behavioral consequences of psychomimetic drugs such as THC and amphetamine (Sainz-Cort et al., 2021; Scopinho et al., 2011; Renard et al., 2016); importantly, these actions do not appear to be associated with detrimental outcomes (Kaplan et al., 2021).

In this article we revisited the findings that support the view that intestinal dysbiosis aggravates the progression of AD, as well as those

* Corresponding author.
E-mail addresses: renato.soriano@ufjf.br, renatonerysoriano@yahoo.com.br (R.N. Soriano).

https://doi.org/10.1016/j.heliyon.2022.e12172
Received 18 February 2022; Received in revised form 23 May 2022; Accepted 29 November 2022

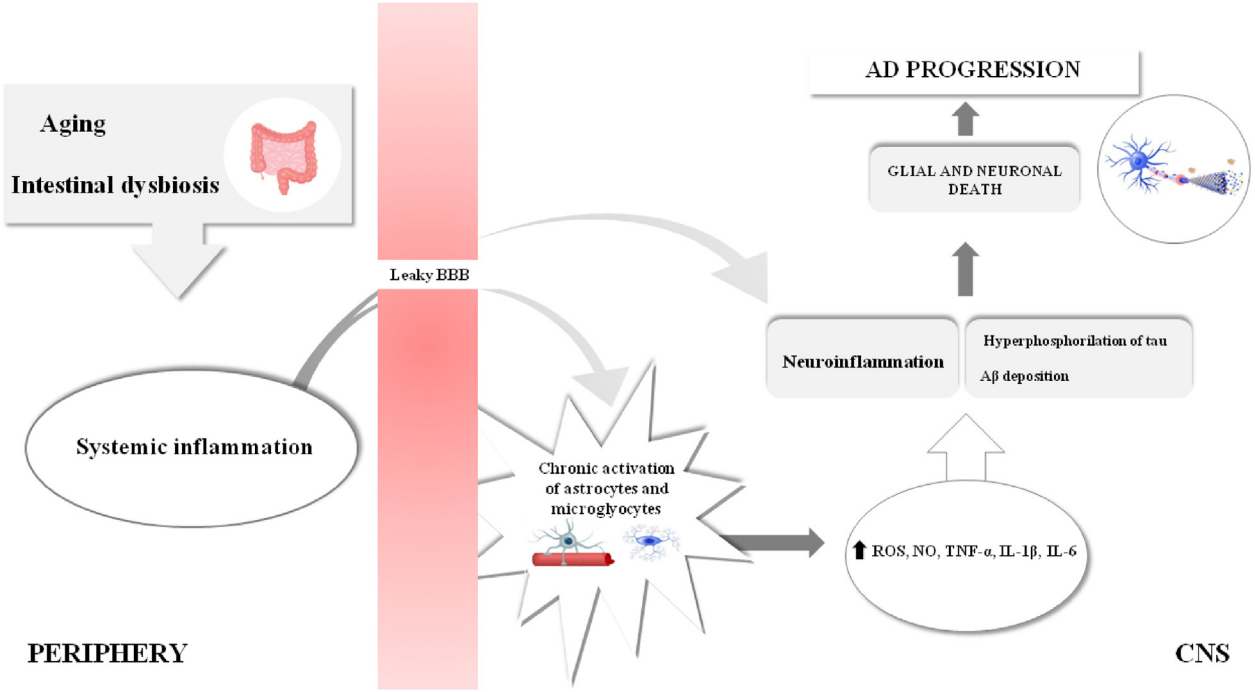

Figure 1. Contributing factors to Alzheimer's disease progression. Aging is associated with higher predisposition to oxidative stress and intestinal dysbiosis. Bloodstream (humoral route) carries bacterial products which induce systemic inflammation (and neuroinflammation) and affect the integrity of the BBB (leaky BBB). The access of LPS, Aβ peptide and pro-inflammatory mediators into the brain parenchyma is higher with a less restrictive BBB. These molecules activate astrocytes and microgliocytes. These cells, when chronically activated, produce ROS, NO, TNF- α, IL-1β e IL-6, which intensify neuroinflammatory processes, hyperphosphorylation of tau, and Aβ deposition. Together, these factors/processes cause (more) glial and neuronal death and contribute to the progression of Alzheimer's disease. BBB, blood-brain barrier; CNS, central nervous system; ROS, reactive oxygen species; NO, nitric oxide. IL-1β, Interleukin-1 beta; IL-6, Interleukin 6; TNF-α, tumor necrosis factor alpha; Aβ, amyloid-beta peptide.

showing that CBD is an adjuvant in the treatment of intestinal inflammation. Taking these findings into consideration, we conjectured that the GM is–besides a villain –, a promising therapeutic target for CBD in the context of AD.

2. Common pathological processes in Alzheimer's disease (AD)

The most studied histopathological landmarks in AD are (i) the amyloid plaques (extraneuronal deposition of fibrils and oligomers of Aβ peptides) and (ii) the neurofibrillary tangles (intracellular aggregation and deposition of hyperphosphorylated microtubule-associated protein tau) (Lane and Hardy, 2018). Other AD-related pathological events has also been reported: dystrophic neuritis (Sharoar et al., 2019), astrogliosis (Pekny et al., 2014) and microglial activation (Hansen et al., 2018; Serrano-Pozo et al., 2011). The amyloid hypothesis proposes that the deposition of pathological forms of Aβ in the brain is the primary process in AD (Lane and Hardy, 2018). Although this theory has been refuted by some researchers (Herrup, 2015) because plaque load does not always correlate with cognitive decline, many authors have demonstrated that soluble Aβ oligomers significantly aggravate disease progression, promoting synaptic and dendritic dysfunction, compromising long-term potentiation (LTP), and culminating in neuronal and glial death (Townsend et al., 2006; Xu et al., 2016).

Many researchers consider that the hyperphosphorylation of tau is a downstream event in the deposition of Aβ. However, neurofibrillary tangles deposition (formed by aggregation of tau) is greatly associated with the degree of cognitive decline and neuronal loss (Spires-Jones and Hyman, 2014; Li et al., 2017), and soluble tau can lead to synaptic loss even in the absence of Aβ (Li et al., 2017). Moreover, neurofibrillary tangle density has been shown to be related to severity and disease duration in several clinical trials (Serrano-Pozo et al., 2011).

Some high impact studies have shown that neurodegeneration in AD is associated with several factors, including neuroinflammation (Luchena et al., 2018), impairment of the blood-brain barrier (BBB) (Montagne et al., 2015), mitochondrial dysfunction (Wilkins, 2016), and oxidative stress (Sayre et al., 2008). Currently, there are many transgenic mouse models of AD providing insights into pathology, mechanisms, progression, and etiology of the disease. These animal models have been used as tools to investigate the effects of the GM on dementia (Table 3 shows some of them: 5xFAD mice, APP/PS1 mice, TAU58/2 mice). Important aspects of the disease have been studied in these models, taking into account the relevance of the promoter that drives the expression of transgenes, and the transgenes used to simulate the pathophysiology of AD, providing important clues to design clinical trials. Mutant human genes such as APP, PSEN1, APOE ϵ4 and ob (leptin) can then be studied in transgenic mouse. Therefore, besides the accumulation of Aβ peptide and tauopathy, the metabolism of cholesterol and insulin have also been studied in these models. More information about these animal models is beyond the scope of the present review, and has been elegantly covered by Esquerda-Canals et al. (2017) and Myers and McGonigle (2019).

2.1. Blood-brain barrier (BBB) impairment in AD

BBB dysfunction may result from (i) endotoxin accumulation (bacterial lipopolysaccharides, LPS) in the systemic circulation and (ii) inflammatory mediators generated within the central nervous system (CNS) (Sochocka et al., 2019), with a cause-and-consequence relationship (Danielski et al., 2018; Jiang et al., 2017). Peripheral (intestinal) pro-inflammatory factors–some of them released by GM bacteria (Friedland and Chapman, 2017; Braniste et al., 2014) –, seem to cause structural changes in the BBB, compromising its permeability (Figure 1) (Jiang et al., 2017; Sochocka et al., 2019).

2.2. Neuroinflammation in AD

Neuroinflammation is a process mediated by astrocytes (Colombo and Farina, 2016), microgliocytes (Regen et al., 2017) and, when recruited, macrophages residing in the most intimate borders of the brain parenchyma (macrophages of choroid plexus, perivascular spaces and meninges; Rua et al., 2019). Activation of astrocytes induces TNF-α, interferon-γ (IFN-γ), and IL-1β release (Liu et al., 2013). Figure 1 shows that systemic inflammation induces chronic activation of astrocytes and microgliocytes, and culminates in glial and neuronal death, contributing to AD progression. Under these circumstances, the NF-kB pathway (nuclear kappa B factor, transcription factor stimulated by "toll-like" receptors, TLRs) is activated, and this pathway has been shown to be involved in the production of reactive oxygen species (ROS) and nitric oxide (NO) and release of TNF-α, IL-1β, and IL-6. Some of these substances contribute to hyperphosphorylation of tau, formation of Aβ (Griffin et al., 2006), oxidative stress (Tonnies and Trushina, 2017), and hyperexpression of pro-inflammatory mediators (Domingues et al., 2017). Hyperactivation of microgliocytes elicits a chronic inflammatory response that occurs simultaneously with the exacerbated—and harmful—activation of astrocytes (brain cells that stabilize BBB integrity) (Sochocka et al., 2019), leading to increased BBB permeability and, consequently, entrance of gut bacterial metabolites (mainly Aβ and LPS) into the CNS (Fung et al., 2017), which generate and/or intensify neuroinflammation (Sochocka et al., 2019; Heneka et al., 2015) (Figure 1).

3. Relationships among the gut microbiota, intestine and brain

The gut microbiota (GM) maintains a mutualistic association with its host, and changes in this relationship affects the brain and also the immunological, digestive and metabolic functions (Matamoros et al., 2013).

Approximately 80% of human immune cells are found in the intestinal mucosa, and this tissue is in close contact with the GM (Sochocka et al., 2019). The gastrointestinal tract contains commensal microorganisms: bacteria, viruses, fungi and protozoans. The population of these microorganisms frequently vary according to diet, drug intervention and diseases (Geng et al., 2022). In this review we highlight gut bacterial populations.

The brain controls, via the autonomic nervous system (ANS), the motility and secretion of the gut, which, in turn, can modulate the brain function via neural routes (vagal afferent fibers) and/or via humoral routes (entero-hormones, other molecules secreted by the enteric nervous system (ENS) and immune cells) (Cryan et al., 2019). Enteroendocrine cells can detect bacterial metabolites (LPS and Aβ) and mediate communication between the intestine and the brain via secretion of (i) agonists of receptors located on vagal afferent endings (neural route) and (ii) entero-hormones and other molecules (humoral routes) (De-Paula et al., 2018; Misiak et al., 2020). Intestinal dysbiosis may compromise the gut and brain homeostasis via the microbiota-intestine-brain axis. The GM, ENS, ANS, CNS, and also the neuroendocrine and neuroimmune systems, constitute the main parts of this axis (Jiang et al., 2017).

The production of typical neurotransmitters of the CNS (dopamine, noradrenaline, serotonin, GABA, acetylcholine and histamine) (Strandwitz, 2019) by the GM can lead to central dysfunctions (Figures 1 and 2). The microorganisms that release the greatest variety of neurotransmitters are: *Escherichia coli* (dopamine, serotonin, noradrenaline) and *Lactobacillus* (serotonin, GABA, acetylcholine, histamine) (Strandwitz, 2019). The GM canproduce neurotransmitter precursors as well, and some of themcan cross the BBB and participate in the synthesis cycle of neurotransmitters in the brain (Chen et al., 2021; Strandwitz, 2019).

Although these molecules can reach the brain, the underlying mechanisms are not completely understood. Some studies indicate that neurotransmitters and its precursors seem to influence the CNS by activating receptors located on vagal afferent endings, possibly modulating the activity of the HPA (hypothalamus-pituitary-adrenal) axis (Strandwitz, 2019; Wei et al., 2021; Vagnerová et al., 2019). However, it is worth noting that clinical trials do not support the existence of the potential

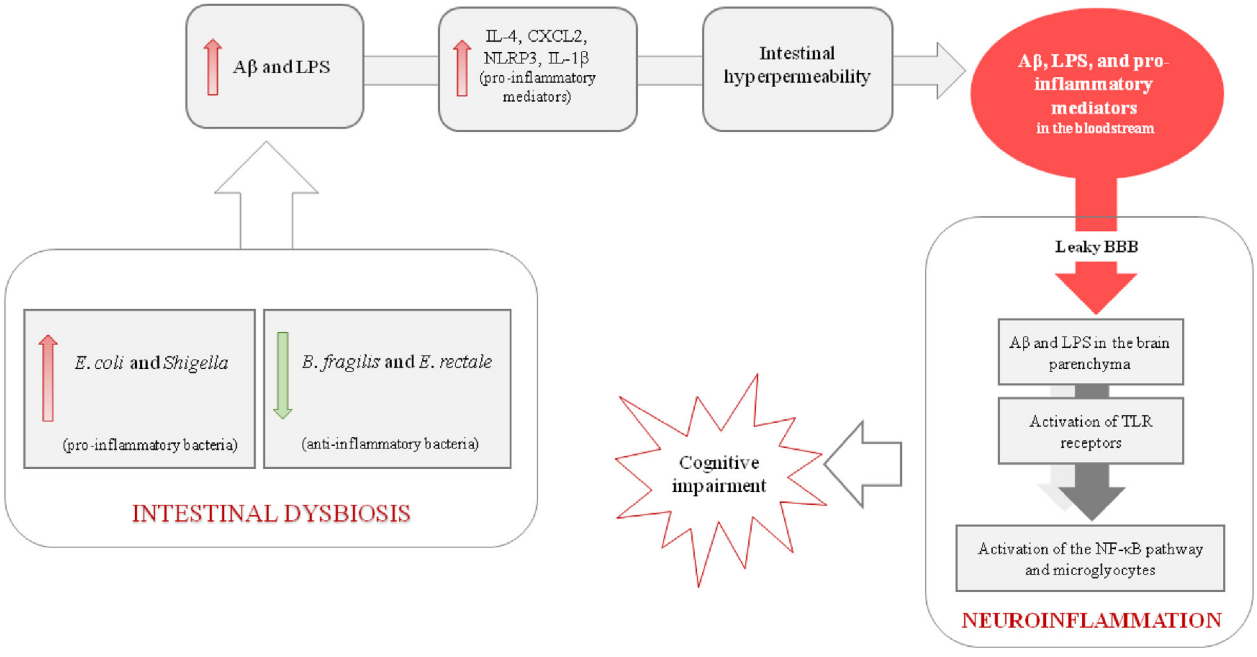

Figure 2. Intestinal dysbiosis intensifies neuroinflammatory processes. Aβ deposition and neuroinflammatory processes have been associated with reduced population of anti-inflammatory bacteria (*E. rectale* and *B. fragilis*) and enhanced population of pro-inflammatory bacteria (*E. coli* and *Shigella* sp.) in the intestine (intestinal dysbiosis). Aβ and LPS elicit an increase in pro-inflammatory mediators (IL-4, CXCL2, NLRP3 and IL-1β) which in turn induce intestinal hyperpermeability, thus facilitating the translocation of products derived from the gut microbiota, such as Aβ and LPS, to the bloodstream and, ultimately, to the brain parenchyma as well, since these factors also affects the BBB integrity (leaky BBB). Activation of TLR receptors in the brain activates the NF-κB pathway and microgliocytes, generating and/or intensifying neuroinflammation. Aβ, amyloid-beta peptide; *E. coli*, *Escherichia coli*; *E. rectale*, *Eubacterium rectale*; *B. fragilis*, *Bacteroides fragilis*; LPS, lipopolysaccharide; TLR, toll-like receptor; NF-κB, kappa B nuclear factor.

functional cross-talking between the microbiota-intestine-brain axis and the HPA axis (Misiak et al., 2020 Strandwitz, 2019). Interestingly, recent studies showed that gut bacteria are capable of regulating the activity of enteric neurons and glia (Vicentini et al., 2021), and drives macrophage-dependent self-renewal of intestinal stem cells via niche enteric serotonergic neurons (Zhu et al., 2022), reinforcing the notion that the GM affects enteric cells and, ultimately, brain neurons and glia.

3.1. Changes in the gut microbiota composition are associated with aging

The phyla Bacteroidetes (gram-negative) and Firmicutes (gram-positive) predominate in the human gut (Mancuso and Santangelo, 2017; Dinan and Cryan, 2017). Although changes in eating habits can induce changes in the human GM (Matamoros et al., 2013), it is worth mentioning that during aging intestinal dysbiosis occurs markedly, as shown in a study by the consortium "ELDERMET". These changes are accompanied by reduced population of *Bifidobacterium*—important probiotics for prevention of infection –, and increased population of *Escherichia coli* (*E. coli*), a pro-inflammatory bacterium (Zapata and Quagliarello, 2015; Cattaneo et al., 2017).

3.2. Intestinal dysbiosis in Alzheimer's disease (AD)

Pathological and/or metabolic processes produced and/or induced by intestinal dysbiosis ultimately reach the CNS, inducing (more) neuroinflammation, cell death and, consequently, AD progressive cognitive decline and behavioral deficits (Kirova et al., 2015). The microbiota-gut-brain axis (see Cryan et al., 2019; Jiang et al., 2017) has been pointed out as the main entrance-route of microbial products into the CNS (Giau et al., 2018; De-Paula et al., 2018). It is well established that AD patients present intestinal dysbiosis (Figure 2) (Zhuang et al., 2018 Jiang et al., 2017; Giau et al., 2018). By analyzing fecal samples collected from participants with AD and healthy controls some studies reported that AD patients exhibit enhanced populations of Proteobacteria and Bacteroidetes (Figure 2) (Vogt et al., 2017; Mancuso et al., 2017). Other works indicate the increase in the class Bacilli (Zhuang et al., 2018), phyla Firmicutes and Actinobacteria (Mancuso et al., 2017), Bacteroidia (Zhuang et al., 2018), the families Bifidobacteriaceae and Ruminococcaceae, and *Bifidobacterium* and *Adlercreutzia* (Vogt et al., 2017; Cattaneo et al., 2017). Moreover, compared to negative amyloid patients, positive amyloid ones present smaller population size of *Eubacterium rectale* (*E. rectale*) and *Bacteroides fragilis* (*B. fragilis*), and increased population of *E. coli* and *Shigella* sp. (Mancuso et al., 2017; Cattaneo et al., 2017) (Figure 2). Some of these bacteria, especially the gram-negative ones, in addition to short-chain fatty acids (SCFA), release molecules considered neurotoxic and pro-inflammatory, such as endotoxins (LPS) and amyloid peptides (D' Argenio, et al., 2019; Sochocka et al., 2019).

3.3. Major findings from the clinical trials

Cattaneo and coworkers (2017) investigated the relationship among Aβ deposition, the GM and peripheral inflammation in AD patients and cognitively healthy subjects. Circulating levels of cytokines were measured in patients with cognitive impairment with (n = 40, Amy+) and without cerebral amyloidosis (n = 33, Amy-), and also in a control group (n = 10; without cerebral amyloidosis and cognitive impairment). In patients with cognitive impairment, serum levels of proinflammatory cytokines (IL-6, CXCL2, NLRP3, and IL-1β) were found to be elevated when compared to patients without cerebral amyloidosis (Cattaneo et al., 2017). In addition, they suggested that increased population of pro-inflammatory bacteria and decreased population of anti-inflammatory bacteria may be associated with cerebral amyloidosis found in AD patients (Cattaneo et al., 2017). The study by Morgan and coworkers (2013) also analyzed the bacterial composition of the human gut and reported that Aβ-positive patients submitted to positron emission tomography (PET) scan exhibited greater abundance of intestinal *Escherichia* and *Shigella*, and reduced population size of *E. rectale* and *B. fragilis* (anti-inflammatory) when compared to Aβ-negative patients (Morgan et al., 2013). In a study with patients with cognitive impairments and controls, Marizzoni et al. (2020) showed a novel association among GM-related products, systemic inflammation and brain amyloidosis, suggesting that short-chain fatty acids (SCFAs) and LPS are candidates for pathophysiologic links between the GM and AD.

3.4. Intriguingly, despite the putative impact of the gut biome on neuroinflammation, therapeutic interventions with drugs and substances with anti-inflammatory properties have not been proven successful for dementia therapy so far

As summarized in Table 1, some of these substances have shown some ability to reduce inflammation (Zhu et al., 2018; Mohamed et al., 2019; Moussa et al., 2017) and Aβ deposition (Thota et al., 2020; Mohamed et al., 2019), but had little or no impact on cognitive decline; and other drugs or substances have exhibited no statistically significant effects: aspirin (Ryan et al., 2020), naproxen (Meyer et al., 2019; ADAPT-FS Research Alzheimer's Disease Anti-inflammatory Prevention Trial Research Group, 2013; 2015), *Melissa oficinalis* extract (Noguchi-Shinohara et al., 2020), ferulic acid (FA), *Angelica archangelica* (AA) (Matsuyama et al., 2020), and the antibiotic minocycline (Howard et al., 2020). We believe that this is due to the fact that the substances are more promising in early stages of dementia, or even in stages that precede the actual disease. In addition, it appears that only a delay in the progression of dementia is achieved with the use of these anti-inflammatory substances, as they do not act on mechanisms actually capable of preventing the development of AD.

Considering that effective oral drug delivery and its impact on the GM composition represent a growing field and holds promise for effective therapeutic interventions of several (gastrointestinal) diseases (e.g., irritable bowel disease, diabetes, obesity, Parkinson's and Alzheimer's diseases), it seems probable that the oral route of therapeutic substances exerts more significant impacts on the GM (Enck et al., 2020). In this scenario emerges the anti-inflammatory potential of (orally administered) cannabidiol (CBD) and its other promising therapeutic properties as well.

3.5. Therapeutic potential of cannabidiol (CBD) in Alzheimer's disease

Over the past years, CBD has been shown to be a promising ally in the treatment of AD, since this compound exhibits the following potential neuroprotective actions (Figure 3; Table 2 and Table 3): (i) prevents tau hyperphosphorylation through the WNT pathway (Esposito et al., 2006a, b) [a signaling pathway that is negatively modulated in AD and is responsible for promoting neuronal homeostasis (Vallé and Lecarpentier, 2016)]; (ii) exerts antioxidant and anti-apoptotic effects (Scuderi et al., 2014; Li et al., 2020; Esposito et al., 2006a,b); (iii) reduces Aβ toxicity (Esposito et al., 2006, 2007; Aso et al., 2016); (iv) exerts anti-inflammatory and immunomodulatory actions (Mecha et al., 2013; Martín-Moreno et al., 2011; Carrier et al., 2006); and (v) promotes cognitive improvements in experimental models (Cheng et al., 2014; Aso et al., 2016). Importantly, some studies investigated the effects of CBD *in vivo* and revealed promising results as well. Table 3 summarizes these relevant outcomes.

Moreover, taking into consideration that intestinal inflammation seems to contribute to the pathology of AD (through the microbiota-gut-brain axis), other actions of CBD in this context have to be highlighted, particularly its potential ability to: (i) reduce the permeability of the human colon (Couch et al., 2019); (ii) prevent experimental colitis in mice (a type of inflammatory bowel disease; Borrelli et al., 2009); (iii) attenuate intestinal inflammation (De Filippis et al., 2011); and exerts other actions (see Table 4).

Table 1. Drugs and substances, other than cannabidiol, with anti-inflammatory potential, have not been proven successful for dementia therapy so far (human studies).

Drug/ substance	Effects	Participants/ Age	Route	Reference
Curcumin	Potential protection against Aβ accumulation and hyper-phosphorylation of tau	Participants aged 30–70 years	Oral route	Thota et al. (2020)
	No significant results in cognitive performance	Cognitively healthy individuals aged 40–90 years	Oral route	Rainey-Smith et al. (2016)
Aspirin	Low-dose is not effective in reducing the risk of AD	Initially healthy community-dwelling individuals aged ≥70 years	Oral route	Ryan et al. (2020)
Melissa ofcinalis (RA-rich extract)	No significant diferences in cognitive measures; RA may help to prevent the worsening of AD-related neuropsychiatric symptoms	Patients with mild dementia due to Alzheimer's disease	Oral route	Noguchi-Shinohara et al. (2020)
FA and AA	FA and AA do not reduce Aβ deposition	Individuals diagnosed with mild cognitive impairment	Oral route	Matsuyama et al. (2020)
Minocycline	No significant influence on dementia and AD	People with dementia (including patients with AD)	Oral route	Howard et al. (2020)
Naproxen	Naproxen does not affect concentrations of CSF immune markers	Cognitively unimpaired serial CSF donors with a parental or multiple-sibling history of "sporadic" AD	Oral route	Meyer et al. (2019)
Lactoferrin	Aβ40, oxidative stress markers, IL-6, and p-tau are significantly reduced upon lactoferrin intake	Patients with a clinical diagnosis of probable AD	Oral route	Mohamed et al. (2019)
Brazilian green propolis	Improves the cognitive function through systemic inflammation reduction	Elderly people living in Xining	Oral route	Zhu et al. (2018)
Resveratrol	Modulates neuro-inflammation, and induces adaptive immunity	Individuals with mild to moderate dementia due to AD	Oral route	Moussa et al. (2017)
BMS-708163 (γ-secretase inhibitor)	Reduces plasma Aβ42 and Aβ40; No changes in total Aβ	Healthy young (aged 18–55 years) and elderly (aged ≥70 years) individuals	Oral route	Soares et al. (2016)
Naproxen and celecoxib	Do not protect against cognitive decline	Old adults with a family history of AD	Oral route	ADAPT-FS Research Alzheimer's Disease Anti-inflammatory Prevention Trial Research Group, 2013; 2015
CHF5074 (γ-secretase modulator)	No effect on cerebrospinal fluid Aβ42; inhibitory effects on soluble CD40 ligand and TNF-α	Patients with mild cognitive impairment	Oral route	Ross et al. (2013)

Aβ, amyloid beta; AD, Alzheimer's Disease; RA, rosmarinic acid; AA, *Angelica archangelica*; CSF, cerebrospinal fluid; Aβ40, amyloid beta-40; IL-6, interleukin 6; p-tau, tau protein; Aβ42, amyloid beta 42; CD40, cluster of differentiation 40; TNF-α, tumor necrosis fator α.

3.6. CBD, the endocannabinoid system and neuromodulation

The endocannabinoid system (ECS) is a retrograde neuromodulatory signaling network (Bhatia-Dey and Heinbockel, 2020; Zou and Kumar, 2018) mediated mainly by the activation of type 1 (CB1) and type 2 (CB2) cannabinoid receptors by endocannabinoids (Bhatia-Dey and Heinbockel, 2020). In addition to CB1 and CB2, the following proteins are ECS receptors as well: TRPV1, PPARγ, PPARα, and GPCRs orphans (Cristino et al., 2020). The endocannabinoids that activate these receptors are: N-arachidonoylethanolamine (AEA, also called ANA, abbreviation for anandamide), 2-arachidonoylglycerol (2-AG) (Russo et al., 2018) and palmitoylethanolomide (PEA) (Van der Stelt et al., 2014). This system exerts anti-inflammatory and neuroprotective actions (Van der Stelt et al., 2014; Cristino et al., 2020; Couch et al., 2018). Evidence suggests that the ECS is capable of modulating both the inflammatory response (Muccioli et al., 2010) and intestinal permeability, thereby regulating the production of pro-inflammatory factors and their access to the bloodstream (Russo et al., 2018). These actions seem to be mediated by cellular responses resulting from the activation of CB1 (Russo et al., 2018; Muccioli et al., 2010). Considering that the ECS exhibits such properties and that CBD is capable of modulating this system, the following question arises: Is CBD able to modulate neuroinflammation in AD through anti-inflammatory actions and regulation of intestinal permeability?

Some studies have found some pieces of the puzzle indicating that CBD seems to be a promising ally. For example, the findings by Aso et al. (2016) revealed that CB2 activation by CBD is associated with Aβ clearance. They administered daily doses of CBD to 6-month AβPP/PS1 male transgenic rats and found that CBD activates CB2 receptors (low affinity) and increases (*in vitro*) the Aβ removal process in the choroid plexus (Aso et al., 2016). Martín-Moreno and co-workers reported that CBD-mediated activation of CB2 receptors leads to reduction of IL-6 in mice injected with Aβ, and in other study (*in vivo*) they documented that CBD was able to reduce microglial activation (Martín-Moreno et al., 2011). Furthermore, the relationship between CBD and peroxisome proliferator-activated receptors (PPARs) was studied by Esposito et al. (2011), reinforcing the potential benefits of the use of CBD as a potential alternative therapeutic agent in AD. The PPARγ isoform (Vallé and Lecarpentier, 2016) attenuates oxidative stress and acts on energy homeostasis, besides negatively modulating the expression of pro-inflammatory mediators (Vallé and Lecarpentier, 2016). Paradoxically, under physiological conditions, PPARγ is expressed at low levels in the CNS, and in AD the cerebral expression of this isoform is high (Vallé and Lecarpentier, 2016; Esposito et al., 2011). The activation of PPARγ can prevent neuronal death in the hippocampus and cerebral cortex,

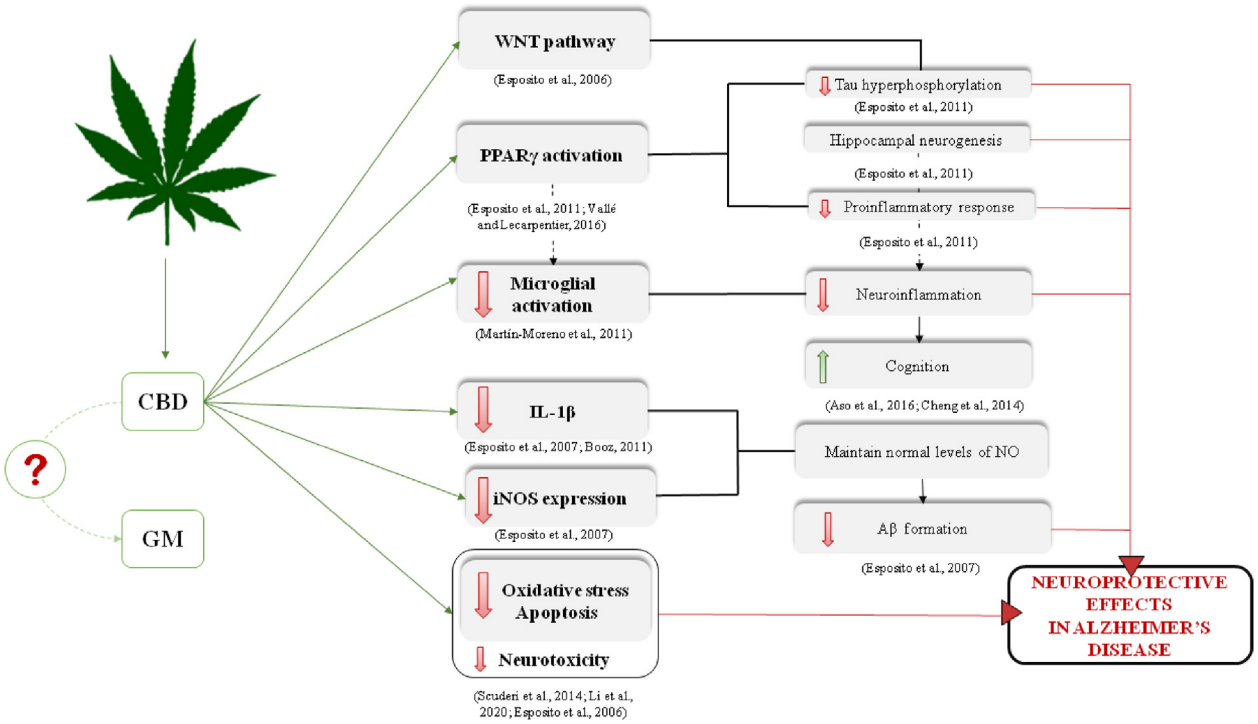

Figure 3. The most remarkable actions of cannabidiol (CBD) indicate it is a promising ally in the treatment of Alzheimer's disease. Cannabidiol (CBD; a non-psychotropic compound of *Cannabis sativa*) has been shown to attenuate several pathological processes in Alzheimer's disease (AD), thus exerting neuroprotective effects. Further studies are needed to demonstrate/confirm that/whether CBD is able to modulate the GM composition (see the symbol "?" in the figure) in AD patients, mitigating intestinal dysbiosis and, consequently, neuroinflammatory processes aggravated by the microbial imbalance. Aβ, amyloid-beta peptide; CBD, cannabidiol; GM, gut microbiota; PPARγ, peroxisome proliferator-activated receptor gamma; iNOS, inducible isoform of nitric oxide synthase; IL-1β, interleukin-1 beta.

Table 2. Neuroprotective actions of cannabidiol: *in vitro* studies.

Mechanism	Effects	Experimental model	Reference
WNT pathway rescue	Inhibits Aβ-induced tau protein hyperphosphorylation	PC12 cells	Esposito et al. (2006)
Negatively regulates caspases	Inhibits neuronal apoptosis; counteracts the Aβ-induced Ca^{2+} increase (antioxidant property)	PC12 cells	Li et al. (2020)
PPARγ interaction	Markedly counteracts apoptosis	SHSY5YAPP + neurons	Scuderi et al. (2014)
Reduces APP expression (via PPARγ activation)	Suppresses pro-inflammatory responses; induces hippocampal neurogenesis	*In vitro:* Rat astroglial/ astrocyte cultures	Esposito et al. (2011)
Interaction with CB1/CB2 receptors and A2A receptors	Promotes ATP-induced $[Ca^{2+}]_i$ and microglial cell migration	Primary Rat Microglial Cultures	Martín-Moreno et al. (2011)

Aβ, amyloid beta; APP, amyloid precursor protein; PPARγ, peroxisome proliferator-activated gamma; CB2, type 2 cannabinoid receptor; CB1, type 1 cannabinoid receptor; $[Ca^{2+}]_i$, intracellular calcium concentration.

besides decreasing microglial activity (Vallé and Lecarpentier, 2016). It has been observed that CBD is capable of activating PPARγ, which consequently reduces hyperphosphorylation of tau induced by APP ubiquitination; thus, it suppresses pro-inflammatory responses generated by the Aβ fragment, decreasing AD neuroinflammation and acting as a neuroprotector (Esposito et al., 2011). Furthermore, *in vivo* (murine models of neuroinflammation induced by intrahippocampal injection of Aβ) and *in vitro* studies documented that activation of PPARγ by CBD may favor the neurogenesis in the hippocampus (Esposito et al., 2011).

3.7. Actions of CBD in mouse models of tauopathy

Many mouse models of tauopathy have been studied over the last years, such as hTau, rTg4510, Tau P301s, and tauP301L (see Esquerda-Canals et al., 2017; Myers and McGonigle, 2019), but only a few studies have investigated the actions of CBD in these mouse models (see Table 3). Casarejos et al. (2013) showed that transgenic mice with tauopathy (PK−/−/TauVLW) had reduced Aβ and tau deposition in the hippocampus and cerebral cortex, reduced gliosis, and reduced neuroinflammation when treated with Sativex, a mixture of delta-9-tetrahydrocannabinol (THC) and CBD. The mechanisms have not been elucidated, but the authors suggested that neuroprotective actions might exert an important positive impact on the treatment of neuropathies (Casarejos et al., 2013). In other mouse model of tauopathy (TAU 58/2 mice at 4 months of age), CBD administration (i) did not change animals' behavior, (ii) prevented sociability or social recognition memory deficits (that are usually seen in transgenic mice with AD), and (iii) reduced body weight and anxiety (G Watt et al., 2020). These findings reinforce the view that CBD is a promising candidate for the treatment of AD, especially *in vivo* (see Table 3).

3.8. Immunomodulatory and anti-inflammatory actions of CBD

Cheng et al. (2014) showed that male transgenic mice (APP swe/PS1ΔE9) submitted to behavioral tests presented cognitive improvement when chronically treated with CBD. The mechanisms have not been elucidated, but the authors suggested that the CBD actions are associated with a decrease in neuroinflammatory processes (Cheng et al., 2014).

In an animal model of AD, administration of CBD caused marked reduction in the expression of IL-1β and iNOS (Esposito et al., 2007).

Table 3. Neuroprotective actions of cannabidiol: *in vivo* studies.

Mechanism	Effect	Experimental model	Route of administration	References
Reduces APP expression (via PPARγ activation)	Suppresses pro-inflammatory responses; induces hippocampal neurogenesis	Adult male Sprague-Dawley rats	Not reported	Esposito et al. (2011)
Impairs NO and IL-1β release	Reduces Aβ toxicity	Mice with human Aβ-42	Intraperitoneal injection	Esposito et al. (2007)
Activates CB2 receptors (#) (association with THC and BDS)	Reduces memory and learning impairment; increases Aβ-42 contents in plaques; decreases the astroglial reactivity to Aβ deposition	APP/PS1 mice	Intraperitoneal injection	Aso et al. (2016)
Unknown mechanism	Cognitive improvement associated with a decrease in neuroinflammation	APPswe/PS1ΔE9 mice	Intraperitoneal injection	Cheng et al. (2014)
Downregulates VCAM-1, chemokines, and IL-1β; attenuates microglia activation; inhibits adenosine uptake mediated by A2A receptors	Reduces neuroinflammation	TMEV-IDD mice	Intraperitoneal injection	Mecha et al. (2013)
Interacts with CB1/CB2 receptors and A2A receptors	Reduces IL-6	Aβ-injected mice	Not reported	Martín-Moreno et al. (2011)
Inhibits adenosine uptake mediated by A2A receptors	Decreases TNFα	LPS-treated mice	Not reported	Carrier et al. (2006)
Enhances the immune system response and autophagy of hippocampal neurons	Inhibits AD pathological process	APP/PS1 mice	Intraperitoneal injection	Hao and Feng, 2021
Enhances IL-33 and TREM2 expression	Improves AD symptoms; delays cognitive decline	5×FAD mice (translational model of familial AD)	Intraperitoneal injection	Khodadadi et al. (2021)
Reduces insoluble Aβ40 levels	Improves social recognition memory and reduces spatial learning deficits	AβPPswe/PS1ΔE9 mice	Intraperitoneal injection	Watt et al. (2020)
Unknown mechanism	Reduces Aβ and tau deposition in the hippocampus and cerebral cortex; reduces gliosis and neuroinflammation	PK−/−/TauVLW mice	Intraperitoneal injection	Casarejos et al. (2013)
(@)	Does not affect behavioral changes	TAU58/2 mice	Intraperitoneal injection	Watt et al. (2020)
Reduces astrogliosis, microgliosis, and inflammatory-related molecules (interaction with THC)	Reduces Alzheimer-like condition when chronically administered during the early symptomatic stage	Male APP/PS1 mice and wild-typelittermates aged 6 months (early symptomatic phase)	Intraperitoneal injection	Aso et al. 2015
Decreases soluble Aβ42 peptide levels and changes plaques composition (interaction with THC)	Induces reduction in the harmful effect of the most toxic form of Aβ peptide	Male APP/PS1 mice and wild-typelittermates aged 6 months (early symptomatic phase)	Intraperitoneal injection	Aso et al. 2015
Chronic treatment normalizes the levels of the pre-synaptic SNAP25 (interaction with THC)	Reduces memory impairment occurring when the progression of the disease is at an advanced stage	Male APP/PS1 mice and wild-type-like (WT).	Intraperitoneal injection	Aso et al. 2016
A2AR-dependent actions; these receptors form heteromers with CB1R at the presynaptic level in hippocampus CA1 neurons (interaction with THC)	Blunts the THC-induced cognitive impairment	Male mice C57BL/6J	Intraperitoneal injection	Aso et al. 2019

Aβ, amyloid beta; APP, amyloid precursor protein; PPARγ, peroxisome proliferator-activated gamma; NO, nitric oxide; IL-1β, interleukin-1 beta; CB2, type 2 cannabinoid receptor; CB1, type 1 cannabinoid receptor; BDS, botanical drug substances; THC, delta-9-tetrahydrocannabinol; VCAM-1, vascular cell adhesion protein 1; A2A, adenosine receptor A2; $[Ca^{2+}]_i$, intracellular calcium concentration; IL-6, interleukin-6; LPS, lipopolysaccharide; IL-33, interleukin 33; TREM-2, triggering receptor expressed upon myeloid cells 2. (#)The authors did not describe the mechanisms. (@) Mouse behavioral tasks were not affected.

Moreover, an *in vitro* study showed that several parameters of microglial activation were attenuated by CBD (Martín-Moreno et al., 2011). According to Mecha et al. (2013), a possible explanation for some of these anti-inflammatory actions of CBD is that it downregulates the vascular cell protein 1 (VCAM-1) expression, which hinders the migration of activated immune cells through the BBB, reducing (i) the brain levels of IL-1β and (ii) the activation of microgliocytes. An *in vitro* study with PC12 murine cells stimulated with Aβ showed that CBD was able to reduce the levels of IL-1β and Aβ, and the expression of iNOS, thus maintaining (normal) the levels of NO (Esposito et al., 2006a,b); these actions reduce both cellular toxicity and neuroinflammation. *In vitro* and *in vivo* experiments indicated that CBD mitigates oxidative stress and hyperphosphorylation of tau, and down modulates NO levels caused by the activation of the Wnt pathway, thereby indicating a neuroprotective effect, since it fights against the Aβ-induced neurotoxicity (Vallé and Lecarpentier, 2016). Immunosuppressive function has also been attributed to CBD due to its inhibitory action on adenosine reuptake, which progressively causes an increase in endocannabinoid-mediated A2A signaling in the post-synaptic membrane (Carrier et al., 2006). Adenosine is an extensively distributed signaling nucleoside which exerts a variety of biological functions in the brain via A_1, A_{2A}, A_{2B}, and A_3 receptors (for a review see Liu et al., 2019). Dysfunction of adenosine receptors has been considered to be involved in the pathology of AD, and the theory of the adenosine receptor balance has received much attention over the last years. A_{2A} adenosine receptor ($A_{2A}R$) is involved in the pathophysiology of different neurodegenerative illnesses. $A_{2A}R$ modulates glutamatergic synaptic transmission in the CNS, and acts on microglia and astrocyte activation, exerting a pivotal role in neurodegenerative diseases, including AD, particularly regulating neuroinflammation via inhibition of NLRP3 inflammasome (a tripartite multiprotein complex including NLRP3, ASC, and procaspase-1; Merighi et al., 2022a; for recent reviews see Merighi et al., 2022b, 2022c). A selective $A_{2A}R$ antagonist (istradefylline) is already approved in the US and Japan as an adjunctive treatment to levodopa and decarboxylase inhibitors in patients with Parkinson's disease (for a recent review see Mori et al., 2022) and this antagonist has been investigated as a putative candidate for the treatment of AD as well; if its effects on AD is confirmed and reproducible, a new hope for AD patients is coming (Merighi et al., 2022a; for recent

Table 4. Anti-inflammatory actions of cannabidiol in intestinal disturbances.

Mechanism	Effect	Animal model or Clinical trial	Route of administration	References
Reduces population size of gram-negative bacteria in the GM (in association with THC)	Suppresses neuroinflammation	Murine models of multiple sclerosis	Intraperitonial injection	Al-Ghezi et al. (2019)
Unknown mechanism	Reduces inflammatory markers; increases *Akkermansia muciniphila* population; promotes some GM changes	Dextran sulphate sodium model of mouse colitis	Gavage in sesame oil	Silvestri et al. (2020)
PPARγ interaction; targets enteric reactive gliosis	Reduces LPS, TNF-α, immunoreactivity for cleaved-caspase-3; reduces iNOS (UC)	LPS-treated mice Biopsies of UC patients	Intraperitoneal injection	De Filippis et al. (2011)
Interaction with CB1	Prevents intestinal hyperpermeability	Caco-2 cells	Application in the apical side of the insert	Alhamoruni et al. (2010)
Changes in aquaporins, tight junction proteins, and receptor expression	Reduces permeability in the human colon	*In vitro:* Caco-2 cells *In vivo:* Healthy human, with induced increased gut permeability caused by aspirin treated with oral CBD	*In vitro*: apical addition *In vivo:* oral administration	Couch et al. (2018), 2019
Reduces colon injury, inducible iNOS expression, and IL-1β, IL-10, and promotes endocannabinoid changes	Prevents experimental colitis in mice	*In vitro:* Caco-2 cells *In vivo:* Murine model of colitis (male ICR mice)	Not reported	Borrelli et al. (2009)
Decreases the colon weight/length ratio, and myeloperoxidase activity (in association with BDS)	Attenuates intestinal inflammation and hypermotility	Murine model of colitis (male ICR mice)	Intraperitoneal injection or oral gavage	Pagano et al. (2016)

GM, gut microbiota; THC, delta-9-tetrahydrocannabinol; PPARγ, peroxisome proliferator-activated gamma; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor alpha; iNOS, inductive isoform of nitric oxide synthase; UC, ulcerative colitis; IL-1β, interleukin-1 beta; IL-10, interleukin-10; BDS, botanical drug substances. ICR mice is a strain of albino mice originating in SWISS and selected to create a fertile mouse line.

reviews see Merighi et al., 2022b, 2022c). Carrier et al. (2006) have raised the hypothesis that the activation of $A_{2A}R$ by CBD, acting as an indirect agonist, reduces the release of tumor necrosis factor-alpha (TNF-α), suggesting anti-inflammatory and neuroprotective effects of CBD. In this context, another interesting discovery, combining *in vivo* and *in vitro* techniques, was that CBD blunts the THC-induced cognitive impairment in an $A_{2A}R$-dependent manner (Aso et al., 2019).

3.9. Other neuroprotective actions of CBD

CBD also appears to act on pathways that overlap or precede neuroinflammation. In a recent study, Hao and Feng (2021) tested this hypothesis in an animal model, demonstrating that CBD enhances the immune response and upregulates autophagy-related genes of AD mice, thus downmodulating neuroinflammatory pathway(s). In this context, an *in vitro* and comparative study investigating human neuroblastoma cells with APP overexpression (SHSY5YAPP+) and neuronal control cells revealed that CBD administration was able to induce APP ubiquitination, causing decreased expression of Aβ, reducing cellular apoptosis, and increasing neuronal survival (Scuderi et al., 2014). These results corroborate findings of a descriptive observational study (conducted by the same authors in 2013) in which it was found (using shsy5y neuronal cell culture) that CBD (in a dose-dependent manner) can reduce Aβ formation from the ubiquitination of APP, decreasing apoptosis rate and, consequently, increasing survival of neurons (Scuderi et al., 2013).

It is well known that the activation of caspase family proteases induces apoptosis. CBD has been shown to reduce caspase levels, inhibiting neuronal apoptosis (Li et al., 2020). CBD has also been able to prevent an increase in Ca^{2+} caused by Aβ (Li et al., 2020). Furthermore, a study in 6-month-old male AβPP/PS1 transgenic animals submitted to daily treatment with CBD for 5 weeks showed that the phytocannabinoid (CBD) favors memory formation in murine models of (advanced) AD (Aso et al., 2016). Additionally, CBD has been shown to prevent cognitive impairment in Aβ-injected mice (Martín-Moreno et al., 2011). Through different mechanisms (see Table 2 and Table 3), recent studies confirm that CBD is able to ameliorate the impaired cognitive function (Khodadadi et al., 2021; G. Watt et al., 2020).

3.10. CBD, the gut microbiota and the associated inflammation

A study conducted in murine models of multiple sclerosis (6 to 8-week-old females C57BL/6 mice) concluded that a combination of CBD and THC was able to promote changes in the GM that suppressed both neuroinflammation and other signs of the disease (Al-Ghezi et al., 2019). Considering that population size of certain gram-negative bacteria, such as Proteobacteria in AD, is higher in AD patients than in normal individuals (Vogt et al., 2017), it is plausible to suggest that an intervention which is able to regulate the population size of Proteobacteria is a powerful ally in the treatment of AD. To investigate this possibility, a recent work studied the effects of the treatment with CBD combined (or not) with fish oil (FO) on inflammation and dysbiosis in dextran sulphate sodium (DSS) mice model of colitis, which also causes behavioral disturbances. Those authors observed the effect of CBD alone and found no difference at any of the doses tested. However, when CBD and FO were co-administered all inflammatory markers were reduced. Although the study did not observe statistically significant changes in the diversity of the GM of DSS mice, the changes were observed at the level of phylum, families, genera and species of intestinal bacteria with the treatments (combined or not). A remarkable result of that study was: the combined treatment was able to increase the population size of *Akkermansia muciniphila* (considered to be anti-inflammatory; Silvestri et al., 2020).

By exploring the isolated action of CBD on the intestine, De Filippis et al. (2011) found a low amount of MAC-3 (a macrophage marker) in the intestine of LPS-injected mice treated with CBD. In the same study, CBD alone significantly reduced the levels of TNF-α and the immunoreactivity for cleaved-caspase 3 (a pro-apoptotic enzyme) (both TNF-α and cleaved-caspase 3 are increased by LPS), suggesting that CBD can control the immune response to inflammation by regulating cellular responses and possibly protects the intestine from damage (De Filippis et al., 2011).

Thus, the possibility of preservation of the intestinal barrier by CBD seems to be a relevant discovery, since it hinders the passage of microbial metabolites and reduce the induction of pro-inflammatory cytokines that generate systemic inflammatory responses which may affect the BBB (Dinan and Cryan, 2017; Pistollato et al., 2016). Other research groups investigated the effects of CBD on the ECS in the intestine. Importantly,

CBD, by activating CB1, was able to prevent intestinal hyperpermeability in an *in vitro* model with Caco-2 cells (Alhamoruni et al., 2010). Similar results were obtained by Coach and colleagues (2019) in a randomized, placebo-controlled, double-blind controlled trial in which some *in vitro* analyses were also performed. In a study conducted in rats with induced colitis (male ICR rats), it was reported that CBD exerts anti-inflammatory effects in the intestine: inhibits FAAH, promotes negative regulation of cytokine expression, and decreases the production of ROS in the epithelial cells, thus contributing to the reduction of oxidative stress (Borrelli et al., 2009) and preservation of intestinal integrity; these findings were also documented by Pagano et al. (2016) (see Table 4).

4. Conclusion and perspectives

Until very recently, most of the attention and research efforts worldwide have focused on the deleterious actions of amyloid plaques and hyperphosphorylated tau. Unfortunately, therapeutic strategies to prevent (or at least reduce) tau aggregation in patients (Gauthier et al., 2016; Lawlor et al., 2018) and immunotherapy interventions against Aβ plaques, although safe, have not been effective in clinical trials (Salloway et al., 2014; Lawlor et al., 2018).

Recent scientific advances showed that changes in the GM composition affect the brain, alter immunological and intestinal functions, and are associated with AD. The imbalance of the microbiota-gut-brain axis can intensify inflammatory processes, including those in the CNS, generating and intensifying processes of the pathophysiology of AD. Therefore, therapeutic interventions which attenuate inflammatory pathways are likely to mitigate the progression of AD. Although the effects of the treatment with CBD alone on the GM composition have not yet been specifically investigated in AD models or patients, the effectiveness of combined treatments with CBD has to be highlighted. Studies with high methodological quality are necessary to investigate whether CBD alone exerts immunomodulatory and neuroprotective effects in animal models of AD and, later, in AD patients as well. If the modulatory effects of CBD on the GM are confirmed, CBD becomes an even stronger ally in the treatment of AD patients.

Thus, the search for truly effective interventions continues and, consequently, some questions need to be raised: (1) Would there be a (some) more promising therapeutic target(s) or a target that should be treated together with the other one(s)? (2) Could this target be the GM? (3) Could CBD, with its broad-spectrum actions, be a promising ally in the treatment of AD?

The international scientific community did not answer these questions completely yet. Nevertheless, the present review article highlights findings that should be taken into consideration, and we encourage research groups to directly investigate (in animal models and/or randomized clinical trials) whether the GM is indeed a promising therapeutic target for CBD, thereby offering remarkable therapeutic advances in the treatment of AD.

5. Limitations

We found studies that documented a relationship between the progression of AD and alterations in the GM composition, including works that investigated CBD mitigating AD pathological processes. Overall, the main limitations were the absence of (i) clinical trials investigating the putative effects of CBD on the GM composition in the context of AD, and (ii) reports showing a direct action of CBD alone on the GM composition.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

The authors thankfully acknowledge the literature access provided by the Institution.

References

Adamczyk-Sowa, M., Medrek, A., Madej, P., Michlicka, W., Dobrakowski, P., 2017. Does the gut microbiota influence immunity and inflammation in multiple sclerosis pathophysiology? J Immunol Res 2017, 7904821.

ADAPT-FS Research Group, 2015. Follow-up evaluation of cognitive function in the randomized Alzheimer's disease anti-inflammatory prevention trial and its follow-up study. Alzheimers Dement 11 (2), 216–225.

Al-Ghezi, Z.Z., Busbee, P.B., Alghetaa, H., Nagarkatti, P.S., Nagarkatti, M., 2019. Combination of cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), mitigates experimental autoimmune encephalomyelitis (EAE) by altering the gut microbiome. Brain Behav. Immun. 82, 25-35.

Alhamoruni, A., Lee, A.C., Wright, K.L., Larvin, M., O'Sullivan, S.E., 2010. Pharmacological effects of cannabinoids on the Caco-2 cell culture model of intestinal permeability. J. Pharmacol. Exp. Therapeut. 335 (1), 92–102.

Alzheimer's Disease Anti-inflammatory Prevention Trial Research Group, 2013. Results of a follow-up study to the randomized Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Alzheimers Dement 9 (6), 714–723.

Aso, E., Sánchez-Pla, A., Vegas-Lozano, E., Maldonado, R., Ferrer, I., 2015. Cannabis-based medicine reduces multiple pathological processes in AβPP/PS1 mice. J. Alzheimers Dis 43 (3), 977–991.

Aso, E., Andrés-Benito, P., Carmona, M., Maldonado, R., Ferrer, I., 2016. Cannabinoid receptor 2 participates in amyloid-β processing in a mouse model of Alzheimer's disease but plays a minor role in the therapeutic properties of a cannabis-based medicine. J. Alzheimers Dis 51 (2), 489–500.

Aso, E., Fernández-Dueñas, V., López-Cano, M., Taura, J., Watanabe, M., Ferrer, I., Luján, R., Ciruela, F., 2019. Adenosine A2A-cannabinoid CB1 receptor heteromers in the Hippocampus: cannabidiol blunts Δ9-tetrahydrocannabinol-induced cognitive impairment. Mol. Neurobiol. 56 (8), 5382–5391.

Bhatia-Dey, N., Heinbockel, T., 2020. Endocannabinoid-mediated neuromodulation in the olfactory bulb: functional and therapeutic significance. Int. J. Mol. Sci 21 (8), 2850.

Booz, G.W., 2011. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. Free Radic. Biol. Med. 51 (5), 1054–1061.

Borrelli, F., Aviello, G., Romano, B., et al., 2009. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. J. Mol. Med. (Berl.) 87 (11), 1111–1121.

Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Tóth, M., et al., 2014. The gut microbiota influences blood-brain barrier permeability in mice. Sci. Transl. Med. 6 (263), 263ra158.

Campos, A.C., Fogaça, M.V., Sonego, A.B., Guimarães, F.S., 2016. Cannabidiol, neuroprotection and neuropsychiatric disorders. Pharmacol. Res. 112, 119–127.

Carrier, E.J., Auchampach, J.A., Hillard, C.J., 2006. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc. Natl. Acad. Sci. U. S. A. 103 (20), 7895–7900.

Casarejos, M., Perucho, J., Gomez, A., Muños, M., Fernandez-Estevez, M., Sagredo, O., et al., 2013. Natural cannabinoids improve dopamine neurotransmission and tau and amyloid pathology in a mouse model of tauopathy. J. Alzheim. Dis. 35 (3), 525–539.

Cattaneo A., Cattane N.,Galluzi S., Provasi S., Lopizzo N.,Festari C., et al. 2017; 49:60-68. doi: .

Chen, Y., Xu, J., Chen, Y., 2021. Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. Nutrients 13 (6), 2099.

Cheng, D., Low, J.K., Logge, W., Garner, B., Karl, T., 2014. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1ΔE9 mice. Psychopharmacology (Berl) 231 (15), 3009–3017.
Colombo, E., Farina, C., 2016. Astrocytes: key regulators of neuroinflammation. Trends Immunol 37 (9), 608-620.
Couch, D.G., Maudslay, H., Doleman, B., Lund, J.N., O'Sullivan, S.E., 2018. The use of cannabinoids in colitis: a systematic review and meta-analysis. Inflamm. Bowel Dis. 24 (4), 680–697.
Couch, D.G., Cook, H., Ortori, C., Barrett, D., Lund, J.N., O'Sullivan, S.E., 2019. Palmitoylethanolamide and cannabidiol prevent inflammation-induced hyperpermeability of the human gut in vitro and in vivo-A randomized, placebo-controlled, double-blind controlled trial. Inflamm. Bowel Dis. 25 (6), 1006–1018.
Cristino, L., Bisogno, T., Di Marzo, V., 2020. Cannabinoids and the expanded endocannabinoid system in neurological disorders. Nat. Rev. Neurol. 16 (1), 9–29.
Cryan, J., O'Riordan, K., Cowan, C., Sandhu, K., Bastiaanssen, T., Boehme, M., et al., 2019. The microbiota-gut-brain Axis. Physiol. Rev. 99 (4), 1877–2013.
D'Argenio, V., Sarnataro, D., 2019. Microbiome influence in the pathogenesis of prion and Alzheimer's diseases. Int. J. Mol. Sci. 20 (19), 4704.
Danielski, L., Giustina, A., Badawy, M., Barichello, T., Quevedo, J., Dal-Pizzol, F., et al., 2018. Brain barrier breakdown as a cause and consequence of neuroinflammation in sepsis. Mol. Neurobiol. 55 (2), 1045–1053.
De Filippis, D., Esposito, G., Cirillo, C., Cipriano, M., Winter, B., Scuderi, C., et al., 2011. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS One 6 (12), e28159.
De-Paula, J.R., Forlenza, A.S., Forlenza, O.V., 2018. Relevance of gutmicrobiota in cognition, behaviour and Alzheimer's disease. Pharmacol. Res. 136, 29–34.
Dinan, T., Cryan, J., 2017. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. J. Physiol. 595 (2), 489–503.
Domingues, C., da Cruz E Silva, O.A.B., Henriques, A.G., 2017. Impact of cytokines and chemokines on Alzheimer's disease neuropathological hallmarks. Curr. Alzheimer Res. 14 (8), 870-882.
Enck, K., Banks, S., Yadav, H., Welker, M.E., Opara, E.C., 2020. Development of a novel oral delivery vehicle for probiotics. Curr. Pharmaceut. Des. 26 (26), 3134–3140.
Esposito, G., De Filippis, D., Carnuccio, R., Izzo, A.A., Iuvone, T., 2006a. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. J. Mol. Med. (Berl.) 84 (3), 253–258.
Esposito, G., De Filippis, D., Maiuri, M.C., De Stefano, D., Carnuccio, R., Iuvone, T., 2006b. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. Neurosci. Lett. 399 (1-2), 91–95.
Esposito, G., Scuderi, C., Savani, C., Steardo, L., De Filippis, D., Cottone, P., et al., 2007. Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression. Br. J. Pharmacol. 151 (8), 1272–1279.
Esposito, G., Scuderi, C., Valenza, M., Togna, G., Latina, V., De Filippis, et al., 2011. Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. PLoS One 6 (12), e28668.
Esquerda-Canals, G., Montoliu-Gaya, L., Güell-Bosch, J., Villegas, S., 2017. Mouse models of Alzheimer's disease. J. Alzheim. Dis. 57 (4), 1171–1183.
Fox, M., Knorr, D.A., Haptonstall, K.M., 2019. Alzheimer's disease and symbiotic microbiota: an evolutionary medicine perspective. Ann. N. Y. Acad. Sci. 1449 (1), 3–24.
Friedland, R.P., Chapman, M.R., 2017. The role of microbial amyloid in neurodegeneration. PLoS Pathog 13 (12), e1006654.
Fung, T.C., Olson, C.A., Hsiao, E.Y., 2017. Interactions between the microbiota, immune and nervous systems in health and disease. Nat. Neurosci. 20 (2), 145–155.
Gauthier, S., Feldman, H., Schneider, L., Wilcock, G., Frisoni, G., Hardlund, J., et al., 2016. Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. Lancet 388 (10062), 2873–2884.
Geng, Z.H., Zhu, Y., Li, Q.L., Zhao, C., Zhou, P.H., 2022. Enteric nervous system: the bridge between the gut microbiota and neurological disorders. Front. Aging Neurosci. 14, 810483.
Giau, V.V., Wu, S.Y., Jamerlan, A., An, S., Kim, S.Y., Hulme, J., 2018. Gut microbiota and their neuroinflammatory implications in Alzheimer's disease. Nutrients 10 (11), 1765.
Griffin, W.S., Liu, L., Li, Y., Mrak, R.E., Barger, S.W., 2006. Interleukin-1 mediates Alzheimer and Lewy body pathologies. J. Neuroinflammation 3, 5.
Hansen, D.V., Hanson, J.E., Sheng, M., 2018. Microglia in Alzheimer's disease. J. Cell Biol. 217 (2), 459–472.
Hao, F., Feng, Y., 2021 Jan 1. Cannabidiol (CBD) enhanced the hippocampal immune response and autophagy of APP/PS1 Alzheimer's mice uncovered by RNA-seq. Life Sci 264, 118624.
Heneka, M.T., Carson, M.J., El Khoury, J., Landreth, G., Brosseron, F., Feinstein, D., et al., 2015. Neuroinflammation in Alzheimer's disease. Lancet Neurol 14 (4), 388-405.
Herrup, K., 2015. The case for rejecting the amyloid cascade hypothesis. Nat. Neurosci. 18 (6), 794-799.
Howard, R., Zubko, O., Bradley, R., et al., 2020. Minocycline at 2 different dosages vs placebo for patients with mild alzheimer disease: a randomized clinical trial. JAMA Neurol 77 (2), 164–174.
Jiang, C., Li, G., Huang, P., Liu, Z., Zhao, B., 2017. The gut microbiota and Alzheimer's disease. J. Alzheim. Dis.: JAD. 58 (1), 1–15.
Joe, E., Ringman, J.M., 2019. Cognitive symptoms of Alzheimer's disease: clinical management and prevention. BMJ (Clinical research ed.) 367, l6217.
Kaplan, J.S., Wagner, J.K., Reid, K., McGuinness, F., Arvila, S., Brooks, M., Stevenson, H., Jones, J., Risch, B., McGillis, T., Budinich, R., Gambell, E., Predovich, B., 2021 Aug 26. Cannabidiol exposure during the mouse adolescent period is without harmful behavioral effects on locomotor activity, anxiety, and spatial memory. Front. Behav. Neurosci. 15, 711639.
Khodadadi, H., Salles, É.L., Jarrahi, A., Costigliola, V., Khan, M.B., Yu, J.C., et al., 2021. Cannabidiol ameliorates cognitive function via regulation of IL-33 and TREM2 upregulation in a murine model of Alzheimer's disease. J. Alzheimers Dis 80 (3), 973–977.
Kim, M.S., Kim, Y., Choi, H., Kim, W., Park, S., Lee, D., et al., 2020. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut 69 (2), 283–294.
Kirova, A.M., Bays, R.B., Lagalwar, S., 2015. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. BioMed Res. Int. 2015, 748212.
Lane, C.A., Hardy, J., Schott, J.M., 2018. Alzheimer's disease. Eur. J. Neurol. 25 (1), 59–70.
Lawlor, B., Segurado, R., Kennelly, S., 2018. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. PLoS Med 15 (9), e1002660.
Li, H., Liu, Y., Tian, D., Tian, L., Ju, X., Qi, L., et al., 2020. Overview of cannabidiol (CBD) and its analogues: structures, biological activities, and neuroprotective mechanisms in epilepsy and Alzheimer's disease. Eur. J. Med. Chem. 192, 112163.
Liu, L., Martin, R., Chan, C., 2013. Palmitate-activated astrocytes via serine palmitoyltransferase increase BACE1 in primary neurons by sphingomyelinases. Neurobiol. Aging 34 (2), 540–550.
Liu, Y.J., Chen, J., Li, X., Zhou, X., Hu, Y.M., Chu, S.F., Peng, Y., Chen, N.H., 2019. Research progress on adenosine in central nervous system diseases. CNS Neurosci. Ther. 25 (9), 899–910.
Luchena, C., Zuazo-Ibarra, J., Alberdi, E., Matute, C., Capetillo-Zarate, E., 2018. Contribution of neurons and glial cells to complement-mediated synapse removal during development, aging and in Alzheimer's disease. Mediat. Inflamm. 2018, 2530414.
Lynch, S.V., Pedersen, O., 2016. The human intestinal microbiome in health and disease. N. Engl. J. Med. 375 (24), 2369–2379.
Mancuso, C., Santangelo, R., 2017. Alzheimer's disease and gut microbiota. Modifications: the long way between preclinical studies and clinical evidence. Pharmacol. Res. 129, 329–336.
Marizzoni, M., Cattaneo, A., Mirabelli, P., Festari, C., Lopizzo, N., Nicolosi, V., Mombelli, E., Mazzelli, M., Luongo, D., Naviglio, D., Coppola, L., Salvatore, M., Frisoni, G.B., 2020. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. J. Alzheimers Dis 78 (2), 683–697.
Martín-Moreno, A.M., Reigada, D., Ramírez, B.G., Mechoulam, R., Innamorato, N., Cuadrado, A., de Ceballos, M.L., 2011. Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease. Mol. Pharmacol. 79 (6), 964–973.
Matamoros, S., Gras-Leguen, C., Vacon, F., Potel, G., Cochetiere, M.F., 2013. Development of intestinal microbiota in infants and its impact on health. Trends Microbiol 21 (4), 167–173.
Matsuyama, K., Yamamoto, Y., Sora, I., 2020. Effect of Feru-guard 100M on amyloid-beta deposition in individuals with mild cognitive impairment. Psychogeriatrics 20 (5), 726–736.
Mecha, M., Feliú, A., Iñigo, P.M., Mestre, L., Carrillo-Salinas, F.J., Guaza, C., 2013. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. Neurobiol. Dis. 59, 141–150.
Merighi, S., Borea, P.A., Varani, K., Vincenzi, F., Jacobson, K.A., Gessi, S., 2022a. A2A adenosine receptor antagonists in neurodegenerative diseases. Curr. Med. Chem. 29 (24), 4138–4151.
Merighi, S., Borea, P.A., Varani, K., Vincenzi, F., Travagli, A., Nigro, M., Pasquini, S., Suresh, R.R., Kim, S.W., Volkow, N.D., Jacobson, K.A., Gessi, S., 2022b. Pathophysiological role and medicinal chemistry of A_{2A} adenosine receptor antagonists in Alzheimer's disease. Molecules 27 (9), 2680.
Merighi, S., Nigro, M., Travagli, A., Pasquini, S., Borea, P.A., Varani, K., Vincenzi, F., Gessi, S., 2022c. A2A adenosine receptor: a possible therapeutic target for Alzheimer's disease by regulating NLRP3 inflammasome activity? Int. J. Mol. Sci. 23 (9), 5056.
Mestre, L., Carrillo-Salinas, F.J., Mecha, M., Feliú, A., Guaza, C., 2018. Gut microbiota, cannabinoid system and neuroimmune interactions: new perspectives in multiple sclerosis. Biochem. Pharmacol. 157, 51–66.
Meyer, P.F., Labonté, A., Rosa-Neto, P., Poirier, J., Breitner, J.C.S., PREVENT-AD Research Group, 2019. No apparent effect of naproxen on CSF markers of innate immune activation. Ann .Clin. Transl. Neurol 6 (6), 1127–1133.
Misiak, B., Łoniewski, I., Marlicz, W., Frydecka, D., Szulc, A., Rudzki, L., et al., 2020. The HPA axis dysregulation in severe mental illness: can we shift the blame to gut microbiota? Prog. Neuro-Psychopharmacol. Biol. Psychiatry 102, 109951.
Mohamed, W.A., Salama, R.M., Schaalan, M.F., 2019. A pilot study on the effect of lactoferrin on Alzheimer's disease pathological sequelae: impact of the p-Akt/PTEN pathway. Biomed. Pharmacother. 111, 714–723.
Montagne, A., Barnes, S., Sweeney, M., Halliday, M., Sagare, A., Zhao, Z., et al., 2015. Blood-brain barrier breakdown in the aging human hippocampus. Neuron 85 (2), 296–302.
Morgan, K.L., 2013. Infection, illness, and fenugreek seeds: was illness a good enough proxy for infection in the 2011 outbreak of shiga toxin-producing Escherichia coli O104:H4 in France? Clin. Infect. Dis. 56 (7), 1055–1056.
Mori, A., Chen, J.F., Uchida, S., Durlach, C., King, S.M., Jenner, P., 2022. The pharmacological potential of adenosine A_{2A} receptor antagonists for treating Parkinson's disease. Molecules 27 (7), 2366.

Moussa, C., Hebron, M., Huang, X., et al., 2017. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J. Neuroinflammation 14 (1), 1.
Muccioli, G.G., Naslain, D., Bäckhed, F., Lambert, C., Delzenne, N., Cani, P., 2010. The endocannabinoid system links gut microbiota to adipogenesis. Mol. Syst. Biol. 6, 392.
Myers, A., McGonigle, P., 2019 Sep. Overview of transgenic mouse models for Alzheimer's disease. Curr. Protoc. Neurosci 89 (1), e81.
Naseribafrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linlokken, A., Wilson, R., et al., 2014. Correlation between the human fecal microbiota and depression. Neuro Gastroenterol. Motil. 26 (8), 1155–1162.
Noguchi-Shinohara, M., Ono, K., Hamaguchi, T., et al., 2020. Safety and efficacy of Melissa officinalis extract containing rosmarinic acid in the prevention of Alzheimer's disease progression. Sci. Rep. 10 (1), 18627.
Pagano, E., Capasso, R., Piscitelli, F., Romano, B., Parisi, O.A., Finizio, S., et al., 2016 Oct 4. An orally active Cannabis extract with high content in cannabidiol attenuates chemically-induced intestinal inflammation and hypermotility in the mouse. Front. Pharmacol. 7, 341.
Pekny, M., Wilhelmsson, U., Pekna, M., 2014. The dual role of astrocyte activation and reactive gliosis. Neurosci. Lett. 565, 30-38.
Pistollato, F., Sumalla Cano, S., Elio, I., Masias Vergara, M., Giampieri, F., Battino, M., 2016. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr. Rev. 74 (10), 624-634.
Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., Liang, S., et al., 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490 (7418), 55–60.
Rainey-Smith, S.R., Brown, B.M., Sohrabi, H.R., et al., 2016. Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. Br. J. Nutr. 115 (12), 2106–2113.
Regen, F., Hellmann-Regen, J., Costantini, E., Reale, M., 2017. Neuroinflammation and Alzheimer's disease: implications for microglial activation. Curr. Alzheimer Res. 14 (11), 1140–1148.
Renard, J., Loureiro, M., Rosen, L.G., Zunder, J., de Oliveira, C., Schmid, S., Rushlow, W.J., Laviolette, S.R., 2016 May 4. Cannabidiol counteracts amphetamine-induced neuronal and behavioral sensitization of the mesolimbic dopamine pathway through a novel mTOR/p70S6 kinase signaling pathway. J. Neurosci. 36 (18), 5160–5169.
Ross, J., Sharma, S., Winston, J., et al., 2013. CHF5074 reduces biomarkers of neuroinflammation in patients with mild cognitive impairment: a 12-week, double-blind, placebo-controlled study. Curr. Alzheimer Res. 10 (7), 742–753.
Rua, R., Lee, J.Y., Silva, A.B., et al., 2019. Infection drives meningeal engraftment by inflammatory monocytes that impairs CNS immunity. Nat. Immunol. 20 (4), 407–419.
Russo, R., Cristiano, C., Avagliano, C., De Caro, C., La Rana, G., Raso, G.M., et al., 2018. Gut-brain Axis: role of lipids in the regulation of inflammation, pain and CNS diseases. Curr. Med. Chem. 25 (32), 3930–3952.
Ryan, J., Storey, E., Murray, A.M., et al., 2020. Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. Neurology 95 (3), e320–e331.
Sainz-Cort, A., Jimenez-Garrido, D., Muñoz-Marron, E., Viejo-Sobera, R., Heeroma, J., Bouso, J.C., 2021 . Opposite roles for cannabidiol and δ-9-tetrahydrocannabinol in psychotomimetic effects of Cannabis extracts: a naturalistic controlled study. J. Clin. Psychopharmacol. 41 (5), 561–570.
Salloway, S., Sperling, R., Fox, N., Blennow, K., Klunk, W., Raskind, M., et al., 2014. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N. Engl. J. Med. 370 (4), 322–333.
Sayre, L.M., Perry, G., Smith, M.A., 2008. Oxidative stress and neurotoxicity. Chem. Res. Toxicol. 21 (1), 172–188.
Scopinho, A.A., Guimarães, F.S., Corrêa, F.M., Resstel, L.B., 2011 Apr. Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists. Pharmacol. Biochem. Behav. 98 (2), 268–272.
Scuderi, C., Steardo, L., 2013. Neuroglial roots of neurodegenerative diseases: therapeutic potential of palmitoylethanolamide in models of Alzheimer's disease. CNS Neurol. Disord.: Drug Targets 12 (1), 62–69.
Scuderi, C., Steardo, L., Esposito, G., 2014. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARγ involvement. Phytother Res 28 (7), 1007–1013.
Serrano-Pozo, A., Frosch, M.P., Masliah, E., Hyman, B.T., 2011. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 1 (1), a006189.
Shannon, S., Lewis, N., Lee, H., Hughes, S., 2019. Cannabidiol in anxiety and sleep: a large case series. Perm. J. 23, 18–41.
Sharoar, M.G., Hu, X., Ma, X.M., Zhu, X., Yan, R., 2019. Sequential formation of different layers of dystrophic neurites in Alzheimer's brains. Mol. Psychiatr. 24 (9), 1369–1382.
Silvestri, C., Pagano, E., Lacroix, S., Venneri, T., Cristiano, C., Calignano, A., et al., 2020 Oct 8. Fish oil, cannabidiol and the gut microbiota: an investigation in a murine model of colitis. Front. Pharmacol. 11, 585096.
Soares, H.D., Gasior, M., Toyn, J.H., et al., 2016. The γ-secretase modulator, BMS-932481, modulates Aβ peptides in the plasma and cerebrospinal fluid of healthy volunteers. J. Pharmacol. Exp. Therapeut. 358 (1), 138–150.
Sochocka, M., Donskow Lysoniewska, K., Diniz, B.S., Kurpas, D., Brzozowska, E., Leszek, J., 2019. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease-a critical review. Mol. Neurobiol. 56 (3), 1841–1851.
Spielman, L.J., Gibson, D.L., Klegeris, A., 2018. Unhealthy gut, unhealthy brain: the role of the intestinal microbiota in neurodegenerative diseases. Neurochem. Int. 120, 149–163.
Spires-Jones, T.L., Hyman, B.T., 2014. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron 82 (4), 756–771.
Strandwitz, P., 2019. Neurotransmitter modulation by the gut microbiota. Brain Res 1693 (Pt B), 128–133.
Szablewski, L., 2018. Human gut microbiota in health and Alzheimer's disease. J. Alzheimers Dis 62 (2), 549–560.
Thota, R.N., Rosato, J.I., Dias, C.B., Burrows, T.L., Martins, R.N., Garg, M.L., 2020. Dietary supplementation with curcumin reduce circulating levels of glycogen synthase kinase-3β and islet amyloid polypeptide in adults with high risk of type 2 diabetes and Alzheimer's disease. Nutrients 12 (4), 1032.
Tonnies, E., Trushina, E., 2017. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. J. Alzheimers Dis 57 (4), 1105–1121.
Townsend, M., Shankar, G.M., Mehta, T., Walsh, D.M., Selkoe, D.J., 2006. Effects of secreted oligomers of amyloid beta-protein on hippocampal synaptic plasticity: a potent role for trimers. J. Physiol. 572 (Pt 2), 477–492.
Vagnerová, K., Vodička, M., Hermanová, P., Ergang, P., Šrůtková, D., Klusoňová, P., Balounová, K., Hudcovic, T., Pácha, J., 2019. Interactions between gut microbiota and acute restraint stress in peripheral structures of the hypothalamic-pituitary-adrenal Axis and the intestine of male mice. Front. Immunol. 10, 2655.
Vallée, A., Lecarpentier, Y., 2016. Alzheimer disease: crosstalk between the canonical wnt/beta-catenin pathway and PPARs alpha and gamma. Front. Neurosci. 10, 459.
Vicentini, F.A., Keenan, C.M., Wallace, L.E., Woods, C., Cavin, J.B., Flockton, A.R., Macklin, W.B., Belkind-Gerson, J., Hirota, S.A., Sharkey, K.A., 2021. Intestinal microbiota shapes gut physiology and regulates enteric neurons and glia. Microbiome 9 (1), 210.
Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A., Harding, S.J., Merluzzi, A.P., Johnson, S.C., et al., 2017. Gut microbiome alterations in Alzheimer's disease. Sci. Rep. 7 (1), 13537.
Watt, G., Shang, K., Zieba, J., Olaya, J., Li, H., Garner, B., et al., 2020. Chronic treatment with 50 mg/kg cannabidiol improves cognition and moderately reduces Aβ40 levels in 12-month-old male AβPPswe/PS1ΔE9 transgenic mice. J. Alzheimers Dis 74 (3), 937–950.
Watt, G., Cheworth, R., Pryzbyla, M., Ittner, A., Garner, B., Ittner, L., Karl, T., 2020. Chronic cannabidiol (CBD) treatment did not exhibit beneficial effects in 4-month-old male TAU58/2 transgenic mice. Pharmacol. Biochem. Behav. 196, 172970.
Wei, D., Zhao, Y., Zhang, M., Zhu, L., Wang, L., Yuan, X., Wu, C., 2021. The volatile oil of zanthoxylum bungeanum pericarp improved the hypothalamic-pituitary-adrenal Axis and gut microbiota to attenuate chronic unpredictable stress-induced anxiety behavior in rats. Drug Des. Dev. Ther. 15, 769–786.
Wilkins, H.M., Swerdlow, R.H., 2016. Relationships between mitochondria and neuroinflammation: implications for Alzheimer's disease. Curr. Top. Med. Chem. 16 (8), 849–857.
Xu, H., Gelyana, E., Rajsombath, M., Yang, T., Li, S., Selkoe, D., 2016. Environmental enrichment potently prevents microglia-mediated neuroinflammation by human amyloid β-protein oligomers. J. Neurosci. 36 (35), 9041–9056.
Yang, T., Santisteban, M.M., Rodriguez, V., Li, E., Ahmari, N., Marulanda, J., et al., 2015. Gut dysbiosis is linked to hypertension. Hypertension 65 (6), 1331–1340.
Zapata, H., Quagliarello, V., 2015. The microbiota and microbiome in aging: potential implications in health and age-related diseases. J. Am. Geriatr. Soc. 63 (4), 776–781.
Zhu, A., Wu, Z., Zhong, X., et al., 2018. Brazilian green propolis prevents cognitive decline into mild cognitive impairment in elderly people living at high altitude. J. Alzheimers Dis 63 (2), 551–560.
Zhu, P., Lu, T., Wu, J., Fan, D., Liu, B., Zhu, X., Guo, H., Du, Y., Liu, F., Tian, Y., Fan, Z., 2022. Gut microbiota drives macrophage-dependent self-renewal of intestinal stem cells via niche enteric serotonergic neurons. Cell Res 32 (6), 555–569.
Zhuang, Z.Q., Shen, L.L., et al., 2018. Gut microbiota is altered in patients with Alzheimer's disease. J. Alzheimers Dis 63 (4), 1337–1346.
Zou, S., Kumar, U., 2018. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int. J. Mol. Sci. 19 (3), 833.
Zuardi, A.W., Rodrigues, N.P., Silva, A.L., Bernardo, S.A., Hallak, J.E.C., Guimarães, F.S., Crippa, J.A.S., 2017 May 11. Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. Front. Pharmacol. 8, 259.