Bioflavonoids for Targeting Gut Microbiome in Alzheimer's Disease

Subjects: Neurosciences

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Alzheimer's Disease (AD), the most common type of dementia, is known as a neurodegenerative disease caused by the accumulation of amyloid beta (Aβ) peptides and tau protein hyperphosphorylation resulting in the formation of neurofibrillary tangles, activation of inflammasomes, sluggish autophagy, and neuronal loss. Several of these hallmarks are linked to alteration in the gut microbiome, also known as gut dysbiosis. Selective bioflavonoids can target gut microbiome to inhibit inflammasomes and resume autophagy to stop AD pathogenesis. Two bioflavonoids, specifically epigallocatechin-3-gallate (EGCG) and genistein (GS), appear to be a new paradigm of treatment for maintaining healthy gut microbiome in AD via modulating crucial AD signaling pathways.

Alzheimer's disease (AD) autophagy bioflavonoids epigallocatechin-3-gallate (EGCG) genistein (GS) gut microbiome

1. Introduction

Alzheimer's Disease (AD), the most common type of dementia, is known as a neurodegenerative disease caused by the accumulation of amyloid beta (Aβ) peptides and tau protein hyperphosphorylation resulting in the formation of neurofibrillary tangles [1][2]. AD is the seventh leading cause of death in the United States (US) [3]. Currently, about 6 million Americans have AD, mostly affecting people above the age of 65 [3]. With increasing age, the likelihood of occurrence of AD also increases, with 32% of people above the age of 84 years being diagnosed with AD [4]. There are two existing categories of biomarkers that are used to identify AD in a patient. The first one is a biomarker detected in the brain amyloid using cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging measurements [1]. The second category involves spotting in CSF the biomarker tau that relates to neuronal injury, using fluorodeoxyglucose (FDG) to analyze metabolic activity, and performing magnetic resonance imaging (MRI) to measure brain atrophy [1].

The phases of AD can be split into multiple stages. First, the pre-symptomatic stage (a few years in length), in which the patient only has mild amnesia and has no signs of AD, but detecting even a single marker of brain amyloidosis in CSF and PET is enough to be diagnosed with AD [5][6][7]. At the beginning of the disease progression, Aβ plaques are formed in the basal, temporal, and orbitofrontal neocortex regions of the brain, while Aβ plaques triggered tau tangle formation takes place in locus coeruleus and trans entorhinal and entorhinal areas [8]. Second, mild stage during which the patients develop amnesia enough to have impediments in their daily lives. Third, moderate stage, in which amnesia worsens to the point of dysfunction in recognizing friends and family. Fourth, a severe stage during which the patient can lose functional abilities, becoming bedridden and resulting in death [5]. During critical stages, Aβ plaques are hypothesized to spread to the mesencephalon, lower brain stem, and cerebellar cortex, while the neurofibrillary tangles (NFTs) spread to the hippocampus and neocortex regions of the brain [8]. There are temporary treatments (prescription drugs) such as cholinesterase inhibitors (Donepezil, Rivastigmine, and Galantamine), glutamate regulators (Memantine), and a combination of a cholinesterase inhibitor and a glutamate regulator (Donepezil and memantine) that alleviate the AD symptoms [9].

2. Bioflavonoids as Novel Therapeutic Option for AD

There are varying potential categories for therapeutic values of acetylcholinesterase enzyme (AChE) inhibitors in the treatment of AD. Polyphenols are known to have enormous potential to regulate diversity as well as the composition of gut microbiota, which is associated with neurological health. Studies have showcased that polyphenols can reduce the neurological deficits that are caused due to neuroinflammation [10][11][12]. Bioflavonoids are a group of natural polyphenolic compounds that are derived from fruits and vegetables. A few examples of fruits and vegetables would include apples, onions, mulberries, and bilberries. Bioflavonoids are popularly consumed via tea, beer, and wine [13]. This subclass of polyphenols of

biological origin is implicated in anti-apoptotic and pro-survival signaling pathways and decreasing the pathological effects of AD [14][15]. Bioflavonoids, which are exclusively derived from biological origins (mainly plants), are also well known for showcasing anti-inflammatory, anti-viral, anti-apoptotic, anti-platelet, and anti-tumoral properties [13][18][19].

Catechins are a group of bioflavonoids that can be extracted from tea, and this group includes epigallocatechin (EGC), epicatechin gallate (ECG), epicatechin (EC), and the most abundant compound EGCG [19]. As shown in **Figure 1**, the chemical structure of EGCG contains A, B, C, and D rings produced from the esterification of EGC with gallic acid [20]. Both the A and C rings have a phenyl group at C2 and a gallate group at C3 positions. The B and D rings of EGCG contain 3,4,5-trihydroxy groups, which have the potential for proteasome activity in vitro [20]. On the aromatic B ring, catechins have di- or tri-hydroxyl groups along with meta-5,7-dihydroxyl groups on the A ring [21]. The presence of phenolic groups in these compounds increases their antioxidant properties. The structure of flavonoids is important in creating a novel therapeutic drug for the treatment of AD.

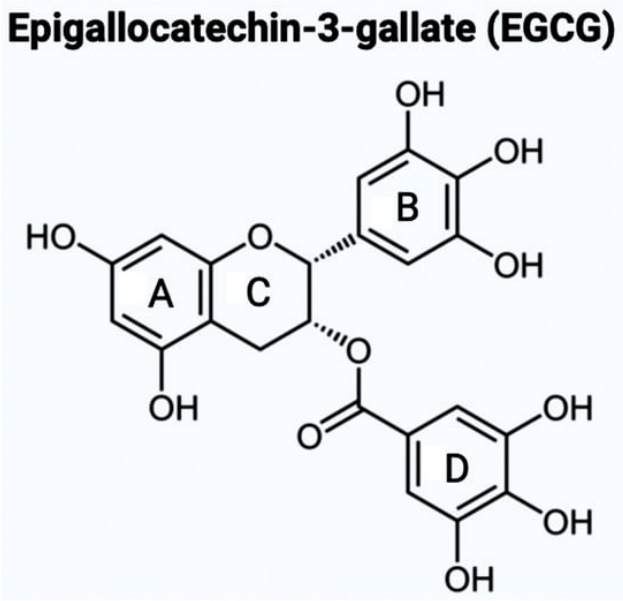

Figure 1. It illustrates the chemical structure of epigallocatechin-3-gallate (EGCG) with the four rings (A, B, C, and D). The B ring feature increases the probability of EGCG being used as an AChE inhibitor. This chemical structure was created with BioRender.com.

The aromatic B ring containing -OH groups mimics the structure of Donepezil, allowing the compound to bind with the peripheral anionic site (PAS) of the AChE gorge [21]. Apart from EGCG, the second bioflavonoid that will be examining for the treatment of AD is GS. While EGCG is part of the catechins subgroup, GS belongs to the subgroup called isoflavones [22]. GS has a structure like estrogen and has the capacity to function as an anti-estrogen. This plant-derived compound has an extensive history of anti-inflammatory properties (**Figure 2**). A crucial component of GS's endocrine effects is due to its similarity to S-equol, a phytoestrogen produced in the intestinal microbiota [23].

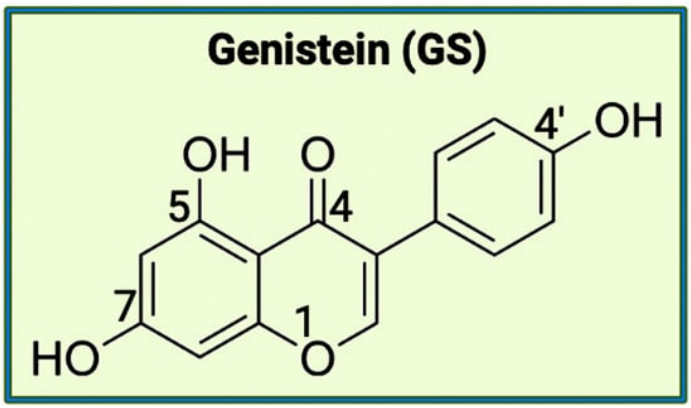

Figure 2. The chemical structure of genistein (4′,5,7-trihydroxy-isoflavone). This isoflavone, mostly present in soybeans, has the potential to behave as a weak estrogen or as an anti-estrogen, along with being implicated in varying biological activities (e.g., apoptosis and cell differentiation). This chemical structure was created with BioRender.com.

Further studies conducted showcase the inhibitory functions of GS with an important cell signaling pathway involving the nuclear factor kappa-B (NF-κB), which is crucial for promoting inflammation. GS has also been implicated in other cell signaling pathways involving prostaglandins (PGs), inducible nitric oxide synthase (iNOS), pro-inflammatory cytokines, and reactive oxygen species (ROS) [22]. EGCG and GS can be used as readily available alternatives for AChE inhibition because they are natural substances derived from plants. However, EGCG and GS can also be useful to target the gut microbiome through varying delivery methods. A function attributed to polyphenols is their ability to foster the growth of beneficial bacteria (*Lactobacillus* and *Bifidobacteria*) in the gut microbiome while limiting the pathogenic bacteria (*Bacteroides* and *Clostridia*) [24].

3. An Overview of the Gut Microbiota

The gut microbiota in every individual is unique, and thus, it is determined through environmental factors rather than being a genetically inheritable trait. In the gut microbiota, the staggering microbial diversity and colonization result in varying complex interactions, diseases, and immune responses. Depending on the area of the gastrointestinal tract being examined, the density and diversity of the gut bacteria fluctuate due to the difference in the local conditions [25]. A proper understanding of the function of microbiota in the gut is crucial for the development of successful therapeutics to target neurological diseases including AD.

3.1. Activity of Gut Microbiota in the Human Body

The intestinal bacteria produce short-chain fatty acids (SCFAs) through the fermentation of non-digestible carbohydrates (NDC) and dietary fiber, and these SCFAs are formate, acetate, propionate, and butyrate, with the presence of acetate being three times higher [26][27][28]. Specifically, an increased presence of formate has been linked to the possibility of higher inflammation [28]. In a study of the introduction of butyrate to isolated germ-free colonocytes, the rate of oxidative phosphorylation increased while autophagy decreased [27]. For fermentation, the source of the carbohydrates used is the ones that were not digested or absorbed in the small intestine [28]. The functions of SCFAs include affecting cellular processes such as gene expression, differentiation, proliferation, and apoptosis [27]. The SCFAs, which are produced from NDC and dietary fiber, also regulate the permeability of the gut and blood-brain barriers [29].

In the CNS, SCFAs play a key role during the production of neural progenitor cells (NPCs) that produce neuronal and glial cell types [30][31]. According to a study conducted recently, the increased concentration of SCFAs positively affected the expression of genes involved in the proliferation of NPCs [32]. Free fatty acids (FFAs), which are the products of the metabolic pathways, are known to function as signaling molecules via interaction with free fatty acid receptors (FFARs) that form a family of G protein-coupled receptors (GPCRs). As the largest group of transmembrane proteins, GPCRs are currently known to be the most successful drug targets. There are a few mechanisms that are regulated by SCFAs to increase the production of NPCs. The first mechanism involves specific FFARs (i.e., GPCRs), most notably FFAR2 (GPR43) and FFAR3 (GPR41), being upregulated due to increased exposure to SCFAs. In the second mechanism, SCFAs regulate the physiological pH that modulates neurodevelopmental effects along with anti-apoptotic effects [32].

3.2. Onset Factors in the Microbiota for Dysbiosis

Dysbiosis occurs when the normal state of the gut microbiota is unbalanced due to varying factors. One of the main examples is when the anti-inflammatory cytokines and the pro-inflammatory cytokines produced by the microbes are not balanced, then dysbiosis takes place. There are three types of dysbiosis: type 1 indicates a decrease of beneficial bacteria, type 2 shows an increase of pathogenic bacteria, and type 3 states a decrease in overall bacterial diversity [34]. The number of factors that can directly affect dysbiosis are many such as diet, birthing conditions (e.g., mode of birth, antibiotic exposure, and hygiene), chemical exposure, psychological and environmental stimuli (e.g., pathogens, sleep deprivation, circadian rhythm dysfunction, toxins, and noise), temperature, and intestinal infection. Diet is one of the crucial regulators of the gut microbiota [26]. In studies comparing a 'Western diet' (high animal protein, high in sugar and saturated fats) and an 'agrarian diet' (low animal protein, low levels of saturated fat and simple sugars), the results displayed the 'Western diet' leading to dysbiosis and lower levels of SCFAs [35]. On the other hand, the 'agrarian diet' results in more production of SCFAs and higher gut bacteria

diversity, which helps limit the growth of potentially pathogenic bacteria that otherwise lead to diseases such as IBD [35]. The reason why the lower animal protein levels in an 'agrarian diet' help with the gut microbiota is due to the side effects of protein and amino acid fermentation [36]. When more protein is consumed, the gut must shift to increase the pH to break down the proteins that result in the production of compounds, including hydrogen sulfide, reactive oxygen species, and ammonia, which are unhealthy for the gut [36][37].

3.3. Gut-Brain Axis (GBA) and Gut Dysbiosis

The relationship between the gut microbiota and the brain is called the gut-brain axis (GBA), and this two-way communication is built using immune, circulatory, and neural pathways (**Figure 3**) [30]. GBA connects the CNS (comprised of brain and spinal cord), autonomic nervous system (ANS), enteric nervous system (ENS), and hypothalamic pituitary adrenal (HPA) axis [38]. Particularly, the function of the HPA axis includes regulating the adaptive responses from the body to any stressors needed [38][39]. An increase in the occurrence of inflammatory cytokines such as interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) through the production of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) is an example of environmental stress that can activate the HPA axis. The bidirectional communication line results in the regulation of intestinal functional effector cells (immune cells, epithelial cells, enteric neurons, smooth muscle cells, interstitial cells of Cajal, and enterochromaffin cells) [38]. Unsurprisingly, the gut microbiota has been implicated in affecting the bidirectional communication between the gut and the brain [38]. The microbes present in the gut produce metabolites such as SCFAs, gamma-aminobutyric acid (GABA), tryptophan, serotonin, catecholamines, metabolites of bile acids and neurotransmitters, and cytokines that can signal to the receptors present in the gut [40]. The dysbiosis of the gut microflora causes an increase in the gut and blood-brain barrier permeability, production of bacterial amyloids, and formation of lipopolysaccharides (LPS) leading up to the deposition of amyloid fibrils in the brain, resulting in the pathogenesis (neuroinflammation, cognitive decline) of neurological disorders such as AD and stroke [41]. There still has not been a complete understanding of the pathways involved in the GBA bidirectional communication line.

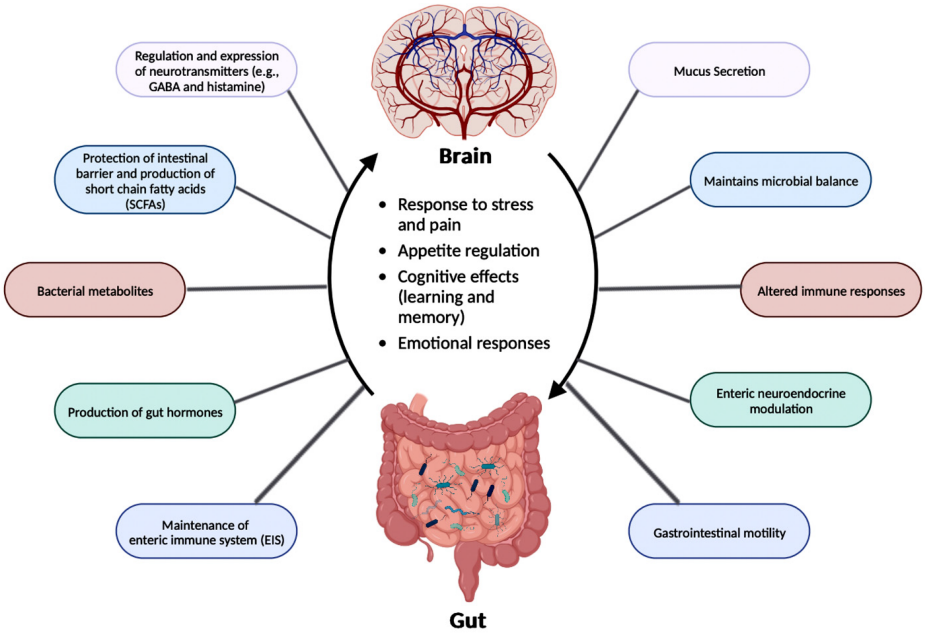

Figure 3. The gut-brain axis (GBA) participates in the regulation of various functions. The link between the brain and the gut flora is important for the regulation of essential functions in the human body, such as the production of neurotransmitters, SCFAs, bacterial metabolites, and gut hormones. GBA is also essential in maintaining microbial balance along with the enteric immune system (EIS). This figure was created with BioRender.com.

The varying functions of the microbiota regarding the immune system and the hormonal changes, including the consequences of a dysfunction in the gut flora, display the importance of analyzing the relationship of the gut microbiota in the context of neurological diseases such as AD.

3.4. GBA and AD

The dysbiosis in gut microbiota directly affects the GBA, which is linked to AD clinical symptoms such as Aβ plaque deposition, cognitive decline, and memory loss (**Table 1**). To explore the change in the microbiota and the Aβ plaque deposition in the brain, studies created AD animal models comparing the microorganisms and SCFAs in fecal samples between AD mice and wild-type animals [42]. The AD mice displayed lower levels of SCFAs, which had the potential to alter multiple metabolic pathways along with increasing the deposition of Aβ plaques [42]. Another study for analyzing the effect of age compared the double transgenic (TG) mice expressing a chimeric mouse/human amyloid precursor protein (APP) and a mutant human presenilin 1 (PSEN1), both APP/PSEN1 mutations ensured an early-onset of D, and C57BL/6 wild-type (WT) mice, and the results unveiled the potential of targeting the gut microbiota in AD animals [43]. The 6-month-old APP/PSEN1 mice, with their gut microflora documented differently from the WT mice, experienced cognitive decline [43]. The microbial diversity of the APP/PSEN1 mice deteriorated along with age with increases in the population of bacteria from the *Helicobacteraceae* and *Desulfovibrionaceae* families [43]. In the *Helicobacteraceae* family, *Helicobacter pylori* (*H. pylori*) participates in causing dysbiosis resulting in gastric disorders such as chronic active gastritis, peptic ulcer disease (PUD), mucosa-associated lymphoid tissue (MALT) lymphoma and gastric carcinoma [44]. The decrease in microbial diversity in the APP/PSEN1 mice highlights the importance of regulating the gut microbiome as a viable therapeutic target for the treatment of AD.

Table 1. Animal model studies for exploring a connection between gut microbiota and AD.

AD Animal Model	Change in Gut Microbiota in AD Mice	Observed Pathological Symptoms	Reference
AD model mice (with varying ages)	Decreased microbial diversity and reduced SCFA levels	Amyloid deposition and ultrastructural abnormalities in the intestine, cognitive dysfunction, and signaling pathway alterations	[42]
APP/PSEN1 mice	Decreased microbial diversity	Cognitive dysfunction	[43]
$APP_{SWE}/PSI\Delta_{E9}$ mice	Varied gut microbial composition	Increased cerebral Aβ pathology	[46]
APP/PS1 mice	Increased pro-inflammatory bacteria during aging	Autism and inflammatory-related disorders	[47]
ApoE-/- mice	*Porphyromonas gingivalis* infection	Neuronal injury	[48]

Apart from the animal models, the resultant consequence of dysbiosis causing AD can be confirmed in patient studies. Again, fecal matter was examined in AD patients and AD-lacking participants [43]. When comparing the fecal samples from AD patients and AD-lacking participants, the microbial diversity exhibited by the AD patients is comparatively lower. Patients with AD had fewer *Firmicutes* and *Bifidobacterium* and excessive amounts of *Bacteroidetes*. Dysfunction in the production and metabolism of bile acid (BA) causes cognitive decline. Studies also show AD patients have a higher amount of secondary BA compared to lower levels of primary BA. Secondary BA, which results from the removal of 7α-hydroxy or 7β-hydroxy group from primary BA, causes toxicity to specific *Lactobacillus* species. The gut microbiota activates 7α-dehydroxylation of cholic acid, resulting in the upregulation of deoxycholic acid and altered conformations of glycine and taurine [43]. Further findings also strengthened the association of amyloid plaque accumulation with pro-inflammatory gut bacteria. A study highlighted the abundance of pro-inflammatory gut bacteria (*Escherichia* and *Shigella*) and a decrease in anti-inflammatory gut bacteria (*E. rectale*) in the fecal matter of elderly patients with cognitive dysfunction [49]. The gut microbiota is extensively involved in crucial aspects of cognitive deterioration in AD due to an increase in neuroinflammation and a decrease in autophagy.

4. Neuroinflammation in AD

Most neurological conditions, such as autism spectrum disorders (ASD), epilepsy, PD, cerebrovascular diseases, and AD, have aspects of neuroinflammation as part of their pathogenesis. Cytokines, produced by microglia and astrocytes, are the central factors that influence all characteristics of neuroinflammation, ranging from pro-inflammatory and anti-inflammatory processes to neuronal injury [50].

4.1. Implications of Gut Microbiota in Neuroinflammation in AD

A trigger for inflammation is the structural components of bacteria, including the by-products (e.g., SCFAs, enzymes, metabolites, LPS, cell capsule carbohydrates, and endotoxins) produced during the metabolic processes involved [51]. Chronic low-grade inflammation or inflammaging is found to cause tissue damage in most age-related diseases, including AD. One of the causes of inflammaging is dysbiosis in the gut microbiota [52]. Studies exploring the inflammation caused by an imbalance in intestinal immunity confirm the involvement of gut microbiota in innate and adaptive immunity, especially in IBD, which eventually can result in PD [28]. These studies use sterile-raised germ-free (GF) mice lacking the microorganisms existing in the gastrointestinal (GI) tract, along with mice without pathogens treated with broad-spectrum antibiotics (ABX). The ABX mice represented the innate immune system in which the myeloid cells in the bone marrow were impaired, resulting in a decrease of granulocytes and, thus, a higher likelihood of bacterial infection. In the GF mice, the development of innate lymphoid cells (ILCs) was disabled, leading to antigen receptors not being expressed. Additionally, this lack of expression affects enteric bacterial infections because the production of IL-22 decreases [28]. Considering the pathogenesis of PD is closely related to AD, the triggers for extreme inflammation could be shared between the two proteinopathies (aberrant protein aggregate diseases). The prominent inflammatory markers generated by the gut microbiota include LPS, SCFAs, bile acids (BAs), C-reactive protein (CRP), and cytokines. The first marker mentioned, LPS, also called endotoxin, is a part of the cell wall of Gram-negative bacteria [54]. In a normal gut state, LPS (concentration ranges from 0 to 1.0 ng·mL^{-1}) is prevented by the gut barrier (intestinal epithelial and mucosal layers) from entering systemic circulation and activating epithelial destruction [55][54]. However, as shown in **Figure 4**, LPS increased enterocyte membrane TLR-4 expression in animal models of inflammation [55].

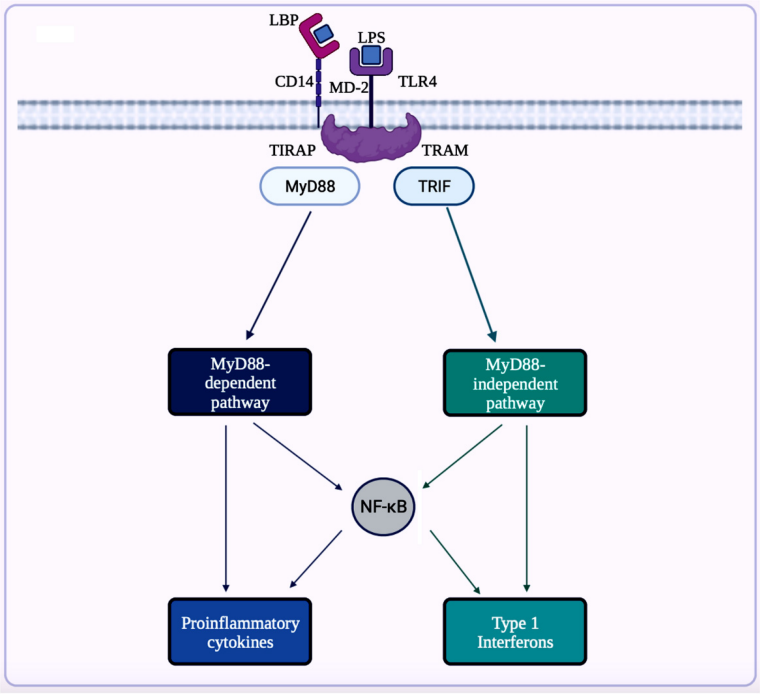

Figure 4. This illustration showcases an overview of LPS/TLR4 signaling. LPS can attach to LPS binding protein (LBP), which assists the transfer of LPS to glycerophosphatidylinositol-anchored protein (CD14). Then, CD14 transfers LPS to the TLR4/myeloid differentiation factor-2 (MD-2) receptor complex. After recognizing LPS, this complex triggers signals via toll-interleukin 1-receptor domain-containing adaptor protein (TIRAP) and myeloid differentiation factor 88 (MyD88) for activation of NF-κB to induce expression of pro-inflammatory cytokines. The LPS/TLR4 signaling can also be mediated via TRIF-related adaptor molecule (TRAM) and TIR domain-containing adaptor protein-inducing interferon-β (TRIF) in the MyD88-independent pathway. These adaptor molecules (TRAM and TRIF) activate the transcription factor, interferon regulatory factor-3 (IRF3), to produce type 1 interferons. This figure was created with BioRender.com.

In colonic inflammation, the level of the genus *Phascolarctobacterium* declines while increasing the amount of CRP. This genus also produces propionate, one of the SCFAs, which inhibits the pro-inflammatory NF-κB pathway and cytokine production [56]. Several bacterial strains, such as *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, *Salmonella*

enterica, *Mycobacterium tuberculosis*, and *Staphylococcus aureus* are also capable of producing functional amyloid [57]. These functional amyloids produced by the bacteria result in the misfolding of neuronal proteins such as α-synuclein [57]. The extensive relationship between the gut microbiota and inflammation has been studied and proven to be implicated in various metabolic disorders (e.g., insulin resistance, glucose intolerance, hyperglycemia, high blood pressure, dyslipidemia, and obesity), cancer, and especially AD [54][57][58].

4.2. Inflammasomes in AD

Inflammasome, which is a cytosolic multiprotein complex, is implicated in causing excessive inflammation in various diseases, including autoimmune diseases, cancers, and neurodegenerative diseases [59]. In the innate immune system, if adverse stimuli (e.g., pathogens, dead cells) are detected, then inflammasomes are the receptors deployed to activate caspase-1, which contains a caspase recruitment domain (CARD), resulting in inflammation [51]. The innate immune response cascade begins with the initiation of germline-encoded pattern recognition receptors (PRRs), transmembrane or cytosolic receptors, by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [60]. PAMPs are the structural moieties present in microorganisms such as Gram-negative bacterial LPS, bacterial or viral nucleic acids, and bacterial peptides (e.g., flagellin). DAMPs are the endogenous molecules activated due to cellular stress, such as chromatin-associated proteins, heat-shock proteins, uric acid, and extracellular matrix fragments [60]. After the PAMPs or the DAMPs activate the cascade, PRRs such as nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), absent in melanoma-2 (AIM-2)-like receptors (ALRs), and tripartite motif-containing (TRIM) proteins form inflammasomes. There are three diverse types of inflammasomes: NLR-associated inflammasomes, ALR-associated inflammasomes, and the pyrin inflammasome [59]. Inflammasomes can be activated through two kinds of inflammasome signaling such as canonical and non-canonical [54]. The canonical inflammasome signaling consists of one or more inflammasome sensors, such as apoptosis-associated speck-like protein containing CARD (ASC) and caspase-1. ASC has a bipartite structure with a pyrin domain (PYD) and a CARD, both of which aid ASC in acting as an adaptor molecule. The non-canonical signaling pathway includes the activation of mouse caspase-11 or human caspase-4 and caspase-5 [51][60].

The NLRP3 (NOD-, leucine-rich repeat- or LRR-, and PYD-containing protein 3) inflammasome is a multimeric protein complex – which is made up of the sensor protein NLRP3, the adaptor protein ASC, and the effector protein pro-caspase-1 – having a role in development of AD [61][62][63]. When the sensor protein NLRP3 is activated, it binds to the PYD of the adaptor protein ASC, resulting in the cleavage of pro-caspase-1 into activate caspase-1 to form the NLRP3 inflammasome (**Figure 5**) [64]. This activates caspase-1, which then activates the inactive pro-inflammatory cytokines pro-IL-1β and pro-IL-18 into their respective mature forms [64]. Along with activating cytokines, the activated caspase-1 can also cause pyroptosis, an inflammatory-related programmed cell death [64]. Among the family of inflammasomes, NLRP3 is the most extensively studied [63].

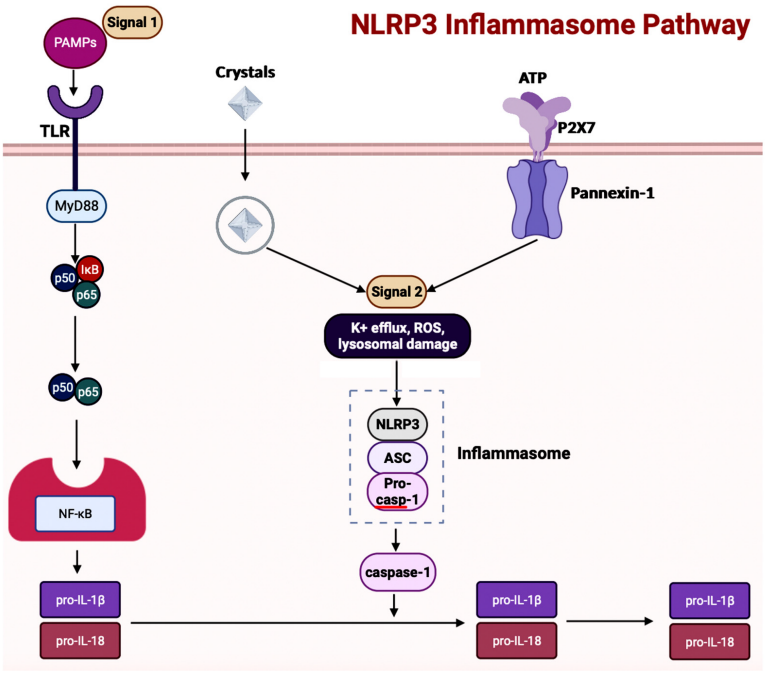

Figure 5. This illustration showcases the sequence of events for activation of the NLRP3 inflammasome pathway. The cascade is triggered through the binding of microbial molecules (pathogen-associated molecular patterns, PAMPSs) to the TLR receptor. NLRP3 inflammasome can also be activated through crystalline substances (uric acid and calcium pyrophosphate dihydrate). This figure was created with BioRender.com.

Studies have shown the influence of the NLRP3 inflammasome in promoting neurodegenerative diseases, such as AD [61]. Specific inhibition of NLRP3 in vivo attenuated the activity of NLRP3 producing promising results, such as the decreased levels of tau and Aβ aggregates and the reduced cognitive impairment [65]. Hence, the activated NLRP3/caspase-1 inflammasome pathway can allow the accumulation of Aβ aggregates. As mentioned before, the formation of Aβ can cause a positive feedback loop in which the Aβ production is unrestricted by the microglia [65][66][67]. Apart from Aβ aggregates, inflammasomes can also influence tau pathology in AD. A study conducted in the NLRP3-inflammasome-deficient mice showed less cleaved caspase-1 and IL-1β along with a decrease in ASC formation [68]. Activation of the NLRP3 inflammasome pathway increases tau hyperphosphorylation through the production of tau kinases [68]. The implications of NLRP3 in both Aβ fibril formations and tau pathogenesis make this inflammasome a potential target for decreasing inflammation in AD.

4.3. Inflammasomes and GBA in AD

Inflammasome activity is influenced by alterations in the gut microbiota and diet [58]. In a ketogenic diet or calorie restriction, the NLRP3 inflammasome gets inhibited because the ketone body β-hydroxybutyrate production in the liver increases [62]. A study exploring sickness-induced anorexia analyzed the relationship between *Salmonella typhimurium* and the GBA [69]. The *S. typhimurium* effector, Slrp, was used to inhibit the inflammasome pathway to hinder anorexia [69]. In the blood and brain samples collected from patients experiencing cognitive decline, an overexpression of NLRP3 in astrocytes and microglia resulting in central inflammation was witnessed [70]. Contrastingly, the same study also analyzed the effects of dysbiosis on the activation of peripheral inflammation, consisting of the innate cells in the gastrointestinal (GI) tract. The results showed that activation of peripheral inflammasomes triggered NLRP3-mediated neuroinflammation in the brain [70]. In a study conducted, the gut microbiota from AD patients was transferred to APP/PSEN1 mice, causing microglial and NLRP3 inflammation leading to the release of inflammatory factors [71]. The GI tract then absorbs the inflammatory factors to cause inflammation. So, targeting the inflammasome signaling pathway through improving the composition of the gut microbiota would be a possible therapeutic option in AD.

5. Autophagy in AD

In AD brains, the main pathological changes are the deposition of Aβ plaques and intracellular NFTs made from hyperphosphorylated tau proteins [72][73]. The accumulation of Aβ plaques begins from the dysregulation of Aβ, which is modulated by autophagy [73]. **Figure 6** showcases autophagy, which is a self-degradative process that plays a critical role in maintaining cellular homeostasis [74][75]. Autophagy is required to degrade the misfolded proteins present in the brain to prevent neurodegenerative diseases. Further studies have shown that the expression of autophagy-related proteins is downregulated in AD, implying the importance of autophagy upregulation as a part of treatments for AD [76].

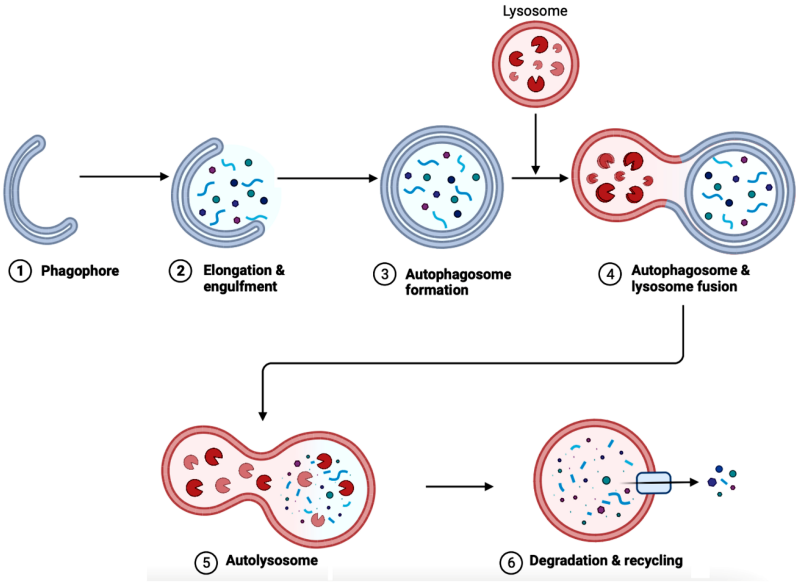

Figure 6. A diagram depicting the steps in autophagy. The elongation of phagophores begins when LC3 attaches to the membrane. (1) The phagophore expands when the cytoplasmic materials (e.g., mitochondria, endoplasmic reticulum, aggregated proteins, bacteria, and virus) are engulfed. (2) Then, the phagophore undergoes both elongation and engulfment. (3) This creates the structure called an autophagosome. (4) Then, the lysosome fuses with the autophagosome. (5) The fusion forms the autolysosome. (6) Lysosomal hydrolases cause degradation and recycling cellular faulty or damaged components. The process of autophagy is crucial for several functions in the body, such as cell survival, degrading protein aggregates, and homeostasis. Autophagy is impaired in AD, blocking the degradation and recycling of faulty proteins and other cellular components. This figure was created with BioRender.com.

There are three categories of different autophagy mechanisms: microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy [73]. Firstly, microautophagy involves the absorption of cytoplasmic material into a lysosome through direct invagination of the lysosomal membrane [77]. Secondly, CMA is selective in targeting certain cytosolic proteins and degrading them in the lysosomal lumen [78]. Thirdly, the unique mechanism in macroautophagy is autophagosome formation, which is used to transport the waste contents to the lysosomes [73][79]. Apart from macroautophagy and microautophagy, CMA is also increasingly known to have an influence on neurodegenerative diseases, including AD. The mechanism for CMA inhibition varies depending on the disease explored. Therapeutic targets directed at diverse types of autophagy can be an exciting avenue for designing treatment strategies for neurodegenerative diseases, including AD.

5.1. Implications of Gut Microbiota in Autophagy in AD

The gut microbiota has direct implications on many factors, including autophagy due to the existence of GBA. One of the ways to scrutinize whether gut flora has any effect on autophagy is to use GF mice. In the colonic epithelium of GF mice, the level of basal autophagy decreased compared to mice with intact gut flora [80]. The study also reinstated intestinal autophagy in vivo using butyrate-producing bacterial stain *Butyrivibrio fibrisolvens*. Bacteria-derived metabolites other than butyrate, such as indole-3-lactate produced by *Lacticaseibacillus*, *Lactobacillus*, *Bifidobacterium*, *Megamonas*, *Roseburia*, or *Ruminococcus* are also alternative options to induce intestinal autophagy [80]. These bacteria-derived metabolites can also modulate intestinal inflammation through the autophagy pathway. *E. coli* regulates autophagy through the NF-κB pathway, which upregulates selective microRNAs (miRNAs) before inhibiting ATG-specific proteins and then autophagy [81]. Dysfunctional autophagy and gut dysbiosis are both in a positive feedback loop due to dysregulated autophagy resulting in impaired intestinal epithelial barrier function through altering the levels of expression of the CLDN2 (Claudin-2) gene that codes for the tight junction protein Claudin-2 in the intestinal mucosa [30]. Then, the increase in bacterial translocation causes gut dysbiosis [30]. Dysregulated autophagy causes gut dysbiosis and vice versa. Targeting gut microbiota would be realistic to decrease dysfunctional autophagy, which in turn would reduce the pathogenic features such as inflammation, oxidative stress, and accumulation of protein aggregates in many neurodegenerative diseases, including AD.

6. The Bioflavonoids EGCG and GS as Therapeutic Agents for AD

6.1. Overview of Regulating Cell Signaling by EGCG and GS

Two bioflavonoids, EGCG and GS, have shown major influences on the NF-κB, mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), insulin-like growth factor (IGF), and mechanistic target of rapamycin (mTOR) signaling pathways to provide neuroprotection in neurodegenerative diseases (**Table 2**). Their mechanisms of action on these signaling pathways show their therapeutic efficacies in AD.

Table 2. Signaling pathways implicated in AD pathogenesis and use of EGCG and GS for amelioration of AD pathogenesis.

Signaling Pathway in AD	Associated Functions	EGCG and GS	References
NF-κB pathway	Regulates pro-inflammatory genes	Both can inhibit the pathway	[29][73][74][75][76]
MAPK pathway	Regulates apoptosis, differentiation, etc.	Both can inhibit the pathway	[77][80][81][82][83]
EGFR pathway	Regulates gene expression and cell proliferation	Both can inhibit the pathway	[84][85][86][87][88][89][90][91]
IGF signal transduction pathway	Regulates cell differentiation, cell survival, and cell maintenance	Both can inhibit the pathway	[91][92][93][94][95][96][97][98][99]
mTOR pathway	Regulates cell proliferation, apoptosis, and autophagy	Both can inhibit the pathway	[100][101][102][103][104]
5-Hydroxytryptamine signaling pathway	Regulates serotonin production	Both can facilitate the pathway	[105][106][107][108]

6.2. Exploration of Bioflavonoids as Therapeutic Options in AD

Through multiple studies, EGCG and GS have been implicated in modulating the signaling pathways related to AD. However, the glaring limitation of using these selective bioflavonoids is their decreased bioavailability. Studies focused on analyzing delivery methods to optimize the absorption and usage of EGCG and GS in the body would be beneficial to develop them as novel therapeutic drugs for the treatment of AD. In this section, multiple methods with goals to administer bioflavonoids to patients are considered: AChE inhibition, diet, fecal microbiota transplantation, neural stem cell therapy, and nanomaterials.

6.2.1. AChE Inhibitor

In AD, there is a change in the function of the cholinergic system. The current treatments available for AD mostly provide temporary attenuation of symptoms through cholinergic and anti-glutamatergic mechanisms [109]. Most of the currently used AChE inhibitors have side effects based on the dosage administered. For example, an overdose of Rivastigmine can result in cases of irregular heartbeat and chest pain [110]. Hence, an alternative AChE inhibitor, especially bioflavonoids, would be of interest. An in vitro study showed that neuronal cells treated with 10 µM EGCG reduced Aβ-induced cytotoxicity, with EGCG becoming an AChE inhibitor [111]. Apart from EGCG, GS can function as an efficient AChE inhibitor. In diabetic mice, GS can improve cognitive decline by inhibiting AChE [86]. The basal cholinergic neurons are affected by apolipoprotein E (ApoE) during the pathogenesis of AD. GS upregulates the peroxisome proliferator–activated receptor gamma (PPARγ), which is induced by Aβ deposits. Then, the upregulation of PPARγ results in the production of ApoE, which can decrease the deposition of Aβ [86]. EGCG and GS have the potential to function as AChE and BChE inhibitors, which can replace the current controversial AD therapeutic options on the market.

6.2.2. Diet

Dysbiosis, which occurs in the gut due to numerous factors and lack of diversity of the microbiota, can be improved through bioflavonoids, some of which contain antioxidant and antimicrobial properties [112]. However, the issue lies with how exactly EGCG and GS can be made available to patients. The attractive method for the availability of bioflavonoids, apart from these molecules acting as AChE inhibitors, is through diet. The high BBB permeability of EGCG increases neuritogenesis (generation, extension, and diverging of neurites), which attenuates neurodegenerative diseases [113]. If taken along with food, the oral bioavailability of EGCG is low in humans. Studies are showing that if EGCG is taken along with nutrients such as fish

oil (omega-3 fatty acids), vitamins (e.g., ascorbic acid), and minerals (e.g., selenium or chromium), then the bioavailability of EGCG improves [113]. Like EGCG, GS also deals with oxidative stress, neuroinflammation, and mitochondrial dysfunction, along with being able to cross BBB to have neuroprotective effects [114]. When the distribution of GS was analyzed, the GS concentration in the GI tract was the highest, followed by the intestine, liver, kidney, lung, heart, brain, reproductive organs, and then muscle [115]. Additionally, the GS concentration in the GI tract was enough to have anti-proliferative effects [115]. Hence, finding ways to properly administer EGCG and GS through a patient's diet could show changes in the progression of neurodegenerative diseases, including AD.

6.2.3. Fecal Microbiota Transplantation (FMT)

Among neurodegenerative diseases, FMT has also shown success in altering dysbiosis in PD patients [116]. In a transgenic mouse model treated with pre-FMT antibiotic treatment to cause dysbiosis, FMT showed the potential to decrease AD pathology [116]. However, FMT from young mice had more significant changes compared to microbiota from aged mice, which resulted in chronic low-grade inflammation or imflammaging. After the FMT in AD mice, the BBB and the metabolite levels were repaired, allowing for attenuation of AD pathogenesis [116]. Bioflavonoids can also help increase the advantages of FMT in diseases. In a study reported in 2021, FMT was conducted using microbiota from EGCG-dosed mice [117]. The results showed that microbiota retrieved from EGCG-dosed mice decreased inflammation and developed the colonic barrier integrity along with producing SCFAs and effective bacteria such as *Akkermansia* [117], also a commensal (neither harmful nor beneficial) microbe making up 1–4% of gut microbes in humans. On a similar note, microbiota from GS-dosed mice increased SCFA production and revived the gut flora, allowing the recipient mice to live longer [118]. The efficiency of FMT with EGCG and GS should be further explored for administering them as an alternative therapeutic strategy for AD patients.

6.2.4. Neural Stem Cell Therapy

Neural stem cells (NSCs) are pluripotent stem cells that exist solely in the CNS. NSCs can proliferate and differentiate into multiple cell types (e.g., neurons, oligodendrocytes, and astrocytes) [119][120]. Cellular therapy makes use of neurogenic or non-neurogenic cells to improve nerve repair and tissue damage, and this method has been widely used to treat CNS diseases [120]. Neural stem cell therapy uses a mechanism of regulating the local microenvironment, increasing blood vessel development and neuron regeneration, and attenuating inflammatory responses [120]. A mice model study used NSCs obtained from the fetal brain tissue, showing the hippocampus of the recipient 3xTg-AD mice improving cognitively through enhanced endogenous synaptogenesis [121]. Further studies have shown human brain-derived NSCs (hNSCs) injected into the hippocampus of APP/PSEN1 model of AD, resulting in a development of neuronal connectivity and metabolic activity, which allowed for a decrease in AD pathogenesis [122]. Other than attenuating cognitive defects, NSCs can also inhibit inflammatory responses, neuronal loss, and regulation of microglia function [123][124]. Tea polyphenols can increase the survival rate of NSCs based on the concentration administered [125]. A study focused on the differentiation of NSCs from mouse cochlear (a fluid-filled, spiral cavity in the inner ear) in which researchers found EGCG stimulating the proliferation and neurosphere formation in the isolated NSCs in vitro [126]. In a study, ischemic stroke was induced in NPCs, and the effect of EGCG in vitro and in vivo was analyzed. After 14 days of treatment with EGCG, the neuronal differentiation was increased in the cultured NPCs [127]. Unfortunately, there are no studies with GS, specifically regarding NSCs. However, a study was conducted in which GS and daidzein (an isoflavone found exclusively in soybeans and other legumes) increased the hippocampus neuronal cell viability and proliferation in vitro [128]. Further studies should be explored to understand the influence of GS on NSC therapy for AD patients. A combination of EGCG and GS could further promote the proliferation and differentiation of NSCs in the treatment of AD.

6.2.5. Nanomaterials

The major issue with administering polyphenols is their low bioavailability. The reasoning can be attributed to intrinsic factors (e.g., chemical structure, molecular weight, and low hydro solubility or solubility in water) and extrinsic factors (e.g., low stability in the GI tract, extensive Phase I and Phase II metabolism, and rapid elimination [129]. A solution to combat this low bioavailability is using polymeric nanoparticle-based delivery systems, which deliver bioactive molecules across the GI tract to target organs [129]. A nanoparticle refers to a small particle that ranges between 1 to 100 nm in size [130]. There are a variety of nanoparticle systems, such as nanospheres (NSs), nanocapsules (NCs), solid lipid nanoparticles (SLNs), cyclodextrins (CDs), liposomes (LSs), and micelles (MCs). Specifically, for polyphenols, biodegradable and biocompatible polymers are the most explored as a nanoparticle system [129]. Existing studies confirm the possibility of delivering EGCG and GS with different

nanoparticles. EGCG was loaded into heat-treated β-lactoglobulin (β-Lg), which stabilizes the structure of the bioflavonoid and helps protect its antioxidant properties [131]. Further studies reaffirm the advantages of using nanomaterials to deliver EGCG. The absorption of EGCG in the GI tract can be improved by using chitosan/trimeric phosphate nanoparticles [132]. With the bioavailability of EGCG increased orally, the amount of EGCG available to plasma and jejunum also increased [132]. Shifting the focus to GS regarding clinical applications, which also have rapid metabolism and excretion, and low oral bioavailability [133]. The mucoadhesive polymers can reside in the nasal pathway longer, regulating drug release and intracellular uptake [133]. The results regarding the efficacy of using EGCG and GS in tandem with nanoparticles look positive and highly promising for the treatment of AD; hence, this is a therapeutic drug delivery method that should be further explored in detail for clinical trials.

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