

Review

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Review

Liposomal Epigallocatechin-3-Gallate for the Treatment of Intestinal Dysbiosis in Children with Autism Spectrum Disorder: A Comprehensive Review

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Abstract: Autism Spectrum Disorder (ASD) is characterized by varying degrees of difficulty in social interaction and communication. These deficits are often associated with gastrointestinal symptoms, indicating alterations in both intestinal microbiota composition and metabolic activities. The intestinal microbiota influences the function and development of the nervous system. In individuals with ASD, there is an increase in bacterial genera such as *Clostridium*, as well as species involved in the synthesis of branched-chain amino acids (BCAA) like *Prevotella copri*. Conversely, decreased amounts of *Akkermansia muciniphila*, and *Bifidobacterium spp.* are observed. Epigallocatechin gallate (EGCG) is one of the polyphenols with the greatest beneficial activity on microbial growth and its consumption is associated with reduced psychological distress. Therefore, the objective of this review is to analyze how EGCG and its metabolites can improve the microbial dysbiosis present in ASD and its impact on the pathology. The analysis reveals that EGCG inhibits the growth of pathogenic bacteria like *Clostridium perfringens* and *Clostridium difficile*. Moreover, it increases the abundance of *Bifidobacterium spp.* and *Akkermansia spp.* As a result, EGCG demonstrates efficacy in increasing the production of metabolites involved in maintaining epithelial integrity and improving brain function. This identifies EGCG as highly promising for complementary treatment in ASD.

Keywords: Autism Spectrum Disorder (ASD); microbiota; epigallocatechin-3-gallate (EGCG); inflammation; oxidative stress

1. Introduction

ASD is a highly heterogeneous and complex disorder, characterized by two major groups of core symptoms: persistent deficits in social communication and interaction, and restricted and repetitive patterns of behavior, interests, or activities [1–5]. Current statistics indicate that the disorder affects approximately 1 in every 160 children worldwide [6].

Characteristic deficits are often associated with a range of gastrointestinal symptoms such as abdominal pain, diarrhea, or constipation [7,8]. Several studies have found that both the composition

of the intestinal microbiota and metabolic activities may be altered in individuals with the disorder [9,10]. Therefore, several authors concur that disruptions in the microbiota and intestinal microbiome, i.e., the collection of microorganisms present in the human gastrointestinal tract and their respective genomes [3,11], could trigger many of the gastrointestinal issues experienced by children with ASD, as well as exacerbate some of the core symptoms of the disorder [12,13].

Microbial colonization begins in infancy through the acquisition of maternal microbiota during vaginal delivery [3]. Subsequently, beneficial microorganisms feed on breast milk, which has a high content of oligosaccharides [14]. Similarly, the composition of the microbiota in the early years may be subject to alterations influenced by the delivery method, hygiene habits and feeding practices and routines. Among these factors, formula feeding has a particularly significant impact [3].

It has been shown that the intestinal microbiota affects the function and development of the immune, metabolic and nervous systems. Regarding the immune and metabolic systems, intestinal microbiota and its metabolites impact host physiology by regulating the function of the intestinal barrier, redox and mitochondrial metabolism, and mucosal inflammatory response through the regulation of intestinal lymphocytes that provide resistance against potential pathogens [15–20]. On the other hand, intestinal microbiota can influence neurochemistry, function, gene expression and the development of the central nervous system (CNS) through the gut-brain axis, which represents a bidirectional link between the cognitive and emotional functions of the CNS and peripheral intestinal function [15,21–23]. It is worth noting that the genus *Bifidobacterium* can metabolize gamma-aminobutyric acid (GABA), *Lactobacillus* spp. can metabolize acetylcholine, *Bacillus* spp. and *Serratia* spp., dopamine, and *Escherichia* spp. and *Saccharomyces* spp., noradrenaline. All these neurotransmitters are essential for the proper functioning of the nervous system as they can enter circulation and directly affect neural processes throughout the body, including the brain [3,24]. Additionally, intestinal proinflammatory cytokines can have an impact on the brain because they make the blood-brain barrier (BBB) more permeable, allowing peripheral immune cells to enter the brain and stimulating brain cells to produce additional proinflammatory mediators [25,26].

All of this has led to the hypothesis that the development of symptoms related to ASD may be influenced by the disturbance of the gut-brain-microbiota axis caused by changes in the intestinal microbiota.

2. Alterations in the intestinal microbiota in ASD

The Firmicutes (40-60%) and Bacteroidetes (20-40%) are the two major phyla of bacteria in the healthy human intestinal flora, followed by Proteobacteria, Actinomycetes, *Clostridium* spp., and Verruciformis [3,27]. However, in ASD, increased levels of bacterial genera such as *Clostridium*, *Desulfovibrio* and *Ruminococcus* have been observed [15,28], along with species that synthesize BCAA such as *Bacteroides vulgatus* and *Prevotella copri*. On the other hand, lower quantities of *Bacteroides fragilis*, *Akkermansia muciniphila*, *Bifidobacterium* spp. and *Enterococcus* spp. have been found [29,30]. Additionally, the ratio of the *Escherichia/Shigella* genera is altered, as *Shigella* spp. is present at higher levels, while *Escherichia coli* is decreased [31].

It should be noted that, despite the consensus regarding these alterations, it is important to consider that not all studies quantifying the microbiota in ASD analyze the same species or genera, leading to some heterogeneity in the results, and various studies emphasize the relationship between the composition of the human intestinal microbiota and the individual's diet, which can lead to variations in composition depending on the region where the analyses were conducted [32]. In fact, a study in the United States highlighted that children with ASD had lower levels of *Bifidobacterium* spp. and *Prevotella* spp., but higher levels of *Lactobacillus* spp., compared to healthy children [33]. Another study in China described that children with ASD had higher levels of the Actinobacteria and Proteobacteria phyla than the control group [34].

Furthermore, Ho *et al.* (2020) indicated that although the results of different studies are not entirely consistent, individuals with ASD generally exhibit a decrease in the percentage of the phylum Bacteroidetes or no significant difference compared to the control group of healthy individuals [35]. This could be due to the fact that within the phylum Bacteroidetes there are bacteria

of the genus *Bacteroides* spp. that are increased, such as *B. vulgatus*, while others are decreased, such as *B. fragilis*, potentially leading to a compensatory effect that results in an unclear profile [30].

The genus *Prevotella* presents a more variable pattern. In the aforementioned review, the authors noted a lower relative abundance of *Prevotella* spp. in children diagnosed with ASD compared to the control group. However, multiple studies indicate an elevated prevalence of *Prevotella* spp. in children with ASD [15,30,31,35] and this variability could be due to dietary factors. Filippo *et al.* (2010) compared the composition of *Prevotella* spp. in the microbiota of children following European and African diets and observed a significant increase in *Prevotella* spp. in the microbiota of African children, likely due to their consumption of a grain-rich diet [36].

Finally, to establish a correlation between gastrointestinal issues and behavioral problems with the microbiota, the high growth rates of *Clostridium histolyticum*, *Clostridium difficile*, *Clostridium perfringens* and *Sutterella* spp., the alteration in the *Escherichia/Shigella* genera ratio, and the decreased Bacteroidetes/Firmicutes phylum ratio have been identified as factors associated with gastrointestinal problems. Furthermore, the relative abundance of *Desulfovibrio* spp., *Clostridium* spp. and *Bacteroides vulgatus* has been linked to behavioral disorders [37].

3. EGCG as an alternative for ASD

Currently, ASD lacks a medical cure, and a deeper understanding of molecular pathogenic mechanisms are necessary to propose therapeutic alternatives to current medications, which are primarily used for treating autism-related symptoms such as anxiety, hyperactivity, obsessive-compulsive behavior or gastrointestinal disorders [38]. Given the previously mentioned disruptions in the microbiota, it is crucial to focus current research on exploring the connection between the microbiota-gut-brain axis to modify the course of the disease. Polyphenols, as bioactive dietary compounds, emerge as a highly promising option. The interest in these molecules stems from their ability to act both in the intestine, where they reach the highest concentrations in the human body after oral administration, counteracting intestinal inflammation and modulating the intestinal microbiota and its metabolites, as well as in the brain, where they have neuroprotective effects upon penetrating the BBB [39].

3.1. Possible role of EGCG in the intestinal microbiota of patients with ASD

Compounds capable of targeting the intestine and modulating the intestinal microbiota, while reducing intestinal inflammation, have been shown to influence memory, cognition, mood and behavior, thereby contributing to the prevention and treatment of various brain disorders [25]. Among these compounds, polyphenols appear to be particularly relevant. Numerous authors have proposed their use in the treatment of neurological disorders due to their stimulating effect on specific intestinal bacteria that utilize and metabolize phenolic compounds [40,41].

Polyphenols are the most ubiquitous phytochemicals in the human diet, with a total daily intake of approximately 1 g [42]. These phenolic compounds, as secondary metabolites in plants, primarily protect them against various aggressions or infections caused by bacteria, insects or viruses [40,41]. These protective properties in plants are expected to be beneficial for humans as well. Polyphenolic compounds found in green and black tea are the most potent inhibitors of microbial growth. These compounds include epigallocatechin gallate (EGCG), epicatechin gallate, epigallocatechin, catechin gallate, epicatechin and catechin [43]. They have shown significant efficacy in inhibiting the growth of pathogens such as *Helicobacter pylori* [44], *Staphylococcus aureus*, *Escherichia coli* O157:H7 [45,46], *Salmonella typhimurium* DT104, *Listeria monocytogenes*, methicillin-resistant *Staphylococcus aureus* [47,48] and *Pseudomonas aeruginosa* [49]. They have also been effective against viruses like HIV and Epstein-Barr [50,51]. Among all the polyphenols, several studies highlighted by Duda-Chodak *et al.* (2015) emphasize the significant role of EGCG [52]. EGCG is the primary catechin in green tea, but it is also found in lower concentrations in certain plant-based foods, such as apples, peaches, kiwis, blackberries, pears and nuts like pistachios, hazelnuts and walnuts [53]. Its consumption is linked to reduced psychological distress [54], possibly by inhibiting the growth of specific pathogenic bacteria such as *Clostridium perfringens*, *Clostridium difficile* [55], *Bacteroides ovatus*, and enterobacteria

(*Salmonella* spp., *Escherichia coli*, *Yersinia pestis*, *Klebsiella* spp., *Shigella* spp. and *Eggerthella* spp.) [46,56–58]. Furthermore, EGCG increases the abundance of *Bifidobacterium* spp. and bacteria of the *Bacteroides* genus (*Bacteroides uniformis*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron* and *Bacteroides cellulosilyticus*), as well as *Prevotella* spp., *Lachnospirillum* spp. and *Akkermansia* spp. [56–59].

A substantial portion of the vital microorganisms present in the fecal microbiota of breastfed infants is comprised of species belonging to the *Bifidobacterium* genus [60]. *Bifidobacterium* spp. has psychobiotic effects that contribute to reduce anxiety (specifically, strains *B. longum* and *B. breve*), stress and other depressive behaviors [61,62]. This bacterial genus is among the first to colonize the intestines of newborns, and a dysbiosis of *Bifidobacterium* spp. may impact infant neurodevelopment [62]. In this context, the increase of *Bifidobacterium* spp. through the administration of EGCG correlates with an improvement in the intestinal microbiota. Previous studies conducted on animal models have demonstrated that a diet enriched with EGCG has the potential to elevate populations of *Bifidobacterium* spp. [63].

Bacteria within the *Bacteroides* genus play a crucial role in the breakdown of complex molecules, particularly carbohydrates, and confer advantages to their hosts by impeding the colonization of potential pathogens in the digestive tract [64,65]. It has been seen that there are bacteria capable of modulating the immune system. For instance, *B. fragilis* has been shown to restore the balance of T-cell populations in mice affected by ASD [66], while *B. uniformis* enhances the production of anti-inflammatory cytokines and improve metabolic and immune dysfunction [56]. Moreover, this genus can improve both social behaviors and physiological abnormalities in individuals affected by ASD [67], indicating that an increase in *Bacteroides* abundance caused by EGCG could enhance the quality of life in patients. Additionally, this polyphenol can reduce *B. ovatus*, the main intestinal commensal responsible for a systemic antibody response in inflammatory bowel disease [68]. These findings suggest that even within the same genus, EGCG may exert different effects on bacterial species.

Prevotella spp. are commensal bacteria in the human microbiota, and their function is to degrade plant polysaccharides and participate in the synthesis of vitamin B1 [69]. Within the *Prevotella* genus, *Prevotella copri* can be found. This species has been associated with improved glucose and insulin tolerance and is commonly found in individuals who follow a fiber-rich diet, suggesting a strong connection between the effects of this bacterium and dietary patterns [70–73]. Consequently, both the bacteria within the *Prevotella* genus and their metabolic activity may hold significant relevance to ASD, which will be further elaborated.

In relation to the *Lachnospirillum* genus, it has been seen to possess anti-inflammatory properties and contribute to the maintenance of intestinal balance by producing butyric acid [74]. This metabolite aids in the elimination of intestinal gases and its absence is associated with irritable bowel syndrome (IBS) [75]. Therefore, the increase of *Lachnospirillum* spp. mediated by EGCG can be seen as a positive impact on the microbiota of ASD patients.

EGCG modulates the composition of the intestinal microbiota and its metabolites, enriching the population of short-chain fatty acid (SCFA)-producing bacteria such as *Akkermansia* spp. This leads to an increased production of these metabolites. [76,77]. Therefore, EGCG promotes an anti-inflammatory and antioxidant state in the intestine. [76]. Specifically, *Akkermansia* spp. utilizes intestinal epithelial mucin as a source of energy. By degrading mucin, it releases nutrients such as monosaccharides, amino acids and SCFAs, which are used by other bacteria in the microbiota, stimulating their metabolic functions [78]. *Akkermansia* spp. is involved in the regulation of glucose metabolism and adipose tissue homeostasis, therefore, the fact that EGCG increases the levels of *Akkermansia muciniphila* improves intestinal dysbiosis and enhances barrier integrity [58,79–81].

Among the bacteria reduced by EGCG, Clostridia stand out as a group of Gram-positive bacilli that, when in excess, can lead to infection in the large intestine [28]. Furthermore, butyrate or butyric acid, along with other SCFAs derived from the fermentation of dietary fiber, are noteworthy compounds produced by Clostridia [82]. Butyrate is an essential metabolite in the human colon as it is the preferred energy source for colonic epithelial cells. It contributes to maintaining intestinal barrier functions and has immunomodulatory and anti-inflammatory properties [83]. However, it promotes intestinal permeability, which may allow the passage of toxic substances into the

bloodstream, potentially leading to inflammation [82]. In individuals with ASD, both the absolute and relative abundance of these bacteria are increased. Thus, the inhibitory capacity of EGCG on this group of bacteria, which can decrease the levels of *Clostridium spp.*, as seen in rats, is beneficial [63]. This activity may be particularly relevant for *Clostridium perfringens*, as its impact on the symptomatology of the disease, including gastrointestinal issues, is significant. Both the bacterium itself and the gene that produces its toxin (CPB2) have been associated with gastrointestinal complications in ASD and are correlated with disease severity. Moreover, the isolated species from children with ASD show greater antibiotic resistance compared to healthy children [84]. On the other hand, the increase of *Clostridium difficile* also has a notably negative impact on ASD, and effective treatments against this bacterium using oral vancomycin have shown improvements in behavior and communication [85,86]. Therefore, the reduction of this strain mediated by EGCG could be beneficial for the clinical presentation of children affected by ASD.

Another group that decreases after treatment with EGCG is enterobacteria. Their presence in the body is common, but uncontrolled growth of these bacteria can lead to infections. Certain species have been linked to specific pathologies. Specifically, *Salmonella typhi* is responsible for typhoid fever, *Shigella dysenteriae* is the causative agent of bacillary dysentery and causes infantile gastroenteritis, and *Yersinia pestis* causes plague [87].

Lastly, it is important to highlight at this stage that specific bacteria increased by EGCG, such as *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Akkermansia muciniphila* and *Prevotella ruminicola*, restore the balance of the intestinal microbiota when added to the diet, thereby reducing oxidative stress in the intestine and the brain [88].

3.2. Outlook on the anti-inflammatory and antioxidant activity of EGCG in autism. Neuroprotective role

Dysregulation of the immune system leading to inflammation and increased oxidative stress has been recognized as a significant contributing factor to ASD [89], which is directly linked to dysbiosis. The presence of multiple comorbid inflammatory conditions associated with immune dysregulation is closely related to the emergence and progression of the key clinical features observed in children with ASD [90–92]. Cytokines constitute a group of small proteins that act as immunomodulatory and endocrine messengers involved in the regulation of inflammation and neurological development [93,94]. Specifically, there is substantial evidence of altered cytokine levels in children with ASD, which are not observed in typically developing children [95]. Particularly noteworthy are the alterations identified in the levels of interferon- α (IFN- α), interleukin-7 (IL-7), IFN- γ -inducible protein-10 and IL-8, with the latter appearing to be particularly relevant to the pathogenesis of the disorder [96]. Additionally, levels of IL-1 β and IL-10 produced by peripheral blood monocytes, along with the IL-1 β /IL-10 ratio and changes in miRNA expression, seem to be relevant in relation to innate immunity [97,98]. All these alterations are closely associated with social behavioral impairments and characteristic cognitive development in children with ASD [99].

Regarding oxidative stress, it appears to have a direct link to the intestinal microbiota, especially in children with ASD. The microbial fermentation of dietary fibers and resistant starch in the intestinal tract leads to the generation of SCFAs [100]. Notably, propionate has been associated with metabolic disturbances in the gastrointestinal system and neuroinflammation, which may elucidate the higher prevalence of gastrointestinal issues, including dysbiosis, observed in children with ASD [101]. Consequently, the response to oxidative stress, closely intertwined with dysbiosis, plays a crucial role in the neuroinflammatory response, thus representing a significant pathogenic factor in the development of ASD [102–106]. It has been observed that there are evident differences in antioxidant capacity and the concentration of various oxidative stress-related metabolites between children with autism and healthy children [107]. Autistic children are more susceptible to oxidative stress, primarily due to an imbalance in intracellular and extracellular glutathione (GSH) levels and a decrease in glutathione storage capacity [108]. Moreover, this increased production of free radicals has been linked to the activity of amyloid precursor proteins (APP) in various human disorders, including neurodevelopmental disorders, with autism being a prominent example [109–111].

At the cerebral level, polyphenols promote neurogenesis and plasticity, elucidating their role as antioxidants that have demonstrated their potential in alleviating autistic symptoms. Additionally, they can reduce intestinal inflammation, leading to a significant decrease in inflammatory cascades such as nuclear factor kappa B (NF- κ B), activator protein-1 (AP-1) and Janus kinase-signal transducer and activator of transcription (JAK/STAT). Furthermore, they modulate inflammatory markers including nitric oxide (NO), tumor necrosis factor-alpha (TNF- α), ionized calcium-binding adapter molecule 1 (Iba1), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Moreover, polyphenols mitigate the production of reactive oxygen species (ROS) and regulate the synthesis of SCFAs. Consequently, they facilitate bidirectional communication between the gut and the brain [39]. All this evidence supports a recent study where rat pups with autistic traits showed a reversal of autistic behaviors following treatment with a polyphenol-probiotic complex, which was accompanied by modulation of the biochemical alterations in IL-6, TNF- α , BDNF, 5-HT, AChE, and the granular layer [112].

Therefore, when analyzing the activity of various polyphenols in inflammation and oxidative stress, particularly EGCG has demonstrated high efficacy in regulating APP levels [113]. This could partly explain its significant effectiveness in mitigating inflammation and oxidative stress. One contributing factor is its ability to cross the BBB, which accounts for its remarkable efficacy in protecting cultured cortical neurons against oxidative stress-induced cell death. Specifically, the cerebral accessibility of polyphenols such as quercetin, cyanidin-3-glucoside (C3G), and EGCG in relation to their neuroprotective capacity was evaluated. Primary cortical neuron cultures were exposed to oxidative stress in the absence and presence of the selected compounds, and both neuroprotection and cerebral accessibility through the BBB were assessed. It was seen that the human BBB model was rapidly crossed by EGCG, followed by slower permeation by C3G, while quercetin did not cross the BBB in any case. Hence, among the different polyphenols, EGCG stands out as a particularly promising neuroprotector [114].

Regarding the cytokines most involved in ASD, as already mentioned, the role of IL-8 possibly stands out. It has been seen that the administration of EGC reduces its levels through the inhibition of intracellular Ca^{2+} levels and the activation of ERK1/2 and NF-kappaB pathways. Furthermore, in the colon, EGCG is capable of inhibiting the production of IL-8 cytokines by regulating genes involved in inflammatory pathways. This suggests that EGCG could be useful for the prevention and/or mitigation of colonic disorders present in autism [115].

Finally, it should be noted that elevated levels of reactive oxygen species (ROS), specifically hydrogen peroxide (H_2O_2) and superoxide (O_2^-), are reported in the autistic intestine as a cause of damage to the epithelial tissue [116–118], and EGCG negatively regulates the inflammatory response in inflamed intestinal epithelial cells, largely through a post-transcriptional regulatory mechanism [119].

3.3. Role of EGCG in the metabolic activity associated with dysbiosis in ASD

Regarding the metabolites that can be modified by the action of EGCG, it should be mentioned that this polyphenol has beneficial effects by regulating the production of SCFAs [39]. This fact may be particularly relevant given the prevalent role of these metabolites in the bidirectional communication between the gut and the brain. Agarwala *et al.* (2021) highlight the significance of succinate and butyrate, which are particularly important and found to be altered in individuals with autism due to microbial activity [120]. Concerning succinate, it is known that an imbalanced ratio of succinate production/consumption can lead to intestinal disturbances, which can affect the gut-brain axis to varying degrees [121]. Altered levels of succinate have been observed to result in disrupted calcium homeostasis and dysregulated metabolic functions in autistic individuals [38].

Regarding butyrate, it has been seen that children with ASD have lower levels of butyrate, as well as a decrease in the abundance of taxa producing this metabolite [122]. Butyrate is particularly relevant in ASD as its production mainly derives from the gut microbiome. Butyrate displays potent anti-inflammatory activity that contributes to gut health, regulates intestinal homeostasis and BBB permeability, and modulates the expression of neurotransmitter genes [123,124]. Furthermore, it

positively modulates the impaired mitochondrial function in ASD, characterized by reduced activity of complex IV in the electron transport chain (ETC) [125], including improvements in oxidative phosphorylation and beta-oxidation. These observations have underscored the significant neuroprotective role of butyrate in children with ASD [126]. In fact, it has recently been seen that maternal treatment with butyrate in the BTBR mouse model of ASD rescues social and partially repetitive behavior deficits in the offspring [127]. Thus, proper butyrate production at adequate levels is crucial, and this depends on the correct development of the gut bacterial community. Oral treatment with EGCG has been shown to increase both the abundance of *Akkermansia muciniphila* and its butyrate production [76], potentially reversing the adverse effects resulting from altered butyrate levels in ASD.

On the other hand, among the altered fecal metabolite profiles in children with ASD (not present in neurotypical children), there is an increase in p-cresol, caprate, aspartate, and a reduction in GABA, nicotinate, glutamine, and thymine [128]. Among all these metabolites, p-cresol is a uremic toxin produced by certain strains of *Clostridium spp.*, which has negative biological effects and appears to adversely affect the homeostasis of colonic epithelial cells in children with ASD. When present in excess, p-cresol induces DNA damage *in vitro* and negatively affects the integrity of colonic epithelial cells [129]. In fact, EGCG may have beneficial effects by reversing the activity of this metabolite. In a recent study, it has been seen that an EGCG-enriched diet reduces plasma and urinary concentrations of p-cresol in mice by suppressing the abundance of Firmicutes at the phylum level and Clostridia at the order level [130].

In conclusion, EGCG has an impact on both the intestinal microbiota and variables directly related to the microbiota such as metabolites, inflammation and oxidative stress, which could provide benefits for patients with ASD (Figure 1).

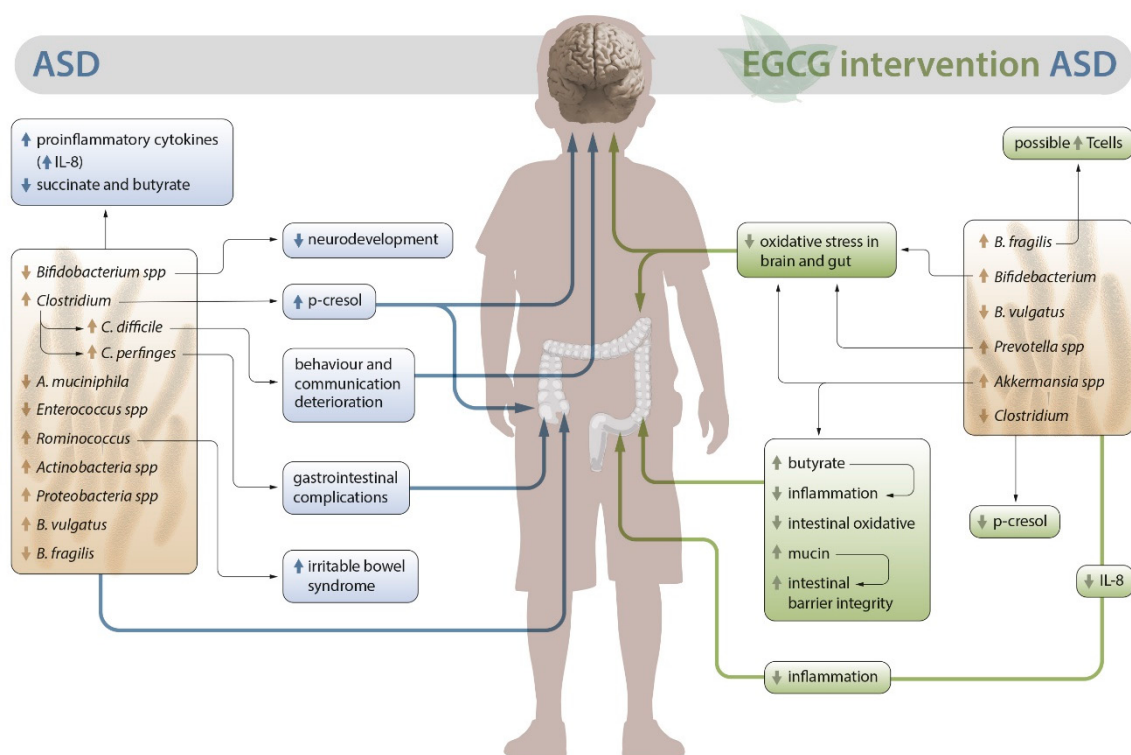


Figure 1. EGCG impact in patients with ASD. Alterations in the intestinal microbiota in ASD and its implications on the left; EGCG impact on both the intestinal microbiota and variables directly related to the microbiota such as metabolites, inflammation and oxidative stress on the right.

It is also interesting to highlight the activity of metabolites that are derived from the polyphenol after its interaction with the intestinal microbiota. Specifically, in rats, the metabolic pathway of EGCG leads to gallic acid (GA) and epigallocatechin (EGC) [131]. EGC is degraded by colonic bacteria to yield microbial ring-fission metabolites, specifically converting to 5-(3',5'-dihydroxyphenyl)- γ -valerolactone (EGC-M5). Then, the bacteria *Adlercreutzia equolifaciens* MT4s-5 and *Flavonifractor plautii* MT42 are capable of degrading EGC. The bacterium *Adlercreutzia equolifaciens* MT4s-5 catalyzes the conversion of EGC to 1-(3,4,5-trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol (EGC-M1), and subsequently, *Flavonifractor plautii* MT42 converts the propan-2-ol to 5-(3,4,5-trihydroxyphenyl)- γ -valerolactone (EGC-M5) and 4-hydroxy-5-(3,4,5-trihydroxyphenyl)valeric acid (EGC-M4). Similarly, EGC-M5 is produced from 1-(3,5-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol (EGC-M3), which is formed from EGC by *Adlercreutzia equolifaciens* MT4s-5 in the presence of hydrogen [120]. A large portion of the formed EGC-M5 is absorbed and undergoes glucuronidation in the intestinal mucosa and/or liver to form EGC-M5 glucuronide (EGC-M5-GlcUA), which is distributed to various tissues through the bloodstream and ultimately excreted in urine [132] (Figure 2).

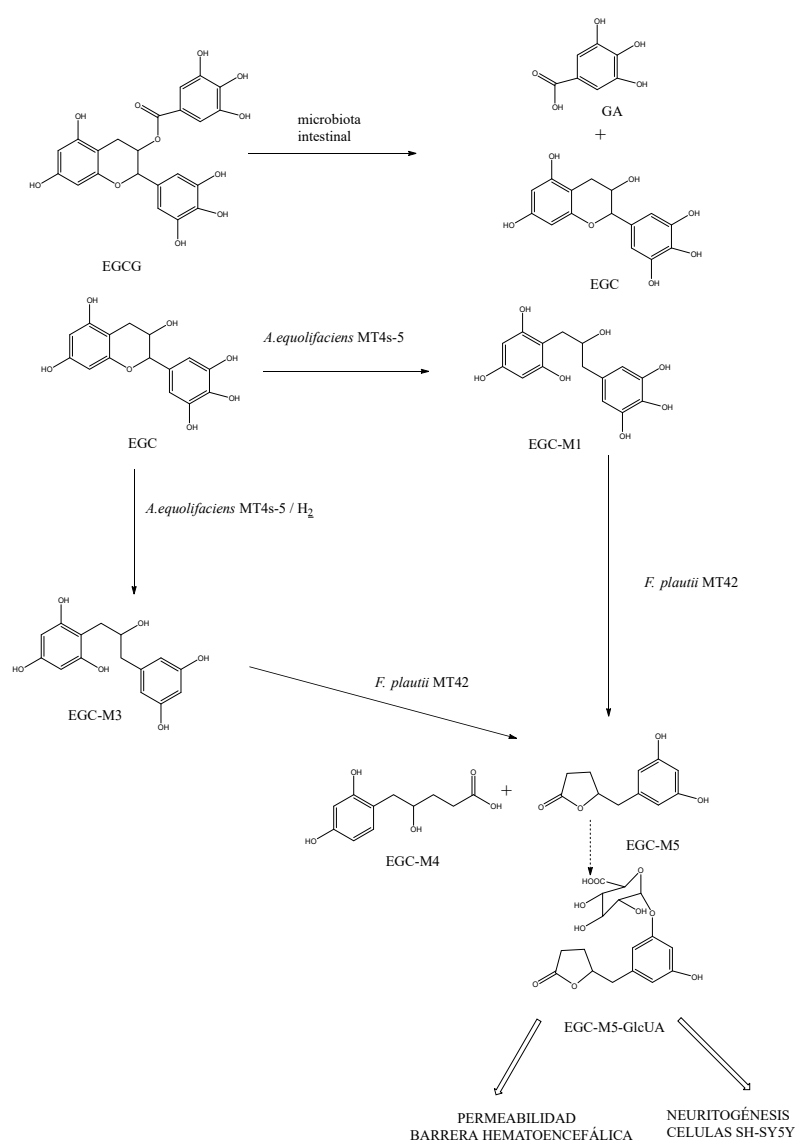


Figure 2. Mechanism of EGCG metabolite generation in the intestinal microbiota. Reciprocal interactions between EGCG and human gut microbiota *in vitro* [56].

The microbial ring-fission metabolites of EGCG are found in plasma in both free and conjugated forms [132], and *in vitro* studies have shown that they may reach the brain parenchyma through the

BBB, promoting neuritogenesis and potentially exerting a relevant activity against the degenerative processes of neurodegenerative diseases. Specifically, when assessing the penetration capacity of these metabolites through the BBB, it has been seen that GA has higher permeability than EGCG and EGC, possibly due to its smaller molecular size [133]. Moreover, comparing only the ring-fission metabolites derived from ECG, EGC-M5 demonstrated greater permeability than its conjugate EGC-M5-GlcUA [131]. Some of these ring-fission metabolites also exhibit anti-inflammatory activity [134]. In particular, EGC-M5 has been found to have immunomodulatory properties, as it enhances the activity of CD4⁺ T cells and the cytotoxic activity of natural killer cells in BALB/c mice [135]. Therefore, it seems evident that the ring-fission metabolites derived from the intestinal microflora of catechins demonstrate a protective capacity against various diseases, including neurodegenerative disorders.

However, it is crucial to understand the metabolic process and bioavailability of green tea catechins and EGCG, particularly in assessing their biological activity and comprehending their beneficial effects on human health. EGCG presents significantly lower bioavailability compared to other components of catechins [136,137]. Therefore, when assessing the activity of EGCG and its metabolites, it is essential to emphasize that their applications are greatly limited due to their low solubility, bioavailability and stability. The use of liposomal formulations may serve as an effective strategy for their administration in autism. Liposomal delivery aims to improve the poor stability of polyphenols against temperature, light, pH and oxygen [28,29], as well as their low permeability across intestinal membranes, which results in only a small proportion of these compounds remaining available for absorption in the human body after ingestion [29,30]. Both stability and oral bioavailability are enhanced through liposomal encapsulation, as it provides protection against degradation when passing through the gastrointestinal tract [31]. Moreover, nanotechnology can promote controlled release of the polyphenol and modulating the interaction between polyphenols and the microbiota, which also represents an intriguing approach [31], and it has been seen that EGCG has significantly improved stability when formulated as dual-drug loaded PEGylated PLGA nanoparticles (EGCG/AA NPs). Following oral administration in mice, EGCG accumulated in all major organs, including the brain, leading to increased synapse formation and reduction of neuroinflammation in Alzheimer's disease [138]. Furthermore, concerning its metabolites and their administration using nanotechnology, Abbasalipour H. *et al.* (2022) studied the neuroprotective effects of gallic acid on oxidative stress-induced cognitive impairment and the expression of the Nrf2/Keap1 gene in an autism model. Gallic acid-loaded nanophytosomes (GNP) were administered, and the results revealed improvements in learning and memory deficits by reducing oxidative stress, enhancing antioxidant enzyme activity and modulating the Keap1/Nrf2 gene expression [139].

4. Conclusions

ASD is a complex disorder characterized by inflammatory processes, high oxidative stress and gastrointestinal disturbances. These issues may be attributed to changes in the intestinal microbiome, resulting in microbial dysbiosis in children with ASD. Polyphenols have demonstrated sufficient antioxidant and anti-inflammatory capacity to counteract ASD symptoms. Their role in dysbiosis has also been studied, revealing their ability to regulate and improve the percentages of beneficial microbial species, thereby enhancing the pathology of ASD and promoting gut-brain axis function, consequently improving brain function. In this regard, EGCG appears particularly effective in improving microbial species and increasing the production of metabolites involved in maintaining epithelial integrity. It also demonstrates effectiveness in reducing inflammation directly linked to ASD by influencing specific pro-inflammatory cytokine levels and reducing oxidative stress. Furthermore, it can modulate the altered metabolic production in ASD by decreasing toxic metabolites such as p-cresol. All of these factors have an impact on brain function, which could provide significant benefits for children with ASD. However, it should be noted that these polyphenols have limitations in terms of intestinal assimilation and bioavailability. Hence, when considering the advantages of nanotechnology in overcoming these limitations, it is advisable to administer them in liposomal form as a complementary treatment for ASD.

Consequently, this review identifies EGCG liposomes as a potential adjunctive therapy for children with ASD, aiming to improve their quality of life and alleviate their symptoms.

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