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POLYPHENOLS AND GUT MICROBIOTA METABOLITES IN AUTISM: PERSPECTIVES FOR NUTRITIONAL MODULATION

POLIFENÓIS E METABÓLITOS DA MICROBIOTA INTESTINAL NO AUTISMO: PERSPECTIVAS PARA MODULAÇÃO NUTRICIONAL

POLIFENOLES Y METABOLITOS DE LA MICROBIOTA INTESTINAL EN EL AUTISMO: PERSPECTIVAS PARA LA MODULACIÓN NUTRICIONAL

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ABSTRACT

Alterations in the microbiota, redox balance, and inflammatory signaling have been investigated in autism spectrum disorder (ASD), increasing interest in nutritional strategies targeting the gut-brain axis. Oxidative stress and neuroinflammation act synergistically in ASD, favoring the activation of inflammatory pathways. Therefore, experimental studies suggest that polyphenols and their metabolites may influence processes related to brain function, including mechanisms involved in memory, cognition, mood, and behavior, constituting a possible avenue of investigation to understand the relationship between diet and manifestations associated with ASD. Polyphenols and microbial metabolites represent a promising area of nutritional research in autism spectrum disorder (ASD), but their potential still requires clinical validation. Controlled clinical trials with standardized protocols and integrated assessment of clinical, metabolic, and microbial outcomes are needed to clarify their mechanisms of action and establish the consistency of potential benefits. Furthermore, the heterogeneity of ASD is a relevant factor in the interpretation of results and the development of individualized nutritional interventions, which may influence the response to polyphenols and microbial metabolites.

Keywords: Autism Spectrum Disorder. Polyphenols. Gut Microbiota.

RESUMO

Alterações na microbiota, no equilíbrio redox e na sinalização inflamatória têm sido investigadas no transtorno do espectro autista (TEA), o que tem ampliado o interesse em estratégias nutricionais voltadas para o eixo intestino-cérebro. O estresse oxidativo e a neuroinflamação atuam de forma sinérgica no TEA, favorecendo a ativação de vias inflamatórias. Nesse contexto, estudos experimentais sugerem que os polifenóis e seus metabólitos podem influenciar processos relacionados à função cerebral — incluindo mecanismos envolvidos na memória, cognição, humor e comportamento —, constituindo

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uma possível linha de investigação para compreender a relação entre a dieta e as manifestações associadas ao TEA. Os polifenóis e os metabólitos microbianos representam uma área promissora de pesquisa nutricional no transtorno do espectro autista (TEA), embora seu potencial ainda exija validação clínica. São necessários ensaios clínicos controlados, com protocolos padronizados e uma avaliação integrada de desfechos clínicos, metabólicos e microbianos, para esclarecer seus mecanismos de ação e estabelecer a consistência de seus potenciais benefícios. Além disso, a heterogeneidade do TEA é um fator relevante na interpretação dos resultados e no desenvolvimento de intervenções nutricionais individualizadas, aspectos que podem influenciar a resposta aos polifenóis e aos metabólitos microbianos.

Palavras-chave: Transtorno do Espectro Autista. Polifenóis. Microbiota Intestinal.

RESUMEN
Se han investigado las alteraciones en la microbiota, el equilibrio redox y la señalización inflamatoria en el trastorno del espectro autista (TEA), lo que ha despertado un creciente interés en las estrategias nutricionales centradas en el eje intestino-cerebro. El estrés oxidativo y la neuroinflamación actúan de forma sinérgica en el TEA, favoreciendo la activación de vías inflamatorias. Por consiguiente, los estudios experimentales sugieren que los polifenoles y sus metabolitos podrían influir en procesos relacionados con la función cerebral —incluidos mecanismos que intervienen en la memoria, la cognición, el estado de ánimo y el comportamiento—, lo que constituye una posible vía de investigación para comprender la relación entre la dieta y las manifestaciones asociadas al TEA. Los polifenoles y los metabolitos microbianos representan un área prometedora en la investigación nutricional sobre el trastorno del espectro autista (TEA), aunque su potencial aún requiere validación clínica. Se necesitan ensayos clínicos controlados, con protocolos estandarizados y una evaluación integral de los resultados clínicos, metabólicos y microbianos, para aclarar sus mecanismos de acción y determinar la consistencia de sus posibles beneficios. Además, la heterogeneidad del TEA es un factor relevante tanto para la interpretación de los resultados como para el desarrollo de intervenciones nutricionales individualizadas, lo cual podría influir en la respuesta a los polifenoles y a los metabolitos microbianos.

Palabras clave: Trastorno del Espectro Autista. Polifenoles. Microbiota Intestinal.

1 INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR), Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in communication and social interaction, as well as the presence of restricted and repetitive patterns of behavior (Batista et al.,2026). Its etiology is recognized as multifactorial, encompassing genetic, epigenetic, and environmental factors, and its heterogeneous presentation results in a significant variability of cognitive, behavioral, and metabolic profiles (AMADI et al., 2022; SCENNA et al., 2026).

In addition to the main neurobehavioral pattern, individuals with ASD present a high prevalence of alterations in eating behavior and gastrointestinal symptoms. Studies estimate that between 49% and 90% of children on the spectrum manifest atypical eating habits, with food selectivity being the most common manifestation, which considerably increases the risk of nutritional deficiencies (ALMEIDA et al ., 2025; LEMES et al., 2023). Favored by behavioral rigidity and alterations in oral sensory sensitivity, selectivity limits the variety of foods consumed. Simultaneously, gastrointestinal disorders such as constipation, diarrhea, and gastroesophageal reflux disease (GERD) occur with high frequency, exacerbating physical discomfort and challenging behaviors (ALMEIDA et al., 2025).

In this context, preclinical and clinical research has directed increasing interest towards the gut-brain microbiota axis, a complex bidirectional network that connects the gastrointestinal tract to the central nervous system through neural, immunological, neuroendocrine, and metabolic pathways (NAUFEL et al ., 2023). Alterations in bacterial composition and diversity , a scenario of intestinal dysbiosis, are related to increased permeability of the intestinal and blood-brain barriers, favoring systemic inflammation and neuroinflammation. The metabolic function of the microbiota is also highlighted, as it is responsible for synthesizing bioactive metabolites that modulate oxidative stress, synaptic function, and the immune response (SCENNA et al, 2026).

In ASD, oxidative stress is a critical factor in the pathophysiology and exacerbation of symptoms, resulting in an imbalance between the production of free radicals and the body's antioxidant capacity. This heightened vulnerability is linked to intrinsic physiological alterations such as reduced glutathione (GSH) levels and impairments in the transsulfuration pathway as well as to dietary intake. Food selectivity and a high consumption of ultra-processed foods limit access to essential exogenous antioxidants. Consequently, an excess of reactive species causes damage to lipids and proteins, while also promoting mitochondrial

dysfunction and neuroinflammation. (MILANI, 2024).

The link between oxidative stress, dysbiosis, and neuroinflammation has prompted the search for nutritional strategies focused on the microbiota-gut-brain axis. Among the options being investigated, polyphenols and their metabolites stand out for their antioxidant and anti-inflammatory actions, helping to neutralize free radicals and inhibit pro-inflammatory pathways (MILANI, 2024; KOSTENKO et al., 2025).

Upon ingestion, polyphenols are metabolized by the gut microbiota, yielding secondary metabolites with greater bioactivity and bioavailability; these are capable of crossing the blood-brain barrier and exerting neuroprotective effects (AMADI et al., 2022). Thus, understanding the interaction between polyphenols and the metabolic function of the microbiota opens new perspectives for complementary nutritional approaches in ASD.

Therefore, the present study aims to analyze the role of polyphenols, phytotherapeutic agents, and microbial metabolites in the intestinal and oral microbiota of individuals with ASD and to discuss their potential as emerging strategies for the development of nutritional interventions

2 THEORETICAL FRAMEWORK

ASD is a neurodevelopmental condition characterized by differences in communication and social interaction, associated with restricted, repetitive patterns of behavior and interests. Although its etiology is multifactorial and the underlying mechanisms are not yet fully understood, evidence suggests that alterations in immune regulation and neuroinflammation may be present in certain subgroups of individuals with ASD. In this context, studies have identified changes in the activity of micróglia cells involved in the central nervous system's immune response as well as in the signaling of pro-inflammatory cytokines, which can interfere with neuronal homeostasis, developmental processes, and synaptic plasticity. However, these findings are heterogeneous, and neuroinflammation cannot be considered a universal feature of the disorder (HUGHES; MORENO; ASHWOOD, 2024).

Oxidative stress is associated with tissue inflammation and neuroinflammation; evidence indicates that it plays a significant role in ASD, potentially exacerbating symptoms and the overall clinical condition. Due to selective eating, characterized by reduced food acceptance, whether stemming from cognitive rigidity, sensory issues, clinical factors, or behavioral patterns, individuals with ASD often have an insufficient intake of micronutrients, rendering them susceptible to oxidative stress (MILANI, 2024).

GSH, a natural antioxidant composed of three amino acids, is linked to glutamate—an excitatory neurotransmitter in the central nervous system (CNS) that is essential for maintaining cellular homeostasis. Excessive concentrations of glutamate in the extracellular environment can lead to excitotoxicity, promoting the production of reactive oxygen species and causing neuronal damage. (MILANI, 2024)

Food selectivity is a challenge frequently observed in individuals with ASD, characterized by a restricted acceptance of food, which may be linked to cognitive rigidity, sensory processing differences, and behavioral issues. The literature indicates that atypical sensory processing is directly associated with an increase in feeding difficulties. (SCHRODER et al., 2022) In a study by Nadon et al. (2011) involving 95 children with ASD, 86% exhibited sensory processing differences; a statistically significant association was observed between the severity of these differences and an increase in dietary restriction. This relationship can contribute to a resistance toward trying new foods—particularly fruits and vegetables, which are important dietary sources—thereby limiting the variety of bioactive compounds consumed by this population. (ESPOSITO et al., 2023)

Polyphenols are a family of phytochemical compounds synthesized by plants, algae, and microorganisms. Flavonoids—a group that includes catechins and anthocyanins—constitute their largest subclass. These compounds are widely found in fruits, vegetables, and nuts/seeds, and they exert protective and regulatory effects directly on the central nervous system (CNS). (PANCHAL; BROWN, 2022)

Through enzymatic hydrolysis, the gut microbiota breaks down polyphenols into intermediate phenolic compounds, which enhances their absorption and bioavailability, while also providing prebiotic and anti-inflammatory benefits. (BIÉ et al., 2023) The metabolites produced by the gut microbiota act as essential chemical messengers within the gut-brain axis, influencing neuronal function, neuroinflammation, mitochondrial bioenergetics, and behavior via neural, neuroendocrine, and immunological pathways. The primary microbial metabolites are short-chain fatty acids (SCFAs), which are produced in the gut through the fermentation of undigested carbohydrates, such as starch and fiber (RISTORI et al., 2019; HORN et al., 2022).

3 METHODOLOGY

This is a narrative review study, in which the search for articles was carried out in September and October 2026, using the Pubmed and Web of Science platforms, considering

articles published between 2016 and 2026, available in English, Spanish or Portuguese, that directly addressed the research topic.

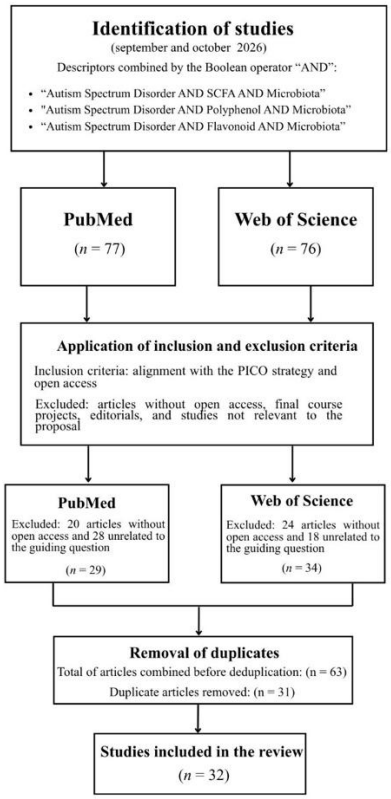
Based on this, the investigation was conducted in virtual databases using MeSH (Medical Subject Headings) descriptors, combined with the Boolean operator "AND": " Autism Spectrum Disorder AND Flavonoid AND Microbiota ", " Autism Spectrum Disorder AND Polyphenol AND Microbiota", "Autism Spectrum Disorder AND SCFA AND Microbiota".

The PICO strategy (SANTOS; PIMENTA; NOBRE, 2007) was applied as follows: P (population): autistic individuals; I (intervention): consumption or supplementation of polyphenols; C (comparison): other natural treatments/strategies with bioactive compounds that influence the oral and intestinal microbiota, placebos or controls; O (outcome/result): antioxidant action, composition of the intestinal microbiota and symptoms related to ASD.

Articles without open access, undergraduate theses, case reports, editorials, and studies irrelevant to the proposal were excluded. (Figure 1)

Figure 1

Flowchart of the process for identifying, selecting, and including studies in the narrative review



Source: Author's own work (2026)

4 RESULTS AND DISCUSSION

Of the articles identified in the databases, a total of 153 articles were found. Of these, 20 were not open access and 28 did not present a theme suitable for the proposal. After removing 4 duplicate articles, 25 articles were selected to compose the final sample.

Table 1 summarizes the selected studies, their characteristics, and methodology.

Table 1

Summary of selected articles on polyphenols, gut microbiota, and SCFAs in ASD.

Study	Design, population and variables evaluated	Key findings
De La Rubia Ortí et al. (2023)	Literature review; ASD and gut microbiota. Discussion of the relationship between EGCG, gut dysbiosis, and ASD. Variables/compounds: Epigallocatechin-3-gallate (EGCG).	EGCG can inhibit potentially pathogenic bacteria, such as Clostridium perfringens and C. difficile, and favor Bifidobacterium spp. and Akkermansia spp.
Jaberi et al. (2024)	Review of neurological diseases related to the gut-brain axis, including ASD. Synthesis of evidence on the interaction of phytochemicals with the gut microbiota, immune system, and neurotransmitters. Variables/compounds: Phytochemicals, including polyphenols and flavonoids.	This study relates intestinal dysbiosis and its potential consequences to gut-brain communication; phytochemicals are discussed as a potential complementary strategy.
Panchal and Brown (2022)	Review of anthocyanins in central nervous system disorders, including ASD. Compilation of evidence on the interaction of polyphenols with the gut microbiota. Variables/compounds: Polyphenols and derivatives; anthocyanins.	Anthocyanins may play a role in reducing oxidative stress and inflammation; their therapeutic potential is promising, but clinical evidence is limited.
Serra et al. (2022)	Study with animals exhibiting behavior similar to ASD. Behavioral tests and analysis of the gut microbiota by sequencing the 16S rRNA gene. Variables/compounds: Blueberry extract rich in anthocyanins.	The treatment increased the abundance of Clostridiales and reduced Lactobacillales, suggesting modulation of the gut microbiota. Studies in humans are needed.
Amadi et al. (2022)	Review of studies in humans with ASD undergoing nutritional interventions. Analysis of nutritional interventions, gastrointestinal symptoms, inflammatory markers, and gut microbiota. Variables/compounds: Antioxidants and phenolic compounds, among others.	Studies with antioxidants report a reduction in inflammatory cytokines and possible improvements in behavioral symptoms.
Horn et al. (2022)	Review on diet and microbiota in psychiatric and neurological disorders, including ASD. Analysis of dietary habits, dietary interventions, and impacts on the gut-brain axis. Variables/compounds: Polyphenols, tryptophan, dietary fiber, and microbial metabolites such as SCFAs.	Diet can affect microbial diversity and influence the brain, with possible anti-inflammatory effects. However, there is insufficient evidence to establish causality.
Ristori et al. (2019)	Review of gastrointestinal symptoms and possible effects of nutritional interventions in ASD. Discussion of how dietary changes can modify the microbiota, metabolites, and gut-brain communication pathways. Variables/compounds: Dietary components, SCFAs, and serotonin (5-HTP).	People with ASD may present with gastrointestinal alterations and changes in the composition of the gut microbiota; diet can modify it and influence the production of SCFAs

Study	Design, population and variables evaluated	Key findings
Taniya et al. (2022)	Review on ASD, gut microbiota, and the gut-brain axis. Discussion of microbiota modulation strategies using microbial compounds and metabolites. Variables/compounds: Dietary fiber, probiotics, prebiotics, and SCFAs.	This study discusses the association between alterations in the gut microbiota and ASD and the possible role of SCFAs in intestinal and neural signaling; it does not establish causality.
Ahmed et al. (2022)	Review of microbiota-derived metabolites and gut-brain communication. Analysis of communication pathways, including immunological, neuronal, and endocrine mechanisms. Variables/compounds: Microbiota-derived metabolites, with emphasis SCFAs.	Microbial metabolites participate in gut-brain communication and can reach the systemic circulation, influencing neural and metabolic processes.
Martin et al. (2018)	Review of preclinical and clinical studies, including animal models, on the gut-brain axis in various pathologies, including ASD. Discussion of evidence on gut-brain communication and strategies for manipulating the gut microbiota. Variables/compounds: Composition and function of the microbiota, microbial metabolites, SCFAs, tryptophan, and serotonin (5-HT).	The microbiota can influence the CNS; SCFAs help maintain the integrity of the intestinal and blood-brain barriers, reducing permeability associated with stress or inflammation.
Lewandowska-Pietruszka et al. (2025)	Observational study with 45 children with ASD, aged 2 to 18 years. Fecal samples and 16S rRNA gene sequencing; microbiota characterization and clinical evaluation. Variables/compounds: Microbial composition and diversity; SCFA-producing bacteria.	It points to a multifactorial relationship between microbiota, diet, and behavioral changes in ASD, including an association between SCFA producing bacteria and gastrointestinal symptoms.
Chamtouri et al. (2023)	Tunisian children with ASD, aged 4 to 10 years, compared with siblings without ASD and children from the general population. Fecal samples; sequencing of the V3–V4 region of the 16S rRNA gene; analysis of alpha and beta diversity and fecal SCFAs. Variables/compounds: Microbial diversity and fecal SCFAs.	Children with ASD presented distinct microbiota profiles; children aged 4–7 years showed higher levels of some SCFAs.
Xiang et al. (2025)	Comparative study with 71 children aged 4 to 12 years: 38 with ASD and 33 with typical development. Fecal samples, 16S rRNA gene sequencing and functional prediction by PICRUST2. Variables/compounds: Alpha and beta diversity, bacterial abundance and SCFAs.	The TEA group showed lower alpha diversity, reduced Firmicutes, and increased Bacteroidetes; functional prediction indicated lower potential for butyrate production and higher potential for acetate and propionate production.
Kalkan et al. (2025)	Narrative review on microbiota, metabolism, metabolic and neurological diseases, including ASD. Discussion of butyrate metabolism and functions, microbiota, and dietary factors related to its production. Variables/compounds: Butyrate, SCFAs, dietary fiber, and resistant starches.	Butyrate contributes to the integrity of the intestinal barrier and may exert anti-inflammatory and immunological effects.
Liu et al. (2025)	Experimental model in mice exhibiting ASD-like behaviors after exposure to valproic acid (VPA). Evaluation of inflammatory cytokines, oxidative stress, and gut microbiota by 16S rRNA gene sequencing. Variables/compounds: Gut microbiota and SCFA-producing bacteria.	Animals exposed to VPA showed deficits in social communication, dysbiosis, and increased levels of IL-1β, IL-6, and TNF-α. Studies in humans are needed.
Deng et al. (2022)	Observational study with 45 children with ASD and 45 with typical development. Evaluation of gastrointestinal symptoms, characteristics related to ASD, fecal SCFAs, and gut microbiota. Variables/compounds: fecal SCFAs and gut microbiota composition.	78% of children with ASD reported gastrointestinal symptoms; higher concentrations of propionic, butyric, and valeric acids were observed, as well as differences in microbial composition compared to controls.

Study	Design, population and variables evaluated	Key findings
Wu et al. (2025)	Animal model exhibiting behavior similar to VPA-induced ASD and a control group. VPA exposure, behavioral and cognitive tests, and microbiota analysis via 16S rRNA gene sequencing. Variables/compounds: SCFAs, producing bacteria, and microbiota diversity.	The microbiota showed reduced alpha diversity and depletion of genera that produce SCFAs.
Zhong et al. (2023)	Animal model with behaviors similar to ASD, compared to controls. Investigation of associations between intestinal dysbiosis, SCFAs, and neurotransmitters in rats subjected to a VPA-induced ASD model. Variables/compounds: fecal SCFAs and metabolites/neurotransmitters in the prefrontal cortex, including tryptophan.	Animals exposed to VPA showed a significant reduction in different SCFAs and tryptophan.
Yang et al. (2026)	Systematic review and meta-analysis of studies with ASD and neurotypical controls. Analysis of 16 studies on the profile of SCFAs in ASD. Variables/composites: Quantitative measurements of SCFAs in observational studies.	Elevated levels of valeric, isobutyric, and hexanoic acids have been reported in people with ASD; differences in acetic, propionic, and butyric acids were not significant.
Dhungel and Bora (2026)	Evidence review on ASD, gut microbiota, and SCFAs. Review focusing on SCFAs and strategies to increase their production. Variables/compounds: SCFAs and producing bacteria.	SCFAs deficiency may be related to dysbiosis and alterations observed in ASD; a reduction in producing bacteria could compromise the intestinal and central nervous system barriers.
Berding and Donovan (2020)	Longitudinal observational study with 58 children aged 2–7 years: 26 with ASD and 32 age- and sex-matched controls. Fecal microbiota by 16S rRNA gene sequencing and SCFAs by gas chromatography; assessment of temporal stability and dietary patterns. Variables/compounds: Microbial diversity and stability, dietary patterns, and SCFAs.	Changes in the microbiota and a reduction in SCFAs were observed during the study; the authors suggest a possible influence of diet and the need to investigate the physiological effects on taxa.
Osredkar et al. (2026)	Cross-sectional study with 229 children: 160 with ASD and 69 controls. Evaluation of fecal SCFAs and tryptophan pathway metabolites. Variables/compounds: total and individual fecal SCFAs and tryptophan pathway metabolites.	The absolute concentrations of total and individual SCFAs and tryptophan pathway metabolites were broadly similar between children with ASD and controls.
Lai et al. (2026)	Review of the pathogenesis of neurodevelopmental disorders, including ASD. Review of the role of metabolites produced or modified by the microbiota in the gut-brain axis. Variables/compounds: SCFAs, tryptophan derivatives, bile acids, and phenolic compounds.	Reports indicate a reduction in specific tryptophan-related metabolites in children with ASD; studies in animal models have demonstrated therapeutic potential.
Jones et al. (2022)	Observational study in children aged 21 to 40 months with early behavioral signs of ASD. Analysis of fecal samples for bacterial and fungal diversity and determination of SCFAs. Variables/compounds: Bacterial and fungal diversity and SCFA concentrations.	Acetic acid concentrations increased with greater severity of autism symptoms; the abundance of bacterial groups also varied. The observational design does not allow for establishing causality.
Son et al. (2026)	Literature review with preclinical and human studies on ASD. Review of the production, functions, and signaling of SCFAs, with emphasis on propionate. Variables/compounds: SCFAs, especially propionate.	The results are heterogeneous, with increases or decreases possibly related to medications, age, diet, and gastrointestinal symptoms.
Melrose (2023)	Narrative review on flavonoids in neurological and neurodegenerative diseases, including ASD. Discussion of flavonoid use, intestinal metabolism, and gut-brain axis mechanisms.	Flavonoids may exhibit antioxidant and anti-inflammatory effects and therapeutic potential; further studies are needed to elucidate the results.

Study	Design, population and variables evaluated	Key findings
	Variables/compounds: Flavonoids and microbial compounds such as quercetin and anthocyanins.	
Shokr, Abu-Elsaoud and Al Raish (2026)	Review of neurological and psychiatric disorders, including ASD. Discussion of oxidative stress, neuroinflammation, mitochondrial function, synaptic plasticity, neurotransmitters, microbiota, and the gut-brain axis. Variables/compounds: Polyphenols, flavonoids, alkaloids, terpenoids, bioactive plant compounds, and probiotics.	Bioactive compounds can modulate processes linked to oxidative stress and inflammation, but they need to be validated by clinical trials.
Avni et al. (2026)	Review on epilepsy and ASD. Analysis of the biological mechanisms related to ASD and epilepsy and the neuroprotective, anti-inflammatory, and microbiota-modulating potential of marine algae compounds. Variables/compounds: Polyunsaturated fatty acids, carotenoids, polyphenols, polysaccharides, and vitamins derived from algae.	Compounds derived from algae exhibit antioxidant and anti-inflammatory properties and the potential to modulate the microbiota; further studies are needed to confirm their therapeutic potential.
Bezawada et al. (2020)	Systematic review of studies with children and adolescents with ASD; included studies had 12 to 104 participants. Systematic review on the role of gut microbiota in ASD; 28 articles included. Variables/compounds: Gut microbiota.	Studies suggest alterations in the gut microbiota in ASD, but more research is needed to clarify cause and effect.
Wang et al. (2019)	Case-control study with Chinese children aged 6–9 years with ASD and controls. Fecal samples; quantification of SCFAs by high-performance liquid chromatography and analysis of association with ASD. Variables/compounds: Total and individual fecal concentrations of SCFAs.	Total and individual concentrations of SCFAs did not differ between TEA and controls; a limitation was the use of only one fecal sample.
Bojović et al. (2020)	Study with 64 children: 36 with neurodevelopmental disorders (including ASD) and 28 controls. Case-control study of fecal microbiota by DGGE of rDNA amplicons. Variables/compounds: Gut microbiota, bacterial diversity, and SCFA-producing bacteria.	The group with neurodevelopmental disorders showed lower diversity and an increase in potentially harmful bacteria, such as Romboutsia. There was no significant difference in SCFAs; the sample with ASD was small (n=5).
Selta et al. (2026)	Review of psychiatric and neurodevelopmental disorders. Literature analysis from 2005 to 2026 on microbiome-based strategies for the treatment of mental health disorders. Variables/compounds: Psychobiotics, SCFAs, probiotics, and fecal microbiota transplantation (FMT).	Initial studies suggest potential benefits in conditions such as ASD, but the literature is limited and derives in part from animal models with short interventions.

Source: Author's own work (2026)

4.1 CHANGES IN THE GUT MICROBIOTA IN ASD

Considering that ASD is a neurodevelopmental condition for which there is currently no treatment, only the use of medications to address its specific symptoms and clinical manifestations, non-pharmacological therapeutic strategies, including nutritional interventions, have been attracting increasing interest, especially given the possible interactions between diet, gut microbiota, metabolism, and brain function. (DE LA RUBIA ORTÍ et al., 2023)

Intestinal dysbiosis is frequently associated with ASD, as is increased intestinal permeability (MARTIN et al., 2018). The literature has already demonstrated alterations in the composition of the intestinal microbiota in individuals with ASD, such as an abundance of Clostridia and Desulfovibrio bacteria and a lower proportion of Bacteroidetes to Firmicutes than typical individuals (DE LA RUBIA ORTÍ et al., 2023; LEWANDOWSKA-PIETRUSZKA ET AL. 2025).

Dietary patterns, such as a diet rich in grains, are more associated with alterations in microbiota composition, with an increase in the abundance of the genus Prevotella. These findings reinforce the possibility that dietary factors contribute to the modulation of the intestinal microbiota and, consequently, its metabolites. This corroborates other findings that demonstrate that the relative abundance of Proteobacteria evaluated in 11 assays was found in individuals with ASD (DE LA RUBIA ORTÍ et al., 2023). Conversely, we have studies that demonstrate lower levels of Prevotella in this population (BEZAWADA et al., 2020).

A clinical trial was conducted with 18 individuals, lasting 2 years, where the treatment also included fecal microbiota transplantation. An increase in the relative abundance of Bifidobacterium and Prevotella was observed in all 18 participants. (TANIYA et al., 2022) It was also found that patients with ASD generally presented higher levels of the genera Lactobacillus, Ruminococcus, Escherichia, and Shigella than neurotypical individuals. Another study analyzed the differences in microbiota composition between children with ASD and their siblings, with the main finding being a reduction in the abundance of Bifidobacteriaceae and an increase in Coriobacteriaceae and Collinsella in children with ASD, in contrast to the lower abundance of Bifidobacterium, which reinforces the difference in the microbiota of individuals with ASD compared to other individuals. (DE LA RUBIA ORTÍ et al., 2023)

4.2 INTERACTION BETWEEN POLYPHENOLS, GUT MICROBIOTA, AND OXIDATIVE STRESS IN ASD

Studies have suggested that supplementation with antioxidant compounds, including polyphenols and flavonoids, may contribute to the improvement of some symptoms associated with ASD, a condition correlated with reduced antioxidant capacity, increased oxidative stress, accumulation of reactive oxygen species (ROS), and an effect on neuroplasticity, in addition to presenting greater vulnerability to oxidative stress due to imbalances in glutathione (GSH) concentrations and a lower glutathione storage capacity

compared to neurotypical individuals (DE LA RUBIA ORTÍ et al., 2023; SHOKR; ABU-ELSAOUD; AL RAISH, 2026).

Oxidative stress and neuroinflammation act synergistically in ASD, favoring the activation of inflammatory pathways. Therefore, experimental studies suggest that polyphenols and their metabolites may influence processes related to brain function, including mechanisms involved in memory, cognition, mood, and behavior , constituting a possible avenue of investigation to understand the relationship between diet and manifestations associated with ASD. (DE LA RUBIA ORTÍ et al., 2023; MELROSE, 2023)

Among phytochemicals, flavonoids also exhibit properties that may be relevant to neurological function, where experiments with animal models have demonstrated that these compounds can reduce oxidative stress and neuroinflammation, such as activation of the Nrf2 pathway and blockade of the pro-inflammatory NF-kB pathway (JABERI ET AL. 2024; MELROSE, 2023; AVNI et.al, 2026).

Furthermore, flavonoids promote increased activity and expression of free radical neutralizing enzymes, such as superoxide dismutase (SOD), glutathione, and glutathione peroxidase, reducing total ROS levels, in addition to inhibiting free radical generating enzymes. (MELROSE, 2023; AVNI et al., 2026).

Polyphenols are a broad class of bioactive compounds present in fruits, vegetables, teas, cocoa, nuts, and other plant-based foods. Some of these compounds reach the intestine in their original form or as metabolites, where they can interact with the microbiota, resulting in the formation of bioactive metabolites and simultaneously modifying the composition and functional activity of microbial communities. (DE LA RUBIA ORTÍ et al., 2023) A systematic review published in 2022 examined diets rich in antioxidants and polyphenols as potential treatments for ASD, highlighting that these compounds are metabolized by the gut microbiota into bioactive antioxidant metabolites. (AMADI et al., 2022)

Epigallocatechin-3-gallate (EGCG), the main catechin present in green tea, is one of the polyphenols that has been investigated for its interaction with the gut microbiota. Experimental studies, especially in animal models, suggest that EGCG can promote changes in the composition of the gut microbiota and favor the presence of certain bacterial groups, in addition to interfering with the production of microbial metabolites. Among the possible effects described is the modulation of bacteria associated with the production of SCFAs, such as acetate, propionate, and butyrate. These metabolites play relevant roles in maintaining intestinal homeostasis and regulating immunological and inflammatory processes, and may

constitute one of the possible pathways through which the microbiota participates in communication between the gut and the central nervous system. (DE LA RUBIA ORTÍ et al., 2023)

This compound has also been associated with improved behavioral symptoms and gut microbiota in children with ASD. (AVNI et al., 2026) Furthermore, bioactive compounds from Camellia sinensis, mainly catechins, exert neuroprotective effects, modulating inflammatory pathways, improving SCFA production and consequently improving insulin sensitivity and reducing inflammation (SHOKR; ABU-ELSAOUD; AL RAISH, 2026)

Another polyphenol that has sparked interest in this area is quercetin, a flavonoid widely distributed in foods such as onions, apples, and red fruits, and has the ability to interact with the gut microbiota and be metabolized by microorganisms, giving rise to compounds that may have biological properties distinct from the original compound (AMADI et al., 2022). This compound is also associated with the attenuation of ROS and activation of the Nrf2 pathway, helping to improve oxidative stress (AVNI et al., 2026).

Some studies also describe that anthocyanins have been associated with the modulation of different physiological processes, through the inhibition of monoamine oxidases (MAO) and mitochondrial enzymes responsible for catalyzing the oxidation of monoamines, reducing the generation of reactive species in the brain (PANCHAL; BROWN, 2022). Another study evaluated whether this could reduce behaviors similar to those observed in ASD in mice and whether these effects could be related to the microbiota-gut-brain axis. After three weeks of treatment, the animals showed partial improvement in social interaction and behaviors; however, it is important to note that not all behaviors were reversed, thus there was an attenuation of symptoms. Analysis of the gut microbiota by 16S rRNA gene sequencing showed an increase in the abundance of Clostridiales and a reduction in Lactobacillales, suggesting modulation of the microbiota (SERRA et al., 2022).

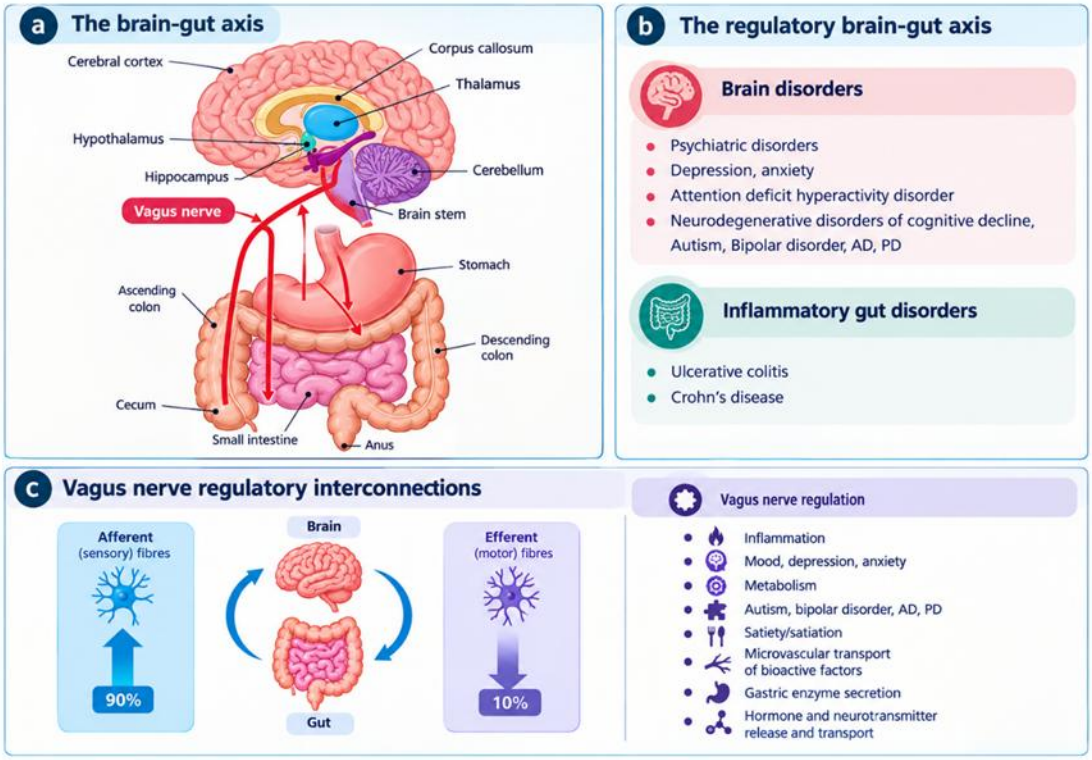
In a clinical trial, children with ASD in Greece received a formulation containing two polyphenols, luteolin and quercetin, for 26 weeks. At the end of the intervention, a significant reduction in IL-6 and TNF concentrations was observed, indicating a possible effect on markers related to inflammation. Furthermore, the use of a formulation containing flavonoids and luteolin in children with ASD between 4 and 10 years of age was associated with improved behavioral aspects after 26 weeks of intervention. (DE LA RUBIA ORTÍ et al., 2023)

Neuroinflammation is recognized as a central factor in ASD, with elevated levels of pro-inflammatory cytokines, including IL-6, IL-1, and TNF, as well as intestinal permeability,

potentially allowing harmful substances to cross the blood-brain barrier. (AVNI et al., 2026) Flavonoids have anti-inflammatory and antioxidant properties available to neural cells; thus, gut bacteria have beneficial effects on mood and anxiety, through bioactive compounds that are transported via the vagus nerve to the brain (MELROSE, 2023), as shown in Figure 2.

Figure 2

Role of the vagus nerve in gut-brain communication and in the regulation of neuroimmune and metabolic functions.



Source: Adapted from Melrose (2023), with graphic elaboration by artificial intelligence (AI).

The interaction between flavonoids and the gut microbiota can also influence the production of biologically active metabolites, including SCFAs which participate in neurochemical signaling and neurotransmitter formation, establishing a possible connection between microbial metabolism, neuronal function, and behavior (JABERI et.al., 2024). where gut bacteria produce SCFAs, which can modulate brain activity and behavior and regulate the serotonergic system (AVNI et al., 2026)

Another polyphenol of interest is resveratrol, which has been investigated for its ability to modulate different components of the gut-brain axis through its participation in pathways related to the serotonergic system, particularly 5-hydroxytryptamine (5-HT), the chemical

name for serotonin. (JABERI et.al, 2024) Research also suggests that this compound has anti-inflammatory action and improves behavioral symptoms, since neuroinflammation can generate behavioral and cognitive deficits. (AVNI et al., 2026)

Together with tryptophan (TRP), an essential amino acid that participates in different metabolic pathways relevant to intestinal and brain function, and is also used by the body as a precursor to serotonin, tryptophan can also be metabolized by intestinal bacteria and is capable of influencing regulation, preventing the excessive release of pro-inflammatory cytokines such as IL-6, thus reducing neuroinflammation (JABERI et.al., 2024 ; HORN et al., 2022). Similar results were found in the work of Lai et al. (2026), where fecal levels of specific metabolites related to tryptophan were decreased in children with ASD.

In contrast, recent evidence from a multiomics analysis by Osredkar et al. (2026) with 226 children does not demonstrate consistent differences between individuals with and without ASD, highlighting the heterogeneity of microbial metabolism in ASD.

Like polyphenols and flavonoids, the gut microbiota can also influence the production and availability of serotonin (5-HT), a process related to diet and, particularly, to the availability of tryptophan, a precursor of this neurotransmitter, impacting serotonergic signaling and potentially the communication established by the microbiota-gut-brain axis. (PANCHAL; BROWN, 2022; JABERI et.al. 2024)

4.3 RELATIONSHIP BETWEEN THE GUT-BRAIN AXIS, SHORT-CHAIN FATTY ACIDS (SCFAS), AND OXIDATIVE STRESS/NEUROINFLAMMATION PROCESSES

Oxidative stress and inflammation processes occur through bidirectional communication of the gut-brain axis, fermentation of non-digestible carbohydrates, generating metabolites known as SCFAs, mainly: acetate, butyrate, and propionate. In cases of dysbiosis, very common in ASD, there is an alteration in the relative abundance of bacteria that produce these metabolites, impacting the permeability of the intestinal mucosa and altering the release of pro-inflammatory cytokines. Depending on the biological context, these alterations can contribute to processes associated with redox imbalance and neuroinflammation (RISTORI et al., 2019).

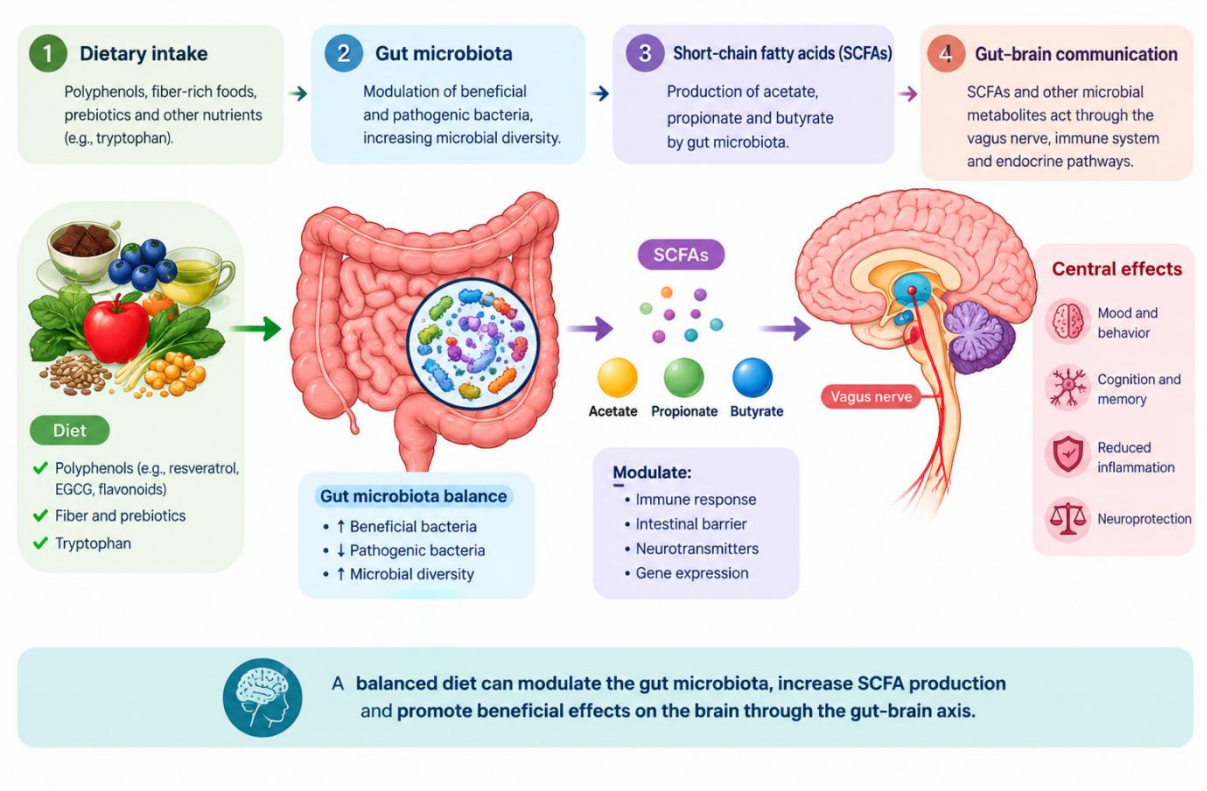
A microbial metabolite that corresponds to SCFAs, which plays an important role in regulating the inflammatory response, is butyrate, produced by certain intestinal microorganisms from the fermentation of non-digestible complex carbohydrates, including

resistant starch. One of its effects is the improvement of intestinal barrier integrity and the modulation of immunological and inflammatory processes. (DE LA RUBIA ORTÍ et al., 2023)

Reduced levels of fecal butyrate and alterations in the abundance of bacterial groups potentially involved in the production of this metabolite in individuals with ASD have been reported. Although these findings do not establish a causal relationship between microbiota alterations, SCFA metabolism, and ASD manifestations, they suggest the existence of mechanisms that deserve investigation, especially considering the role of butyrate in intestinal barrier integrity, immune modulation, and communication via the gut-brain axis (KALKAN et al., 2025; DE LA RUBIA ORTÍ et al., 2023), where SCFAs can modulate central nervous system function through multiple pathways (SELTA et al., 2026), as shown in Figure 3 below.

Figure 3

Relationship between diet, gut microbiota, SCFA production, and communication via the gut-brain axis.



Source: Adapted from SELTA et al., 2026 with graphic elaboration by artificial intelligence (AI).

Evidence that individuals with ASD have an altered SCFA profile was found in the study by Yang et al. (2026), where valeric, hexanoic, and isobutyric acids were increased, but no significant differences were found for acetic, propionic, or butyric acids in general. In

contrast, the work conducted by Berding and Donovan (2020) shows a reduction in all SCFAs analyzed: acetate, propionate, butyrate, isobutyrate, isovalerate, and valerate. Mixed results are also found in the literature review by Son et al. (2026).

In a study conducted by Bojovic et al. (2020), which evaluated 36 children with developmental disorders, including five diagnosed with ASD, lower concentrations of SCFAs were found in the evaluated group, although without statistical significance, which may be due to the small sample size. In contrast to studies that reported alterations in SCFAs in individuals with ASD, Wang et al. (2019), in a case-control study with 45 children with ASD and 90 neurotypical controls, did not identify significant differences in the fecal concentrations of SCFAs evaluated. However, the results are from only one fecal sample.

In children with ASD, alterations in the composition of the gut microbiota and in the SCFA profile can vary according to age and severity of the disorder, with more pronounced alterations observed during early childhood, since in the work of Chamtouri et al., 2023 there were higher levels of propionic acid in children aged 4-7 years, which was not consistent with the 8-10 year age group, although no significant differences were identified in SCFA concentrations when the entire sample was analyzed together.

In the study by Xiang et al. (2025), which analyzed fecal samples from two groups of 10 children with ASD and a control group, alterations were indicated in pathways related to the metabolism of these SCFAs, with a reduction in pathways associated with butyrate biosynthesis and an increase in pathways related to acetate and propionate production. These pathways show upregulation with increased Bacteroidetes, alterations that may decrease the anti-inflammatory butyrate and contribute to behavioral symptoms. In another study, acetic acid concentrations increased with greater severity of autism symptoms, although the observational design does not allow for establishing causality. (JONES et al., 2022) In contrast, propionic acid alone has been associated with oxidative stress and alterations in social behavior in animal models of ASD. (AHMED et al., 2022)

In the study by Liu et al. (2025) using mice exposed to valproic acid (VPA) with the aim of reproducing characteristics similar to ASD, a reduction in bacterial groups associated with the production of SCFAs was revealed, showing an increase in neuroinflammation markers; however, these results are based on functional prediction and not on direct measurement of metabolites.

In comparison to this, the study by Wu et al. (2025) analyzed whether animals exposed to VPA and with characteristics similar to TEA showed a reduction in the alpha diversity of

the gut microbiota and, at the familial level, depletion of SCFA producing taxa, along with an increase in markers of oxidative stress and inflammation, such as increased IL-6.

In contrast, Zhong et al. (2023) found no significant differences in alpha diversity, but SCFAs were reduced in the ASD group, as did the study by Deng et al. (2022), although they hypothesized that these are associated with gastrointestinal symptoms.

5 FINAL CONSIDERATIONS

Based on the evidence analyzed, it is observed that polyphenols show potential for action in ASD, especially in mechanisms associated with oxidative stress and the gut microbiota. Some studies point to possible effects of these compounds in modulating behavioral changes and inflammatory and antioxidant markers, suggesting that they may represent a promising perspective in the context of nutritional interventions.

However, the available evidence is still insufficient to recommend the use of polyphenols or other antioxidants as an established therapeutic strategy for ASD, since the available studies do not demonstrate a consistent microbial signature among the ASD population, highlighting the phenotypic heterogeneity that accompanies the spectrum, as well as the interaction between genetic, environmental, and clinical factors.

Considering, primarily, the predominance of experimental studies in animal models and the limited number of clinical studies in humans, further studies are needed, especially well-designed clinical trials with larger samples, to better understand the role of these compounds in individuals with neuroatypical conditions.

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