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Polyphenols as bioactive food components in relation to autism spectrum disorders: An overview of the literature

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ABSTRACT

Autism spectrum disorder (ASD) known as a set of behavioral and neurocognitive problems that are identified by challenges in difficulties interacting and communicating with others, as well as heightened repetitive and/or restrictive behaviors. Elevated immune reaction and enhancements in pro-inflammatory cytokines have been discovered in the brains of those who have ASD. A recent article associated autism with abnormalities in mitochondrial respiratory control. Based on various studies, mitochondrial dysfunction is caused by oxidative stress, inadequate nutrition, insufficiency of vitamins, compromised immune system, contact with harmful environmental substances, and modified calcium signaling. Polyphenols found in our diet are active compounds that have the potential to prevent and treat various chronic illnesses including, neurodegenerative and neurodevelopmental problems. This is mainly due to their ability to regulate crucial pathways that cause inflammation and oxidation in the body. The application of polyphenols may result in a reduction of neuroinflammation, facilitating an improvement in the manifestations of ASD. This review focused on the preclinical and clinical studies that documented the beneficial impacts of diet related for the modulation of ASD.

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INTRODUCTION

Autism spectrum disorder (ASD) known as a set of behavioral and neurodevelopmental problems that are identified by challenges in social interaction and communication, as well as heightened repetitive and/or restrictive behaviors (1). Over the last years, there has been a significant increase in the occurrence of ASD (2). According to Zeidan et al. (3), 1 in 100 children worldwide are thought to have ASD. ASD has a complicated and incomplete etiology. Studies have linked this complicated illness to both genetic and environmental variables, particularly those affecting prenatal and early childhood growth (4). Although research on twins with ASD has showed a high extent of heredity (38–54%), multiple meta-analyses studies have also demonstrated the existence of genetically unrelated explanations of ASD (5). Present research, nonetheless, proposes that modifications in hormones, amino acids, and various biochemical indicators may function as intermediaries in people with ASD (6,7). Additionally, the underlying pathogenesis of ASD has been hypothesized to include immune system dysfunction, disordered lipid metabolism, altered glutamatergic signaling pathways, and increased vulnerability to oxidative stress (8). Oxidative stress is associated with ASD and may contribute to mitochondrial dysfunction. A recent article links autism to defects in mitochondrial respiratory regulation (9). According to several research, oxidative stress, malnutrition, vitamin deficiencies, weakened immunity, exposure to environmental toxins, and altered calcium signaling all contribute to mitochondrial dysfunction (10-12). In fact, oxidative stress abnormalities and mitochondrial dysfunction are found in several neurological and psychiatric disorders, such as Alzheimer's, Huntington's, Parkinson's, bipolar disorder, multiple sclerosis, schizophrenia, depression, ASD, chronic fatigue syndrome, and aging (13-18). Many studies have shown that people with ASD exhibit immunological problems such as autoimmune manifestations, deficient cell-mediated immunity, misdirected cytokine production, and other soluble immune mediators (19-22).

Although there is no effective treatment for ASD, numerous alternative psychosocial therapies have been prescribed to address both the primary symptoms of ASD and its comorbid symptoms (23). Affected people experience a broad range of symptoms that differ greatly. Each patient receives a unique treatment plan (24). The lack of data on the etiology and primary causes of ASD still limits the ability to discover and implement therapeutic interventions. As a result, efforts have focused solely on treating the comorbidities of the condition (1). Children with ASD are often given antiepileptic drugs, stimulants, antidepressants, and antipsychotics such as risperidone and aripiprazole (25). But numerous long-term negative effects from these medications are anticipated.

The need for safe and effective drugs for proper treatment of ASD is essential. Phytotherapy and food-based treatments are becoming increasingly popular as part of ASD treatment because of the limited options for coping with the disease symptoms, financial concerns, and psychotherapeutic adverse reactions (26-28). Having fewer adverse effects, appropriate herbal remedies may lessen ASD clinical symptoms (25). Within the category of external antioxidants, numerous plants and edibles encompass polyphenols, a type of bioactive compound that is soluble in water (such as flavonoids, tannins, hydroxycinnamate esters, and lignin). Their higher reactivity as hydrogen or electron donors, capacity to stabilize and delocalize unpaired electrons, and ability to bind transition metal ions all contribute to their antioxidant characteristics (29). Polyphenols are unique substances that have proven highly effective in the prevention and treatment of a variety of chronic diseases, neutralizing oxidative stress, inflammation, and other pathological conditions, including neurodegeneration. The ability of these dietary polyphenols to fight and prevent neurodegenerative problems is attributed not only to their ability to enter the brain, which depends on their chemistry and direct interaction with brain cells, but also to their abilities to regulate the communication between the gut and the brain (30). An enduring subclinical inflammation impacting both the gastrointestinal tract and the central nervous system could potentially give rise to the manifestations of ASD (31). In the brains of autistic people, heightened immune response and increases in pro-inflammatory cytokines have been discovered (32). The treatment with polyphenols may result in reduced neuroinflammation, thereby encouraging an amelioration in the ASD symptoms. However, there is few data that suggests polyphenols as a class of natural chemicals crucial for reducing ASD symptoms. This review focused on preclinical and clinical studies that documented beneficial impacts of dietary polyphenols for the modulation of ASD.

Beneficial Impact Of Resveratrol On ASD

Resveratrol is a polyphenol phytoalexin found in grapes, berries, peanuts and wine. Since resveratrol can control mitochondrial activity and malfunction, which are frequently found in ASD patients, it may be a promising chemical for treating ASD symptoms (29, 33). Resveratrol injection for 12-13 days in a valproic acid model of ASD protects or attenuates from sensorial and social deficits (34-36). Oral resveratrol administration restored normal behavior, including social interaction and stereotype in the propionic acid model of ASD, as well as other behavioral changes that were also replicated in the propionic acid animal model, including hyperlocomotion, anxiety, spatial learning, memory, and depressing behaviors (37).

According to a new study, resveratrol can be used to understand the pathophysiology of ASD. Resveratrol, 3.6 mg/Kg, was injected subcutaneously daily during pregnancy had significant protective benefits against valproic acid-induced substantial disorganization in the medial prefrontal cortex (mPFC) neuronal cytoarchitecture. Resveratrol lowered the occurrence and ratio of somatostatin+, parvalbumin+, and calbindin+ neurons (subregion-specific way) (38).

Numerous epidemiological research suggested a potential link between maternal hormone therapy and ASD (39-40). Consequently, resveratrol was examined with prenatal and postnatal exposure to progestins. Resveratrol (20 mg/kg) administered orally for a month was found to alleviate the repetitive behavior assessed by the marble burial technique in male rats and social communication in both sexes (41).

Consistent with results from experimental models of ASD, resveratrol has been shown to support mitochondrial long-chain fatty acid oxidation (mtFAO) in cultured human fibroblasts from individuals with hereditary FAO abnormalities. In fibroblasts with carnitine palmitoyl transferase 2 (CPT2) gene mutation, resveratrol increases CPT2 activity and returns FAO rates to normal (42). Resveratrol may improve mtFAO in human FAO-deficient cells, according to similar effects that have already been observed in fibroblasts from individuals with long-chain acyl-CoA dehydrogenase impairment (43). Resveratrol markedly boosted the fibroblasts mtFAO isolated from ASD-diagnosed individuals (10 kids aged 7.4-3.2 years) and the control children (5 children of comparable age who did not display any recognized medical ailments or hereditary issues). The significant mtFAO modifications in reaction to resveratrol had been witnessed in fibroblasts extracted from individuals with ASD who displayed much pronounced manifestations on the Social Responsiveness Scale overall, as well as the awareness, communication, motivation, and cognition subcategories (44).

Resveratrol was investigated as a potential treatment drug in the autism BTBR genetic model (45-48). Resveratrol (20–40 mg/kg, i.p.) suppresses the persistent self-grooming noticed in BTBR mice (as a surrogate for stereotypies and repetitive actions in kids diagnosed with ASD) (46). ASD etiology may be influenced by hereditary defects in the mouse oxytocin receptor gene. Injections of resveratrol reduced the social deficits observed in oxytocin receptor gene knockout mice. Resveratrol supplementation increased the expression of the early growth response factor 3 (Egr3) and silent information regulator 1 (Sirt1) genes in the amygdala of oxytocin receptor-deficient mice (49).

The outcomes of a double-blind, placebo-controlled randomized trial that examined the possible medicinal benefits of resveratrol plus risperidone on irritability in individuals with ASD (average age eight years) was recently published by Hendouei et al. (50). Risperidone, a medication for antipsychotic purposes, is utilized in ASD to manage linked behavioral shortcomings, was administered to all the study participants. At the same time, the experimental group only began receiving resveratrol 250 mg twice daily. The results were compared to those of a placebo group administered only risperidone. At the initial, week 5, and week 10, a comprehensive evaluation was conducted on all participants to determine any behavioral symptoms related to ASD. The participant who were administered resveratrol exhibited a significant decrease in scores related to hyperactivity and non-compliance, which was a secondary outcome. Nonetheless, the enhancements observed in the primary outcome (anxiety) and 3 ancillary outcomes (lethargy/isolation, repetitive actions, and improper communication subscales) among the resveratrol treated participants were markedly indistinguishable from

those of the placebo participants. They were virtually equivalent, and the improvements were similar. Anxiety (25.8%), constipation (19.3%), and loose stools (19.3%) were the primary probable side effects observed in the children who were given resveratrol, and they did not vary significantly from those experienced by the placebo children. The tolerability of resveratrol was indicated by the similarity in the occurrence of extrapyramidal symptoms and weight gain with risperidone, observed in both the placebo and resveratrol groups of children.

Trans-resveratrol is an effective compound that can be used for extensive research on ASD, investigating both behavioral and molecular pathways. A pilot study, which was published recently with an open-label approach, examined the safety and potential benefits of trans-resveratrol in managing behavioral disorders and eight microRNAs concerning the immune system in children with an autism diagnosis. The study, included five male children (ages 10 to 13) diagnosed with ASD. They were administered 200 mg/day of trans-resveratrol over 90 days (51). Following the administration of trans-resveratrol, there was a significant decrease in the total score of both the Aberrant Behavior Checklist and Irritability ($p<0.05$), while the subscales measuring Stereotyped Behavior, Hyperactivity, and Lethargy/Social Withdrawal were unchanged. Three of the kids showed notable progress in their behavior, as evaluated using the Clinical Global Impression Scale, one had a slight improvement, and the other had no changes. An essential regulator of inflammatory and immune pathways, microRNA-195-5p, was significantly upregulated by the trans-resveratrol therapy ($p<0.05$). Administration of trans-resveratrol had no negative effects or impact on clinical laboratory tests outcomes.

Studies on the capability of resveratrol to mitigate symptoms of ASD were outlined (Table 1).

Table 1: Studies on the capability of resveratrol to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	Wistar rats	RES (3.6 mg/kg) daily subcutaneous injection	E6.5-E18.5 (13 days)	Improved social behavior	(34)
VPA	Wistar rats	RES (3.6 mg/kg) daily subcutaneous injection	E6.5-E18.5 (13 days)	-Enhanced sensory behavior -Stopped the changes in the WNT behavioral assay -Maintain the arrangement of cortical layers and the dispersion of PV-positive cells in the PSSA -Restored the usual ratio of GABAergic PV-positive neurons in the amygdala -Maintained protein expression level of gephyrin in PSSA	(35)
VPA	Wistar rats	RES (3.6 mg/kg) daily subcutaneous injection	E6.5-E18.5 (13 days)	-Prevented reduced total reciprocal social interaction -Prevented miR134–5p upregulation	(36)
PPA	Sprague-Dawley rats	RES (5, 10, and 15 mg/kg) daily oral	Day 2-day 28 (4 weeks)	-Recovered in a manner that relied on the dosage, all the impairments relating to neurological, sensory, behavioral, biochemical, and molecular aspects -TNF-α and MMP-9 expressions were reduced, oxidative-nitrosative stress was inhibited, and mitochondrial function was hampered.	(37)
VPA	Wistar rats	RES (3.6 mg/kg) daily subcutaneous injection	E6.5-E18.5 (13 days)	-Safeguarded from VPA-triggered disruption in the neuronal cytoarchitecture of the mPFC. -Reduced SOM+ neuron incidence and the ratio of	(52)

				SOM+, PV+, and CB+ neurons in a certain subregion	
Progestin	Sprague-Dawley rats	RES (20 mg/kg) daily oral	For 4 weeks (28 days)	-Ameliorated ASD-like repetitive behavior -Prevented progestin-reduced ERß expression in the amygdala -Stimulated ERß leading to the activation of its designated genes, through the process of demethylating DNA and histones on the ERß promoter -Reduced progestin-triggered oxidative environments and the impairment of brain mitochondria and altered lipid metabolism	(41)
The VLCAD- and CPT2-deficient human skin fibroblasts	Human skin fibroblasts	In vitro 75µM RES	48h	- Elevated FAO flow in human fibroblasts (dependent on dosage and duration) -Restored typical FAO abilities in a group of human' fibroblasts with mild variations (carrying diverse haplotypes) of CPT2 or VLCAD insufficiency	(42)
The VLCAD- and CPT2-deficient human skin fibroblasts	Human skin fibroblasts	In vitro 75µM RES	48h & 72h	-Increased palmitate oxidation in control and VLCAD- and CPT2-deficient human skin fibroblasts -Restored normal FAO rates in all the cells treated for CPT2 or VLCAD deficiency -A three-day therapy involving RSV restored the production of long-chain acylcarnitine in all treated cells with CPT2 or VLCAD deficiencies	(43)
Human skin fibroblasts	Human skin fibroblasts	In vitro 75µM RES	48h	-More activity on the mtFAO -The greatest mtFAO variations in reaction to RSV were noticed in fibroblasts derived from individuals with more pronounced indications on the Social Responsiveness Scale overall score and its subscales such "Awareness, Cognition, Communication, and Motivation".	(44)
Genetic models	BTBR and C57BL/6 mice	RES (20 & 40mg/kg) daily intraperitoneal injection	7 days	-Decreased the CCR and CXCR production and expression in CD4+ T cells -CCR and CXCR mRNA expression levels in the	(45)

				spleen and brain tissues were reduced -Down regulated the chemokine receptor levels	
Genetic models	BTBR and C57BL/6 mice	RES (20 & 40mg/kg) daily intraperitoneal injection	7 days	-BTBR mice exhibit less repetitive behavior (self-grooming) - Stimulation of Foxp3+ and decrease of IL-17A+, GATA-3+, and T-bet+ expression in CD4+ lymphocytes -Enhanced Foxp3 mRNA expression and reduced levels of GATA-3, IL-17A, T-bet, and RORγt expression in the spleen and brain tissues -Reduced the protein expression of GATA-3, IL-17, RORγ, and T-bet while enhancing BTBR and Foxp3 in C57BL/6 rodents	(49)
Genetic models	BTBR and C57BL/6 mice	RES (20 & 40mg/kg) daily intraperitoneal injection	7 days	-Decrease in the number CD4+ T cells secreting IL-6+ production -Decrease in IL-6 mRNA compared to B6 and protein expression compared to BTBR in the brain tissue -Decrease in TNF-α mRNA and protein expression compared to BTBR in the brain tissue -Decreased mRNA expression and protein level of IFN-γ in BTBR brain tissue -Inhibited JAK1 expression -Decreased in the count of CD4+STAT3+ cells in BTBR	(47)
Genetic models	BTBR and C57BL/6 mice	RES (20 & 40mg/kg) daily intraperitoneal injection	7 days	-Reduced mRNA and protein levels of TLR2, TLR3, TLR4, NF-κB, iNOS, and COX-2 in brain tissue	(48)
Genetic and VPA	Oxtr-KO and mice	Prenatal treatment with RES intraperitoneal injection at 30 mg/ kg Oxtr-KO and VPA mice	24 h before the three-chamber test	-Reversed the social impairments caused by Oxtr gene deficiency and VPA -Increased the expression of Sirt1 in amygdala of Oxtr-KO mice but not VPA-ASD mice	(49)
Double-blind, placebo-controlled randomized clinical trial (January 2018 - April	Human (62 patients)	RES dosage was 250 mg twice daily	10 weeks	-Declined hyperactivity/non-compliance	(50)

2019)					
Open-label pilot trial	Human (5 boys)	RES 200 mg/day	12 weeks	-Diminished the overall score of Aberrant Behavior Checklist and decreased the level of Irritability -Improved the behavior on the Clinical Global Impression scale -Increased the miR-195-5p	(51)

ASD: Autism spectrum disorder; VPA: Valproic acid; E: Embryonic day; RES: Resveratrol; WNT: Whisker nuisance task; PSSA: primary somatosensory area; PV+: Parvalbumin+; PPA: Propanoic acid; TNF-α: Tumor necrosis factor-alpha; mPFC: Medial prefrontal cortex; CB: Calbindin; SOM+: somatostatin+; VLCAD: Very long chain acyl-CoA dehydrogenase; CPT2: Carnitine palmitoyl transferase 2; FAO: fatty acid ß-oxidation; CCR: C-C chemokine receptor; CD4+: Cluster of differentiation 4-positive; IL-6: Interleukin 6; IFN-γ: Interferon-gamma; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; TLR: Toll-like receptor; NF-κB: Nuclear factor-κB; iNOS: Inducible nitric oxide synthase; COX-2: Cyclooxygenase-2; Sirt1: Silent information regulator 1; miR-195-5p: MicroRNA-195-5p; Oxtr-KO: Oxytocin receptor gene knockout; MMP-9: Matrix metalloproteinase-9; CXCR: C-X-C motif chemokine receptor

Beneficial Impact Of Curcumin On ASD

Curcuminoids, which include curcumin and its mono and dimethoxy derivatives, are a type of hydrophobic polyphenol that are derived from the rhizome of the turmeric plant (Curcuma longa) (53). Curcumin is a non-toxic compound that has the ability to traverse the blood-brain barrier (54). Several research have emphasised its numerous pharmacological properties, including its anti-inflammatory, antioxidant, anti-carcinogenic, and neuroprotective properties. Additionally, curcumin is believed to have beneficial effects on the therapies of ASD because it interferes with a number of cellular events. Some of its impacts consist of increasing the concentrations of reduced glutathione, mitochondrial impairment, reactive oxygen and nitrogen species decreasing proinflammatory elements, and protein destruction, preventing serious toxicity induced by heavy metals, and aiding the liver's detoxification procedures (55-56).

In a valproate-rat model of autism, Shu-juan et al. (57) demonstrated that curcumin has the potential to be a neurotherapeutic agent by decreasing autistic behavior and increasing brain-derived neurotrophic factor levels. The ASD rat's social behavior was dramatically increased by curcumin, and its latency to social activity was decreased along with its tendency to repeat behavior. Curcumin elevated the integral optical density values of brain derived neurotrophic factor in the cerebral cortex of autistic rats.

The rats with ASD induced by propanoic acid exhibited neurological, behavioral, biochemical, and molecular abnormalities, which were significantly and dose-dependently reversed post curcumin treatment (4 weeks daily). Curcumin supplementation also recovered many sociability indicators in rats with propanoic acid-induced ASD. By reducing oxidative-nitrosative stress, mitochondrial dysfunction, TNF-α and matrix metalloproteinase-9 (MMP-9) in rats with ASD caused by PPA, curcumin repaired the main and related symptoms of autism (24). The therapeutic effect of curcumin is remarkable in reducing the neurological damage associated with prenatal valproic acid-induced ASD in rats. Curcumin can also help with delayed maturation and abnormal brain weight (58).

In BTBRT+ltpr3tf/J (BTBR) mice model of ASD, Zhong et al.(59) studied the impact of neonatal curcumin therapy on behavior and hippocampus neurogenesis. Treatment of neonatal with curcumin reduced repetitive behaviors, raised sociability, and lessened cognitive deficits in BTBR mice with ASD-related traits. Moreover, neonatal curcumin therapy significantly improved the inhibition of hippocampus neurogenesis in BTBR mice, resulting in an improvement in neurogenic activities and a boost in NPC development. Recently (60) showed that, in BTBR mice, which are employed as an idiopathic in vivo rodent model of ASD, curcumin reduces abnormal oxidative stress (as it increased the cerebral cortex concentration of superoxide dismutase and catalase) and ameliorates ASD-like symptoms (improved the social impairments without changing locomotors activity or anxiety-like behaviors). In vitro, curcumin potentiates α7-nicotinic acetylcholine receptors in the brain of the whole cell patch clamp model.

Daily use of curcumin in the diet has been demonstrated to increase synaptic plasticity and enhance cognitive function. The proof supporting the neuroprotective properties of curcumin is adequate to justify its use in forthcoming investigations pertaining to autism and other connected ailments, notwithstanding the absence of convincing evidence from clinical trials validating curcumin's effectiveness in humans (61).

Studies on the capability of curcumin to mitigate symptoms of ASD were outlined (Table 2).

Table 2: Studies on the capability of curcumin to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	Rats	Curcumin (10 g/L) daily intraperitoneal injection	2 weeks	-More rats engaging in social behavior -Reduced lag time for social behavior -Decreased repetitive behavior -Elevated BDNF levels in the temporal cortex	(55)

PPA	Sprague–Dawley rats	Curcumin (50, 100, and 200 mg/kg) daily oral	4 weeks	-Reduced the non-social interaction -Increased duration of interaction with foreigner 2 in social novelty test -On the social preference test, more time was spent with the rat than the object -Reduced the repetitive self-grooming -Increased duration of interaction with unfamiliar male and female social partner in partition test - Reduced brain lipid peroxidation and nitrite -increased brain glutathione, superoxide dismutase and catalase -Increased cytochrome c oxidase enzyme -reduced TNF-α and MMP-9	(25)
VPA	Wistar rats	Per oral 1 ml of curcumin (1g/kg) at 7 days after birth	Single dose	-Preserved normal body and brain weight -Restored normal levels of IFN-γ, 5-HT, glutamine CYP450, IL-6 and glutamate	(58)
Genetic models	C57BL/6J (C57) and BTBR mice	Curcumin daily intraperitoneal injection at 20 mg/kg	From P6 to P8	-Increased the sociability of and reduced repetitive behaviors -Rescued short-term memory deficits -Enhanced NPC proliferation in the DG -Rescued inhibited NPC differentiation	(59)
Genetic models	BTBR T + Itpr3tf/J (BTBR) mice	Curcumin daily intraperitoneal injection at 25, 50, and 100 mg/kg	28 days	-Increased sociability index -Increased SOD in the hippocampus -Increased CAT in the cerebellum	(60)

ASD: Autism spectrum disorder; PPA: Propanoic acid; MMP-9: Matrix metalloproteinase-9; VPA: Valproic acid; IFN-γ: Interferon-gamma; 5-HT: 5-hydroxytryptamine; CYP450: Cytochrome P450; IL-6: Interleukin 6; P: Postnatal day; NPC: Neural progenitor cells; DG: Dentate gyrus; Superoxide dismutase; CAT: Catalase; BDNF: Brain derived neurotrophic factor; TNF-α: Tumor necrosis factor-alpha

Beneficial Impact Of Anthocyanins On ASD

Anthocyanins are naturally active hydrophilic flavonoids belonging to the phenolic compounds among the primary groups of fruits and flowers colorants (orange, red, purple, and blue hues) (62-63). Anthocyanins offer a broad spectrum of medicinal advantages, encompassing antioxidative and anti-inflammatory characteristics, as well as the potential to avert chronic diseases associated with aging, such as cancer, heart disease, and ocular disorders. Additionally, anthocyanins exhibit antiviral effects (64). Anthocyanins and their byproducts are additionally valuable in the treatment of neurodegenerative ailments as a result of their antioxidant characteristics, roles in maintaining calcium balance, and ability to balance pro-survival and pro-apoptotic signals (65-66). Treatments in people of all ages who consume anthocyanin-rich foods have exhibited encouraging outcomes in cognitive function, both over extended and shorter durations (67). Research has established a connection between anthocyanin and the maintenance of gastrointestinal microbiota, which is associated with safeguarding towards neuroinflammation by encouraging the kynurenine pathway's role in tryptophan metabolism (68).

A recent study conducted by Serra et al. (69) has suggested that anthocyanins derived from blueberries grown in Portugal could be an effective means of mitigating ASD symptoms by modulating the microbiota-gut-brain axis. The administration of anthocyanin-rich extracts not only reduced ASD-like behaviors in mice that had been exposed to valproic acid while in utero but also boosted serotonin levels in both the gut and cerebral prefrontal cortex, lowered inflammation in the gut and nervous system, and improved synaptic dysfunction in ASD-afflicted mice (30).

Studies on the capability of anthocyanins to mitigate symptoms of ASD were outlined (Table 3).

Table 3: Studies on the capability of anthocyanins to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	Rats	Per oral treatment with anthocyanins rich extract from Portuguese blueberries daily at 30 mg/kg	3 weeks	-Restored the sociability deficit -Elevated the amount of overall duration dedicated to social engagement -Increased social engagement with mice that are unfamiliar -Prolonged interactions with social partners	(69)

				-Decreased in rearing exploration -Ameliorated repetitive behaviors -Reduced the expression of microglia stimulation indicators (IL-6, TNF-α, CD11b, and IL-1β) -Reduced the quantity of microglial cells expressing Iba-1 in the cerebral cortex -Decreased the TNF-α, IL-6, COX-2, and IL-1β mRNA expressions in the intestine -Elevated the levels of serotonin in both the prefrontal cortex and the digestive system	

VPA: Valproic acid; TNF-α: Tumor necrosis factor-alpha; CD11b: Integrin αM; COX-2: Cyclooxygenase-2; IL-6: Interleukin 6; Iba-1: Ionized calcium-binding adapter molecule-1; IL-1β: Interleukin 1-beta

Beneficial Impact Of Quercetin And Various Herbal Mixture Containing Quercetin On Asd

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a type of polyphenol that falls under the flavonoid category and is found in diverse edibles like apples, crimson onions, grapes, citrus fruits, cherries, broccoli, and capers (70-71). This compound possesses various medicinal characteristics, such as anti-inflammatory and antioxidant effects (72-73). Several researches have indicated that quercetin has the potential to enhance cognitive abilities, memory retention, and learning capabilities. Additionally, it can also function as a safeguarding agent for the nervous system (74-75). Quercetin is advantageous in combating the oxidative pressure usually linked with ASD (76). The research carried out by de Mattos et al.(77) revealed that quercetin can provide neuroprotective benefits in cases of ASD induced by valproic acid. Quercetin administered prenatally in rats was found to be effective in preventing the behavioral alterations and harm caused by valproic acid (77) .

Moghaddam et al. (78) explored the impact of quercetin and nanophytosomes containing quercetin on behavioral impairments, cerebellum oxidative stress and apoptosis in a simulation of ASD triggered by separation from the mother. The application of quercetin with a dose of 40 mg/kg ameliorated specific behavioral abnormalities. Additionally, in the cerebellum of the quercetin (40 mg/kg)-treated animals, an amelioration in the parameters of oxidative environment and the gene expression of nuclear factor erythroid 2-related factor 2and apoptotic factors was noted. The administration of nanophytosomes containing quercetin at doses of 10 and 40 mg/kg showed a notable improvement in anxiety-like behavior, line crossing, and grooming index, as well as lipid peroxidation reduction, and increased levels of glutathione peroxidase, reduced glutathione, catalase and superoxide dismutase. Additionally, nanophytosomes containing quercetin markedly decreased the expression levels of caspase-3 and Bax, while enhancing the expressions of Bcl-2 and nuclear factor erythroid 2-related factor 2 (78).

A pilot research was conducted by Taliou et al. (79) with 50 ASD-diagnosed kids. For 26 weeks, a daily oral product containing a luteolin + quercetin + rutin was provided. According to their findings, ASD kids who received the polyphenols exhibited a notable increase in communication and attention, along with a decrease in unusual behaviors with no significant harmful effects.

Thirty seven child with ASD were given a dietary mixture formed of luteolin along with quercetin and rutin, enclosed in a liposomal formula of olive kernel oil, and it was reported that the symptoms of the disorder significantly improved. The majority of the recipients (75%) reported significantly improved gastrointestinal characteristics, such as shape, odor, form, and color of the feces. In around 50% of kids, behaviors were improved within a time frame of two to three weeks. Also the "allergic-like" manifestations were significantly diminished. Around 50% of people experienced an improvement in their level of attentiveness and eye connection. Moreover, approximately 30% to 50% of individuals exhibited acquired habits and communal dealings, while roughly 10% of juveniles commenced articulating isolated terms or concise expressions (80).

Tsilioni et al.(81) study found that children treated with quercetin, luteolin, and rutin mixture showed not only improvements in ASD-like behaviors but also significantly reduced IL-6 and tumor necrosis factor-alpha (TNF-α) serum concentrations compared to the start levels.

Additionally, the initiation of developmental thyroid hormone deficiency can serve as a model of ASD and can impede the formation of new neurons in the hippocampus. A regimen comprising of thioctic acid as an antioxidative agent and α-glycosyl isoquercitrin, in conjunction with more than ten supplementary linear glucose units, exhibits antioxidative properties. The retrieval of α-glycosyl isoquercitrin led to the reactivation of certain antioxidant enzyme genes like NAD(P)H dehydrogenase [quinone] 1 and thioredoxin 1, which in turn revived post-mitotic granule cells that were NeuN-positive, as well as interneurons that were positive for parvalbumin and somatostatin. The two antioxidants restored the expression of a gene related to GABAergic interneurons called orthodenticle homeobox 2, while α-glycosyl isoquercitrin restored the expression of AMPA subunit 3 (82).

Seventeen kids with ASD were registered for steroid therapy. Each one of them had ample eye contact and reciprocal social engagement prior to undergoing regression. Regression referred to the absence of previously developed societal abilities and to communicate through language. The therapeutic regimen was formulated with a dosage of 1 mg/kg deflazacort over a period of three months, proceeded by gradual reduction throughout the course of six months. A month before discontinuation of corticosteroid therapy, quercetin (250 mg/day) was introduced and intended for at least sixteenth months. A total of fifteen patients finished their steroid therapy and are currently undergoing quercetin administration for a duration of 10-25 months, with an average of 18 months. Out of these, seven patients showed a significant improvement in their global condition, five patients showed a considerable improvement, and three patients showed a minor improvement. Enhancement in social engagement (heightened eye contact, mutual communication, and peer engagement) was significant in 8 individuals, moderate in 4 individuals, and negligible in 3

individuals. Knowledge of receptive languages showed significant enhancement in six individuals, moderate improvement in six individuals, and slight improvement in three individuals. On the other hand, the expressive language exhibited minimal to moderate progress in only 11 patients (83).

Studies on the capability of quercetin and various herbal mixture containing quercetin to mitigate symptoms of ASD were outlined (Table 4).

Table 4: Studies on the capability of quercetin and various herbal mixture containing quercetin to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	Rats	Intragastric treatment with quercetin daily at 50 mg/kg	13 days	-Prevented the increase in latency -Prevented the reduction in social interaction time -Prevented the increase in tail flick latency -Prevented the brain increase in CAT and decrease in GPx -Prevented the reduction of the activity of ALA-D in hippocampus	(77)
Maternal separation	Wistar rats	Quercetin and quercetin-loaded nanophytosome (10 and 40 mg/kg) daily oral	P 21 - P 42 (21 days)	-Decreased line crossing -Improved locomotor activity -Improved the number of rearing -Increased the duration spent in the center -Improved anxiety-like behaviors -Reverses the excessive self-grooming behavior -Increasing the social interaction -Increased cerebellar CAT, GPx, and SOD activities -Enhanced cerebellar GSH and reduced cerebellar MDA -Increased cerebellar expression of the Nrf2 gene -Increased cerebellar Bcl-2 expression and reduced cerebellar Bax and caspase-3 genes expression	(78)
Clinical trial	Human (37 patients)	The dose used was 1 soft gel capsule (quercetin (70 mg) + luteolin (100 mg) + rutin (30 mg))/10 kg/day	ND	-improved the bowel color, form and habits within 2-3 weeks -Reduced skin allergic-like symptoms -Improved eye contact and increased attention to directions - Improved retained learned tasks and social interactions -10% of kids commenced uttering phrases or sentences	(80)
Prospective, open-label trial (January 2018 - April 2019)	Human (50 patients)	The dosage was 1 soft gel capsule (10 kg/day) containing quercetin (70 mg), luteolin (100 mg), and rutin (30 mg)	26 weeks	-Enhanced adaptive action and general behavior	(79)
Open-label clinical trial	Human (40 patients)	The dosage was 1 soft gel capsule (10 kg/day) containing quercetin (70 mg), luteolin (100 mg), and rutin (30 mg)	26 weeks	-Enhanced behavior -Improved VABS age-equivalent scores -Reduced serum IL-6 and TNF-α	(81)
6-Propyl-2-thiouracIL-induced developmental	Rat	α-Glycosyl isoquercitrin (5,000 ppm) and α-lipoic acid	From P 21 to P 77	-Returned expression of NQO1, Txn1, Otx2, and Gria3 -Recovered NeuN-expressing granular cells, parvalbumin, and	(82)

hypothyroidism		(1,000) ppm were dietary administered at and		interneurons expressing somatostatin.	
Patients diagnosed with regression ASD	Human (17 patients)	Per oral quercetin daily at 250 mg + 1 mg/kg deflazacor	18 months	-Improved global condition -Enhanced social engagement -Enhanced receptive language abilities	(83)

VPA: Valproic acid; CAT: Catalase; GPx: Glutathione peroxidase; ALA-D: Aminolevulinic acid dehydratase; GSH: reduced glutathione; Nrf2: Nuclear factor erythroid 2-related factor 2; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; ND: Not detected; TNF-α: Tumor necrosis factor-alpha; P: Postnatal day; NQO1: NAD(P)H dehydrogenase [quinone] 1; Txn1: Thioredoxin 1; Otx2: Orthodenticle homeobox 2; Gria3: Glutamate ionotropic receptor AMPA type, namely subunit 3; PV: parvalbumin; VABS: Vineland adaptive behavior scales; SOD: Superoxide dismutase; MDA: Malondialdehyde; IL-6: Interleukin 6

Beneficial Impact Of Luteolin On ASD

Luteolin (3′, 4′, 5, 7-tetrahydroxyflavone), a type of plant-derived polyphenolic flavonoid, can be found in various vegetables, fruits, and herbs. It has been linked to a host of advantageous characteristics such as anticancer, antioxidant, and anti-inflammatory effects (84-86). Various research has demonstrated the favorable impact of a combination of herbal extracts comprising luteolin and quercetin in improving ASD (as previously demonstrated in Table 4) (79, 80, 81).

A 10-year-old ASD patient who took microparticles containing luteolin and palmitoylethanolamide twice daily for a year shown improvement in ASD-like behaviour, according to a single case study (87). Similarly, social and nonsocial behaviors were seen in mice that had developed ASD due to valproic acid following administration of the same formulation. The immunoreactivity to TNF-α and IL-1β was regulated by the same formula containing luteolin and palmitoylethanolamide (87). The recent study published by Tassinari et al. (88) examined the potential positive impact of administering luteolin on the cognitive and behavioral aspects of brain development in a female mouse with a heterozygous Cdkl5 (+/−) genotype, which is used as a model for ASD. It was discovered that the chronic use of luteolin to restrain neuroinflammation the motor stereotypies, hyperactivity level, and memory potential in mice with Cdkl5 haploinsufficiency. Administering luteolin also amplified the production of new neurons in the hippocampus and helped improve the development of dendritic spines as well as the branching of dendrites in cortical and hippocampal neurons (88). Moreover, Recently, Alsubaiei et al. (89) revealed that Lacticaseibacillus rhamnosus GG and luteolin demonstrated efficacy in mitigating the biochemical characteristics of ASD in brain homogenates induced by propionic acid in rodents. These characteristics included reduced glutathione, glutathione peroxidase, TNF-α, and IL-6.

Studies on the capability of luteolin to mitigate symptoms of ASD were outlined (Table 5).

Table 5: Studies on the capability of luteolin to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	C57/BL6 mice	Per oral treatment with ultramicronized palmi-toylethanolamide with luteolin (1.5% (w/v) carboxymethylcellulose in saline) daily at 1 mg/kg	-2 weeks for behavior, immunohistochemistry, and western blot -3 months for neurogenesis studies	-Prolonged the stay duration in stranger side -Increased sociability index -Increased time in open arm - Decreased expression of hippocampus and cerebellum iNOS, GFAP, NF-kB p65, and Bax -Increased expression of hippocampus and cerebellum IkBa and Bcl-2 -Decreased brain expression of IL-1β, TNF-α, chymase, and tryptase	(86)

A patient diagnosed with ASD (May 2012–2013)	Human (1 patient)	Per oral treatment with ultramicronized palmitoylethanolamide with luteolin at 700 mg+70 mg twice daily.	1 year	-Improved behavioral outcome -Reduced most indices of hyperactivity -Improved cognitive behavior -Improved eye contact -Increased ability to understand simple commands -Decreased the nights with enuresis	(86)
Genetic models	Cdkl5 KO mice	Luteolin daily intraperitoneal injection at 10 mg/kg	7 or 20 days	-improved the motor stereotypies -Normalized the stereotyped behavior -Improved the hyperactive phenotype - Improved the memory performance -Recovered the microglial alteration both in the hippocampus and somatosensory cortex -Promoted hippocampal neurogenesis -Enhanced development of nascent cells in the dentate gyrus -Enhanced the dendritic structure in neurons located in the hippocampus and cortex -Improved spine maturation in the brain -Boosted BDNF/TrkB signaling pathways in the cortex	(88)
PPA	Sprague-Dawley rat	Per oral combination of Lacticaseibacillus rhamnosus GG and luteolin (50 mg/kg/day)	27 days	-Increased the brain homogenates GPx, and GSH levels -Decreased the brain homogenates TNF-α, and IL-6 levels	(89)

VPA: Valproic acid; IκBa: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL-1ß: Interleukin 1-beta; NF-kB p65: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α: Tumor necrosis factor-alpha; TrkB: Tyrosine receptor kinase B; GPx: Glutathione peroxidase; GSH: Reduced glutathione; IL-6: Interleukin-6; iNOS: Inducible nitric oxide synthase; GFAP: Glial fibrillary acidic protein; BDNF: Brain derived neurotrophic factor

Beneficial Impact Of Catechin On ASD

Catechin is a flavonoid subgroup of polyphenols, which serves as a secondary metabolite and plays a significant role as an antioxidant. Tea and pome fruits are the primary dietary sources of catechins (90). Green tea has been discovered to exert a beneficial impact on cognitive abilities, particularly in regards to working memory and attentiveness (91). The the catechins in green tea possess the ability to improve cognitive deficiencies, lower oxidative stress by eliminating radicals, and work as an antioxidative agent. It restrained DNA from undergoing oxidative harm and aided in the fight against cognitive deterioration (92-93).

(+) Epigallocatechin-3-gallate reversed fundamental behavioral alterations caused by valproic acid in rats. The intake of (-)-epigallocatechin-3-gallate has been linked to safeguarding neurons from the effects of valproic acid-induced ASD. (-)Epigallocatechin-3-gallate displays neuroprotective properties, potentially attributed to its antioxidative action, which safeguards neurons from damage (94).

A recent research disclosed that in a rat model of ASD induced by propanoic acid, the oral intake of (±) catechin hydrate effectively improved behavioral, biochemical, neurological, and molecular abnormalities. (±) Catechin hydrate exhibits promising properties as a neurotherapeutic medication for ASD by targeting oxidative and nitrosative environments mediated by the nitric oxide pathway (95).

Studies on the capability of catechin to mitigate symptoms of ASD were outlined (Table 6).

Table 6: Studies on the capability of catechin to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	Wistar rats	(-) Epigallocatechin-3-gallate at 2mg/kg	P 21-P 90	-Decreased fear and anxiety as it increased the time spent and number of open arms entries (peripheral and central movements) -Controlled stereotypic forms of locomotion -Reversed the altered exploratory activity, grooming and rearing	(94)
PPA	Sprague-Dawley rats	Per oral treatment with (±) Catechin hydrate daily at 25, 50, and 100 mg/kg	Day 3 to day 29	-(100 mg/kg) increased social interaction time -(50 and 100 mg/kg) increased (action of burying marbles, SOD, GSH, CAT), improved (grip strength) and reduced (the quantity of intersections and accesses to the innermost circle, immobility time, TNF-α) -(25, 50, and 100 mg/kg) decreased (self-grooming time, count of ambulations and rearings, anxiogenic behavior, caspase-3, MDA, NO, IL-6, IFN-γ, NF-κB, and homocysteine) and increased (duration of interaction with unique rodent 1 as opposed to object and the time spent with novel rat 2)	(95)

VPA: Valproic acid; PPA: Propanoic acid; P: Postnatal day; IFN-γ: Interferon-gamma; NO: Nitric oxide; SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde; IL-6: Interleukin-6; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; GSH: Reduced glutathione; TNF-α: Tumor necrosis factor-alpha

Beneficial Impact Of Naringenin On ASD

(±)-Naringenin is a type of flavonoid that is commonly present in grapefruit, oranges and tomatoes skin (96). Because of its effect on several pathogenic pathways, both directly and indirectly, naringenin exhibits high neuroprotective promise (97-98). Experts like Bhandari et al.,(99 developed a pharmacokinetic and pharmacodynamic model and determined that naringenin can serve as an additional neurotherapeutic agent in mitigating neuropsychiatric conditions linked to ASD, such as sensorimotor dysfunction, hyperactivity, anxiety-related behaviors, social interactions, and repetitive behaviors.

Naringenin and its encapsulated nanocarriers possess robust clinical possibilities as a supplementary neurotherapeutic element in mitigating neuropsychiatric illnesses linked with ASD. Naringenin and its nano-sized particles effectively remedied behavioral and biochemical inadequacies in ASD phenotype (100).

Studies on the capability of naringenin to mitigate symptoms of ASD were outlined (Table 7).

Table 7: Studies on the capability of naringenin to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
PPA	Sprague-Dawley rats	Per oral treatment with (±) naringenin 3 times daily at 25, 50, and 100 mg/kg	Day 2 to day 29	-Naringenin (25, 50 and 100 mg/kg) decreased (duration stayed in non-social interaction, repetitive self-grooming, the number of ambulations and rearings, anxiety like behavior, immobility time, MDA, NO, TNF-α, MMP-9) and increased (duration stayed in social interaction, duration of interaction with unique rodent 1 as opposed to object, interaction time with stranger 2 (unfamiliar rat), duration stayed in interaction with unfamiliar male and female partners, marble-burying activity, SOD, GSH, CAT) -(±) Naringenin (50 and 100 mg/kg) increased the fall off time in rotarod test	(100)

PPA: Propanoic acid; GSH: Reduced glutathione; MDA: Malondialdehyde; NO: Nitric oxide; CAT: Catalase; MMP-9: Matrix metalloproteinase-9; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-alpha

Beneficial Impact Of Hesperetin On Asd

Citrus fruits include the flavonoids hesperidin and hesperetin, which have a broad spectrum of biological impacts. Hesperidin is abundantly present in lemon, sweet oranges, bitter orange, citron, clementines, and mandarins. Hesperetin is derived from the same variety of plant sources as hesperidin and may be thought of as a byproduct of hesperidin (101). Hesperidin has the ability to act as an antioxidant, reduce inflammation, protect against neurological damage, prevent seizures, alleviate depression, and reduce anxiety (102). In certain recent preclinical studies, hesperidin's ability to protect the nervous system has been confirmed in cases of lipopolysaccharide-induced neuroinflammation (through the modulation of Toll-like receptor 4/nuclear factor-κB signaling) and amyloid beta-induced neurodegeneration (by regulating nuclear factor erythroid 2–related factor 2/Toll-like receptor 4/nuclear factor-κB signaling) (103-104). Hesperetin displays neuroprotective effects and may be effective in managing ASD in the valproic acid animal model during pregnancy and lactation (105)(Khalaj, Hajizadeh Moghaddam and Zare, 2018).

Studies on the capability of hesperetin to mitigate symptoms of ASD were outlined (Table 8).

Table 8: Studies on the capability of hesperetin to mitigate symptoms of ASD

Model of ASD	Species	Dose	Duration	Results	Reference
VPA	Wistar rats	Per oral treatment with hesperetin daily at 10 and 20 mg/kg	E 0 to P 30	-Reduced anxiogenic-like behavior -Decreased animal activity -Increased the stay time in the compartment with a conspecific rat -Decreased the stay time with familiar rat and increased time with stranger rat -Decreased repetitive behavior and freezing -Increased SOD	(105)

VPA: Valproic aid; E: Embryonic day; P: Postnatal day; SOD: Superoxide dismutase

CONCLUSION

The fact is becoming increasingly clear that naturally occurring molecules with antioxidant and anti-inflammatory properties can provide consistent relief from symptoms in individuals with ASD. The above-mentioned results might be achieved by using particular natural antioxidants, like polyphenols, which consist of substances such as resveratrol, curcumin, anthocyanins, quercetin, luteolin, catechin, naringenin, and hesperetin. After analyzing the results of the research, it came to our attention that there were more laboratory tests performed than clinical trials. Therefore, we propose increasing the number of evaluations carried out on children diagnosed with ASD.

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Conflict Of Interest

The authors confirm that there is no conflict of interest.

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