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# Therapeutic Role of Nutraceuticals in Ameliorating Neurodevelopmental Disorders: A Focus on Autism Spectrum Disorder (ASD) – State of Art Review

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**Abstract**

Nutraceuticals are beneficial compounds present in foods that act as therapeutic and preventive agents against diseases. By following a diet designed for the diseased condition, the nutraceuticals provide an ameliorating effect. Nutritional foods comprise active components like polyphenols, flavonoids, and alkaloids with unquestionable antioxidant activity. For many disorders, oxidative stress and free radicals are the foremost causes. So, the antioxidant activity of functional foods has the capability to fight against countless physiological defects. The most intricate disorder with an unpredictable, definite cause with a high range of aetiology in infants these days is Autism Spectrum Disorder (ASD). Treatment for ASD is a highly challenging research field for upcoming researchers on the same side. ASD patients also needed an effective treatment without side effects. Then diet-based approaches are the main aim, due to their beneficial effects with less toxicity, to maintain the homeostatic condition of the ASD patients. Foodiceuticals ameliorate the adverse effects of neurodevelopment, neurodegenerative disorders, and other metabolic disorders. The upgrading effects of superfoods like resveratrol, curcumin, crocin, catechin, lycopene, probiotics, melatonin, withaferin, and carotene, etc., are examined in the ASD animal models with varied dosages. However, it showed a better effect in improving ASD behaviour via mediating the genetic alterations. In this review, the detailed mechanisms of pharmaceutical foods are reviewed. The potential therapeutic value of nutraceuticals and functional foods in ASD lies in their antioxidant capability and ability to modulate

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genetic alterations. Promising such results are reported from foods, such as resveratrol, curcumin, and probiotics in preclinical studies related to ASD behaviours. The results further warrant clinical trials to establish their efficacy and safety. The article highlights their antioxidant activity, ability to modulate genetic alterations, and promising effects in preclinical studies, emphasizing the need for clinical trials to confirm efficacy and safety. Based on the review of nutraceuticals given a clear-cut point in the treatment of ASD, there is a positive result in prevention and treatment not only in ASD but in other diseases too.

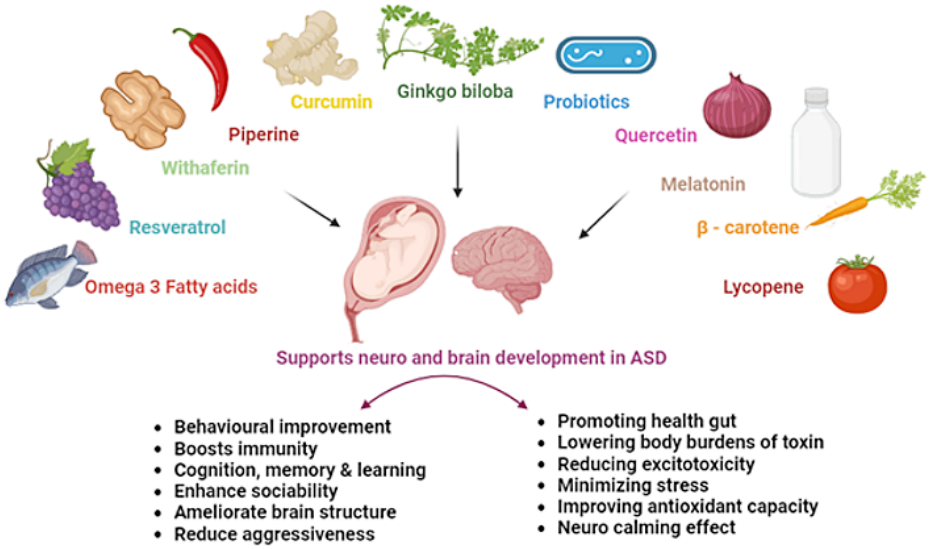


**Fig. No. 1 Graphical abstract**

**Abbreviations**

Autism Spectrum Disorder (ASD)
Short-chain fatty acids (SCFAs)
propionic acid (PPA)
Estrogen receptor related receptor (ERR)α
resveratrol (RSV).
BTBR T+Itpr3tf/J mouse (BTBR),
Il – interleukin
COX – cyclooxygenase
Toll-like receptor (TLR)
Phospho-STAT3 (P-STAT3)
VPA = valproic acid
PND – postnatal days
microRNA - miRNA

**Introduction**

Food is the essence of the living system; we need it each and every time. Apart from the stomach-filling substance, it has numerous nutrients that act as prevention and treatment hacks for diseases and disorders. “Prevention is better than cure,” said Dutch philosopher Desiderius Erasmus (1500). As he said, food definitely plays a foremost role in the prevention of diseases and treatment too. The precise chemical compound present in fruits, vegetables, flowers, species, pulses, and cereals is called a nutraceutical compound. A nutraceutical compound is any substance that is a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease. Nutraceutical is a future trend in the food and medicine industries. By approaching various techniques, they are planning to implement the nutraceutical compound into the formulated therapeutic drug for specific diseases along with the food. Nutraceutical compounds include lycopene, piperine, curcumin, gingerol, cinnamaldehyde, resveratrol, quercetin, vitamins, minerals, rosmarinic acid, eugenol, tannins, catechins, phytosterols, fatty acids, capsaicin, and diosgenin. This type of

compound is naturally present in food sources; if we consume the enriched food in a regulated diet, the particular compound definitely fights against diseases. Many researchers are currently working on nutraceuticals against many metabolic, genetic, neurological, and psychological disorders like diabetes, ASD, obesity, dementia, epilepsy, microbial infections, atherosclerosis, etc. In this review, we elaborately discuss the relationship between nutraceuticals and neurological disorders, especially autism spectrum disorder. And how nutraceuticals act on genetic manipulation to give symptomatic relief in ASD conditions and also prevent the alteration of brain structure in neonatal conditions examined in the varied animal models.

**Animal Models in Autism Spectrum Disorder**

ASD is a neurodevelopmental neurological disorder caused predominantly by hereditary, prenatal exposure to specific drugs and by environmental factors. These causative agents alter the brain structure, cause gene mutations, and disrupt the gene regulation process. It shows the effect on physiological and behavioural changes. Due to its complexity, the development of the autistic model is still under investigation. Because many of the neurological disorders have a similar symptomatic experience, a deep gene analysis only discloses the specific neurological disorder. In the case of ASD, the main target must be a neurodevelopmental disorder specifically caused by some prenatal exposure to drugs and precise gene mutations.

**Probiotic and Autism**

Probiotics are non-pathogenic, beneficial, and living microorganisms like bacteria and yeast. It has multiple valuable effects on the human system, like initiating good gut bacteria development, removing toxic substances in the gut, improving neural development, having positive effects on the CNS, boosting immunity, maintaining digestive tract linings, preventing diabetes and obesity, and helping in the digestion and absorption of food and medications.[1] Probiotics such as *Lactic Acid Bacteria, Lactobacillus sp., Bifidobacterium sp., Firmicutes, E. coli, Staphylococcus aureus,* etc. are present in fermented food products like kimchi, curd, buttermilk, hemp, and kombucha. Apart from other biological activities, probiotics play a major role in 'gut-brain-Axis'. It's a bidirectional connection between the central nervous system and the enteric nervous system, mediated by vagus nerves. It carries neurotransmitters like tetanus neurotoxin, serotonin, and SCFA produced by microbial action.[2] So, the probiotic food increases the good bacterial colonisation in the gut, which helps in the absorption and synthesis of nutrients and neurotransmitters that's definitely helpful in cognitive development and neurological disorders. Mintál3 examined the ameliorating effect of a probiotic and antibiotic mixture in a valproic acid-induced ASD rat model. *Lactobacillus* spp., and *Bifidobacterium* spp., are the probiotic mixtures they used. The probiotic-treated rats showed no significant effect on body weight change when compared with the control group. The result of latency to the first exploration in 3 chamber social interaction test, the stranger cage latency is 16.00 s, empty cage is 150.25 s, sociability index is 0.45, social zone exploration frequency 24.81±6.98, nonsocial zone exploration frequency 20.44±6.99, total distance moved (cm) 2856.05±637.81, no. of rearing behavior 15.38±3.02 and number of grooming behavior 4.25±0.94. Based on the results of the social interaction test compared with the control and VPA-treated groups, the probiotic mixture increases social interaction and behavioural stability in the ASD animal model. The concentration of SCFA in the treatment of probiotics shows no significant difference between the probiotic and antibiotic probiotic mixtures. But the probiotic mixture alone retains the normal gut microbiota in the ASD model and prevents the degradation of intestinal gut microorganisms. El-Ansary[4] studied how probiotic treatment attenuates the autistic-like excitation-inhibition imbalance in juvenile hamsters that is induced by PPA and clindamycin. The probiotic treatment reduces the growth of *Candida albicans* and *clostridia.* The ratio of $Na^{+}/Mg^{2+}$ ratio was significantly decreased by the probiotic treatment when compared with the induced group. In the ratio of glutamate/GABA, the PPA + probiotic-treated group showed a significant reduction compared to another group. Based on the results, the probiotic treatment is definitely beneficial for the ASD treatment by regulating the excitation response of neurotransmitters. The periodic treatment of the *L. plantarum* ST-III strain suggestively improved the social behaviour in the triclosan-induced ASD female mice model compared to male mice.[5]

**Resveratrol and Autism**

Resveratrol (trans-3,5,4'-trihydroxystilebene) is a biologically active compound synthesised by plants under the conditions of infections and ionising radiation. A polyphenol has two phenol rings linked by an ethylene bridge and is present in glycosylated forms in dietary products known as piceid. Rich sources of resveratrol are red grapes, red wine, and pomegranates. Resveratrol has dynamic neuroprotective effects and ameliorates neurodegenerative disorders like Parkinson's and Alzheimer's disease. The possible mechanism followed by resveratrol in neuroprotective activity is to decrease cholinergic neurotransmission, brain-derived neurotrophic factor expression, oxidative stress, and neuronal apoptosis.

It promotes beta-amyloid peptide clearance and anti-amyloidogenic cleavage of the Amyloid precursor protein. Two studies[6,7] examined the therapeutic effect of resveratrol in a prenatally valproic acid-induced ASD animal model. In the reciprocal sociability test, resveratrol-treated animals showed increased time in prosocial behaviours than VPA and the control group, but there was no change in food preference or repetitive self-grooming.The miRNA miR134-5p is most highly expressed in the VPA group; resveratrol decreased the expression. miR134-5p and miR138-5p expression were also decreased by resveratrol. Marchezan[8] conducted the pilot trial with 5 boys ages 11 to 13 with ASD with a treatment of resveratrol 200 mg/d for 90 days. The resveratrol treatment reduced aberrant behaviour and irritability but was less effective in altering stereotypical behaviour and lethargy. In the molecular lever, resveratrol exhibited a promising effect in modulating the immunological effect and anti-inflammatory effects via increased expression of miR-195-5p. The administration of resveratrol doesn't show any adverse effects. Another study[9] analysed the effect of resveratrol in the treatment of ASD in two different conditions, which are prenatal and postnatal exposure to progestin and norethindrone.

The resveratrol showed an amending effect on ASD-like behaviour via activation of ERβ. The progestin decreased Erβ and social interaction, but prenatal resveratrol treatment almost reversed the negative effect into an optimistic one and increased the expression of SOD2, Erβ, and ERRα in the amygdala. The mechanism exhibited by resveratrol is demethylation of DNA and histone on the Erβ promoter. The other study[10] investigated the preventive effect of resveratrol on behavioural and sensory alteration in ASD models induced by valproic acid. The result of nest-seeking behaviour: resveratrol treatment helps in the correct selection of choices and averts over responsiveness in the direct whisker stimulation test. Moreover, prenatal exposure to RSV treatment prevents the defect in cortical organisation and maintains the cortical organisation, increasing the number of medium-sized pyramidal neurons in layers II–III and the largest and most granulated pyramidal neurons in IV–V layers (somatosensory cortex, typical laminar distribution).

In the amygdala, RSV reestablished the typical proportion of $PV^{+}$ neurons. The anti-inflammatory effects in BTBR T $^{+}$ Itpr3tf /J autistic mice via diminishing the pro-inflammatory cytokines and activation of the JAK1-STAT3 pathway. [11] Resveratrol decreased the number of $CD^{+}$ T cells secreting IL-$6^{+}$, TNF-α expression, and INF-ɣ and decreased pSTAT3 (Tyr705). It also examined the inhibition of neuronal toll-like receptors and the COX-2 signalling pathway by resveratrol, which helps in the improvement of neuroimmune dysregulation. Via diminutions of TLR2, TLR3, TLR4, iNOS, COX-2 mRNA, and NF-κB, along with decreased protein expression levels in the brain. Hidema[12] and their team examined the therapeutic effects of single-dose resveratrol in the ASD model to improve their social behaviour in two different animal models (Oxtr-KO, WT/VPA mice model). Single administration of resveratrol before the 24 hours of behavioural test. Both mice model spent more time around the stranger than the familiar mice, and social novelty preference was also increased by the resveratrol treatment.

The upregulation of Egr3 and Sirt1 mRNA is expressed in the amygdala and mediated by resveratrol in the Oxtr-KO mice model but not in the WT-VPA amygdala sample. This mRNA expression is essential for the improvement of social interaction. Sunand[13] explored the coactive effect of resveratrol with pterostilbene (varying concentrations) in the postnatal exposure of a VPA-induced autistic mice model. The combined effect showed prominent behavioural improvements in negative geotactic, active swimming performance, motor coordination,

locomotor activity, thermal nociception, and social interaction was improved. The SOD, catalase, and GSH levels were improved after the treatment; the MDA, nitrite level, and AchE enzyme activity were inhibited and reduced by effective dosage treatment. The resveratrol and pterostilbene combo recovered the degenerated Purkinje fibres in the cerebellum and helped in the development of neurogenesis.

**Melatonin and Autism**

Phyto melatonin (N-acetyl-5-methoxytrptamine) is an indoleamine derivative of the amino acid tryptophan chemically in plants.[14] Melatonin, a ubiquitous molecule in nature, is a biological modulator of sleep, wake cycle, mood, body temperature, motor coordination, locomotion, food intake, preference, immune system, sexual behaviour, circadian rhythms, antioxidants, and retinal systems in animals and humans.[15] Coffee beans, tomatoes, sunflowers, fennel, grapes, fenugreek, jujube, white radish, kidney beans, apples, and mustard are rich sources of Phyto melatonin.

The melatonin administration stimulated CaMKII/ PKC/PKA phosphorylation in the hippocampus, as examined in a VPA-treated rats/mice model. In the 4$^{th}$ week of melatonin treatment, decreased CaMKII phosphorylation in the hippocampal CA1 pyramidal was reversed, the phosphosynapsin-I (Ser603) and pho-CaMKII (Thr286) in the hippocampus were increased, and the GluR1 (Ser-831) level was restored. The phosphorylation of NMDAR1 (Ser896) and MARKS (Ser152) was also significantly restored by melatonin administration. PKA (Thr197) and Phospho-GluR1 (ser845) were also regained by the chronic administration of melatonin (5 mg/kg). Long-term potentiation in the hippocampal CA1 region (6.8% of the base line) increased from 1–5 minutes to 56–60 minutes.[16]

**Piperine and Autism**

Piperine is a bioactive nutraceutical compound present in black and white peppers. Piperine is an alkaloid-pungent in the Piperaceae family. IUPAC: 1-(5-[1,3-benzodioxol-5-yl]-1-oxo-2,4-pentadienly) piperidine. The predominant role of piperine is to act as a bio-enhancer and increase the bioavailability of other therapeutic nutraceuticals, such as antioxidants, anti-inflammatory agents, nerve conduction agents, anti-depressants, reducing cholesterol, anticonvulsants, and anti-tumour agents.[17] The effective dosage of piperine ameliorates the effect of VPA-induced ASD by improving behavioural changes. The VPA increased the time duration of negative geotaxis activity, but the chronic administration of piperine (20 mg/kg) decreased the time duration taken in mice model. The beneficial protective effect shown on thermal nociception, motor coordination, and social behaviour increased learning and memory capacity, and rapid locomotor activity was reduced. The total time spent by the VPA-treated animal in the elevated plus maze test was low, but the dosage of 20 mg/kg increased the number of entries and time spent in open arms. Reduced glutathione levels were increased after treatment with piperine, malondialdehyde, total nitrite, and serotonin, which were decreased by piperine administration and showed a moderate protective effect. Histopathology studies showed the regeneration of the granular cell layer and the Purkinje cell layer of the cerebellum.[18]

**Withaferin and Autism**

Nutraceuticals like Ashwagandha predominantly have a superior role in ayurvedic medicine.19 Also known as Indian winter cherry or Indian ginseng, is a member of the Solanaceae family. The series of bioactive components in ashwagandha is withaferin A, withanone, and withanolide, sitoindosides, and withanosides. Each and every part of ashwagandha is used in treatment for epilepsy, anti-inflammatory, coagulation disorder, scavenging free radicals, neurocalming effect, depression, diabetes, pyrexia, and neuroregenerative activity[20] *Withania sominifera* extract showed a dosage-based therapeutic effect against VPA-induced ASD when examined in the BALB/c mice model via improving behavioural activity. At a dosage of 200 mg/kg, WS reduced the latency in negative geotactic behaviour, motor coordination, locomotor activity, dose-dependent beneficial effect in mid-air righting reflex, moderate increase in number of entries, time spent in the open arm in the plus maze test, and increased nociceptive response. The stress factor is also reduced by WS, like MDA, or total nitrite. The free radical was scavenged by increasing the level of reduced glutathione. Rejuvenation of the granular cell layer and Purkinje layer happened in the cerebellum by WS treatment.[21]

**Curcumin and Autism**

Curcumin, an alkaloid, is the predominant compound present in *Curcuma longa, the Zingerberaecae* family (turmeric), the golden spice of traditional medicine. It is used as a food additive in Asian cuisine and as a colouring agent in the beverage industry. In both in vivo and in vitro studies, curcumin showed positive effects in treating diseases via gene alterations, protein expression, and miRNA regulation. Curcumin has extensive applications in anti-inflammatory, anti-bacterial, antifungal, antimicrobial, antirheumatic, antidiabetic, cardio, nephron, hepato-protective, immunomodulatory, anti-neoplastic, anti-neuroinflammatory, reducing oxidative stress, effective against neurodegenerative and neurodevelopmental disorders, and scavenging free radicals.[22]

The varied concentrations of curcumin (50, 100, and 200 mg/kg) showed an advantageous effect on improving the behavioural characteristics of PPA-induced ASD. repetitive self-grooming, arena exploration sniffing, and crawling time were decreased. The social interaction with new mice is initiated, and food preference and new food choices were also exhibited by curcumin-treated rats. In the concept of memory, learning, and relearning, the treated rats are able to recognise the unfamiliar mice and social partners. Repetitive behaviour in PPA was increased and confirmed by the marble-burying assay; it was reversed by curcumin treatment at a dosage of 200 mg/kg rather than a lower dosage. In the role of reduction in oxidative nitrosative stress, thiobarbituric acid reactive substances (TBARS) were reduced and mitochondrial complex I, complex II, complex III, complex IV enzymes, glutathione, superoxide dismutase, and catalase were increased by curcumin treatment to achieve antioxidant activity. The dose-dependent effect of curcumin exhibits anti-TNFα and anti-MMP-9 potentials.[23]

Another study[24] investigated whether neonatal curcumin treatment attenuates hippocampal neurogenesis and improves autistic behavior. In the treatment of PND 8, it showed a promising effect on the proliferation pool of neural progenitor cells in the hippocampal dentate gyrus. On the same side, on PND24, the neurogenesis increased, and it was confirmed by immunofluorescence. Based on the results, curcumin definitely has neuroregenerative properties. The autistic symptoms in BTBR mice were reduced by promoting sociability; repetitive behaviours were reduced; and cognitive impairments were ameliorated.

Even though curcumin had a behavioural-improving effect in ASD cases, the synergistic compound of curcumin was also examined with eugenol and rosemary acid by Harika.[25] They examined a VPA-induced autistic Swiss albino mice model, a postnatal model. Based on their combinations, curcumin+ eugenol +rosemary acid showed a more beneficial effect than curcumin alone. The synergistic effect increased the bioavailability of drugs, neuroprotective activity, memory, cognitive, and antioxidant activities. Based on the histopathology results, the synergistic compound prevents the degeneration and demyelination of the hippocampus.

***Ginkgo biloba* and Autism**

The endemic species and left extract of *Ginkgo biloba* are widespread herbal medicines in China, with effects against Alzheimer's disease, cerebrovascular diseases, cognitive deficits, antioxidant, anti-mutagenic, anti-microbial, anti-obesity, anti-hypertensive, hepatic, reno, neuroprotective, anti-ageing, anti-fungal effects. The extract was effectively improving cognitive functions.[26] The phytoconstituents of *Ginkgo biloba* are ginkgolides, ginkgoghrelins, ginkgetin, ginkgotides, ginkgolic acids, quercetin, kaempferol, isorhamnetin, myricetin, luteolin, apigenin, and catechin derivatives.[27]

*Ginkgo biloba* ameliorated the VPA-induced autistic behaviour by mediating antioxidant and anti-inflammatory activity. In-depth analysis of *Ginkgo biloba* showed reducing the MDA by increasing the glutathione range and serotonin. The IL-6, TGF-β1, and IL-17 were also reduced. The social approach of autistic mice was rescued. Expression of myelin basic protein was decreased by VPA exposure, but *Ginkgo biloba* treatment supports the expression of myelin basic protein to promote sequential neurotransmission along with the Purkinje, outer molecular layer, and inner granular layer of the cerebral cortex, which was maintained in a good structure in the treatment of *Ginkgo biloba* examined by toluidine blue staining, H&E, and immunohistochemistry.[28]

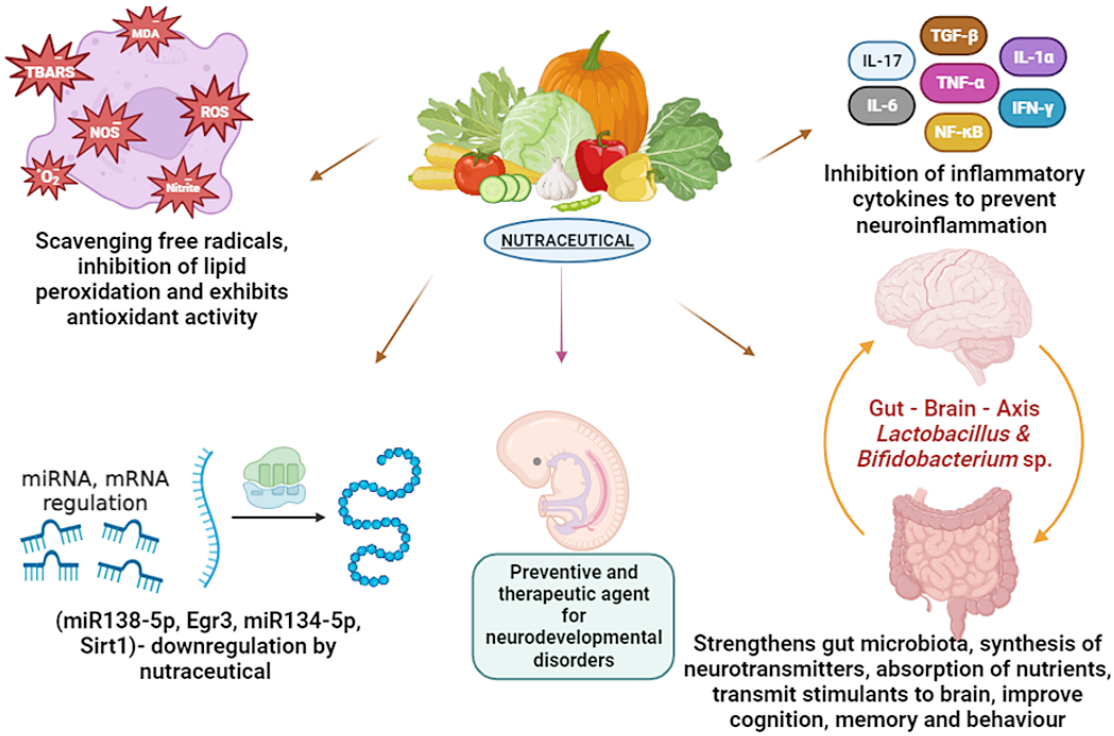


**Fig. 2 Mechanism of nutraceutical in ASD**

**Lycopene and Autism**

Lycopene is a red-coloured carotenoid pigment and non-provitamin A. The metabolic derivatives are lycopenals, lycopenols, and lycopenoic acid.[29] Sources of lycopene were tomato sauce, watermelon, tomato paste, fresh tomato, carrot, pink guava, apricot, papaya, and ketchup. Lycopene handles multiple mechanisms to exhibit neuroprotective effects, like increasing mitochondrial enzymatic activity, suppressing the release of 4-AP-glutamate, oxidative stress-causing factor scavenging, improving biochemical and behavioural actions, reducing neuroinflammation.[30] Lycopene has actions like protecting against hippocampal neurotoxicity, memory impairment and suppressing hyperactivity of neuro-signalling enzymes and inflammation:[31, 32] scrutinised the anti-inflammatory and oxidative stress-reducing activity of lycopene in PPA-induced ASD. Serum and brain MDA concentrations decreased, and the serum lycopene level increased, which proves the bioavailability of therapeutic drugs was stabilized. Based on the results of western blot analysis, the levels of IL-1α, IL-8, TNF-α, and NF-κB in the brain were reduced, and Bax, HO-1, and Nrf2 were increased by the lycopene administration. In terms of physical performance, the lycopene-treated rats showed better activity in swimming and spatial memory acquisition.

**Quercetin and Autism**

Quercetin is a plant secondary metabolite, nutraceutical, flavonoid, and basic component of the human diet. The richest source of quercetin is onion; other than that, plums, grapes, tea, tomatoes, mangoes, citrus fruits, cherries, and buck wheat.33 The wide-spread application of quercetin was anti-SARS-CoV-2, anti-ageing, antioxidant, anticancer, anti-inflammatory, and anti-viral, mediated by reducing lipid profile, increasing mitochondrial enzymatic activity, inhibiting inflammatory cytokines, reducing stress factors, oxidative stress, and inhibiting pro-apoptotic gene expression.34 The prenatal VPA exposure reduces the weight of the pups, but quercetin restores the weight gain profile. Locomotor activity, social interaction, and nociceptive skills were improved. The oxidative stress-causing agents ROS, nitrite, and TBARS are eliminated, and antioxidant enzymes like SOD, GPx, GST, and CAT enzymes were increased in cerebral cortex, striatum, and hippocampus brain samples.

The stress marker ALA-D (5-aminolevuliniv acid) activity was only reduced in the hippocampus.[35]

**Omega 3 FA**

Omega-3 fatty acids are unsaturated fatty acids absorbed only from the diet; enriched sources are fatty fish, cod liver oil, and vegetable oils. Essential for the neuro, growth, and memory growth of humans. O3FA has a promising and significant therapeutic character in a wide range of conditions like hypertriglyceridemia, maternal health during pregnancy and the health of children, cardiovascular disease, diabetes, Alzheimer disease, dementia, cognition, depression, rheumatoid arthritis, retinopathy, fatty liver, epilepsy, premenstrual syndrome, brain development, and asthma.[36]

The fatty fish diet enriched with omega-3,6 fatty acids (DHA, EPA, DPA, ALA, AA, and LA) had an ameliorating effect against the neurotoxic effect caused by PPA. The fatty acid profiles were estimated in brain homogenates by gas chromatography. Saturated fatty acid, MUFA, and PUFA levels were increased by the fish diet. There was no significant difference in LDH, GSH profile, CK level, or dopamine, but 5-HT was increased in the *Lethrinus nebulose* and *Epinephelus marginatus* fish diets. Decreased level of glutathione in *Scaridae-fed* rats. Lipid peroxidase levels were significantly reduced in *Lethrinus nebulose*-fed rats. Three fish varieties fed to rats' brain samples were analysed for altered brain structure in the cerebrum, cerebellum, and hippocampus. By the fatty fish treatment, the adverse effect of PPA in the brain was restored; it increased the density of Purkinje cells, and neuronal density in the CA4 region, particularly neuroinflammation, was inhibited.[37]

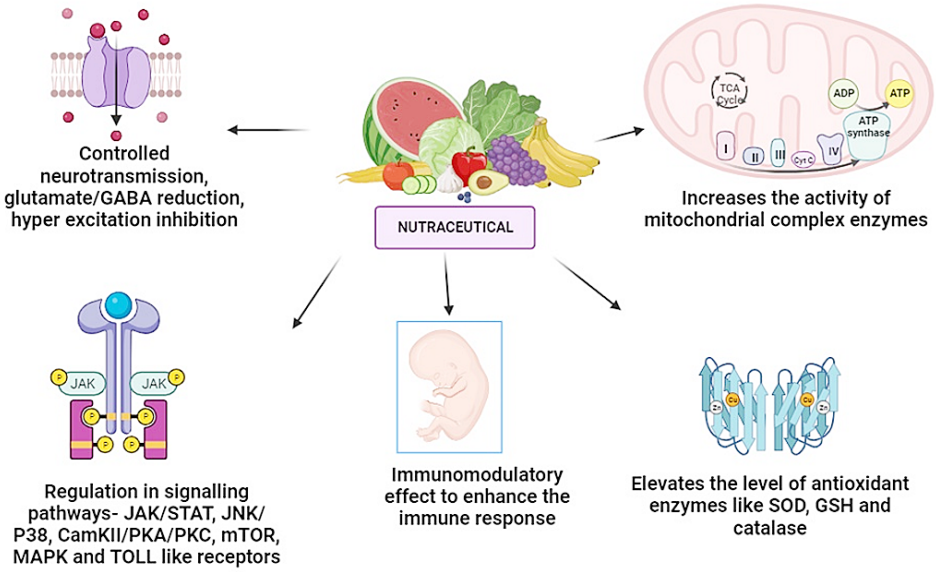


**Fig. 3 Mechanism of nutraceutical in ASD**

**Catechin and Autism**

Catechin is a natural flavonoid, present in green tea (*Camellia sinesis*) and a variety of fruits and vegetables. It had a great impact on antioxidant activity, neutralised reactive nitrogen and oxygen species, chelated metal ions in redox reactions, boosted SOD, glutathione peroxidase, glutathione reductase, glutathione s-transferase, anti-cancer, neuroprotective, anti-obesity, anti-inflammatory, anti-microbial, fungal, bacterial, and hypotensive.[38]

Based on the varied concentration dosage of epigallocatechin-3-gallate, it showed a beneficial effect in treating the prenatally exposed VPA-induced autistic behavior. The increased levels of 5-HT, total nitrite level, and glutamate were reduced in the hippocampus and cerebellum. When compared with three dosages (1, 2, and 5 mg/kg), 2 mg/kg of (Epigallocatechin gallate) EGCG is efficient in reducing the oxidative stress-causing components.[39] The anti-inflammatory role of catechin helped

ameliorate the Intracerebroventricular infusion of PPA-induced autistic behaviour, mediated by inhibition of nitric oxide in neuroinflammation. But in this case, the catechin was combined with varied compounds like L-arginine and (N(ω)-nitro-L-arginine methyl ester) L-NAME. The social time interaction elongated by catechin hydrate alone but combined with the other two compounds has not shown any additional beneficial effect. In social behaviour, social novelty preference, latency of fall, locomotor activity, and social preference, catechin hydrate and the L-NAME complex showed significant sociability. The self-grooming, TNF-α, IL-6, IFN-ɣ, NF-κB, homocysteine, iNOS, and caspase-3 were reduced by 3 combinations; repetitive behaviour was reduced; and swimming performance was increased by the catechin and catechin + L-arginine combo. Catechin + L-arginine are only effective for anxiogenic behavior. MDA and nitrite levels were effectively reduced, and glutathione, SOD, catalase enzyme, and mitochondrial enzymes were increased by catechin hydrate.[40]

**Saffron and Autism**

Saffron (Crocus sativus), a medicinal plant, is used as a therapeutic agent. The bioactive nutraceutical components of saffron are crocin and crocetin (carotenoid, yellow to red), safranal, and picrocrocin.[41] The mechanism of saffron constituents in the nervous system was reduction of MDA, CRP, inflammatory cytokines, oxidative stress, free radical scavenging, increasing GSH, total thiol, improving cognitive deficits, altering brain availability to serotonin, and elevating SIRT1, BDN, and BDNF expression.[42] Other biological effects of saffron are cardioprotective, anti-hypertension, anti-atherosclerosis, bettering respiratory functions in chronic obstructive pulmonary disease, asthma. The bio effects extended to irritable bowel syndrome, corn's disease, ulcerative colitis, gastric cancer, diabetic nephropathy, and renal ischemia. Fresh saffron powder and the bioactive nutraceutical compound of saffron, 'crocin', were investigated against prenatal exposure to VPA-induced ASD behaviour and reducing the effectiveness of oxidative stress. Both crocin and saffron showed extremely promising effects in reducing oxidative stress (confirmed by estimating the stress markers, MDA-reduced), increasing antioxidant enzymes (GSH and CAT-increased), and improving autistic behaviours and senses after 28 days of treatment. The bettering effect of crocin and saffron on behaviours like anxiety, pain responses, motor coordination, and locomotion was observed.[43]

**Beta Carotene and Autism**

Beta-carotene is a pro-vitamin A, carotenoid, secondary metabolite synthesised by plants. Food sources of beta-carotene are carrots, papaya, pumpkin, and beetroot. The therapeutic application of beta-carotene in cardiovascular diseases, cancer prevention, erythropoietic protoporphyria, age-related macular degeneration, hyperlipidemia, oral leukoplakia, and scleroderma is known. The molecular mechanism followed by carotene-neuropathic inhibition of Parkinson's disease extended to ALS enzyme activation, microglial stimulation, inhibition of Aβ-aggregation by inhibiting JNK/p38 pathway, inhibiting NF-κB activation, P13k/Akt, MAPK pathway, activation of autophagy, antioxidant, and anti-inflammatory.[44] When given at birth, beta-carotene dramatically boosted T-maze alternations, resulting in longer time spent in the "three-chamber test" with a new mouse and shorter time in the empty chamber. Additionally, there were reductions in grooming and bedding behaviors, increased time spent in the reciprocal social interaction test and open field test, increased brain CD38, BDNF, retinoic acid gene expression, and serum oxytocin levels. There were no observable changes in neurological scores. By boosting brain neuroplasticity without causing harm, beta-carotene oral supplementation at birth dramatically decreased repressed and stereotyped behaviors and interests45 while increasing social interactions, communication, CD38, and oxytocin in BALB/c and BTBR mice.

**Synthesized Discussion**

The incorporation of nutraceuticals into therapeutic strategies for autism spectrum disorder (ASD) has been the subject of great interest in recent years. Such a focus indeed represents a paradigm shift toward a holistic approach combining nutrition and medicine, particularly given the etiology of ASD, which is multifactorial in nature, incorporating genetic, environmental, and neurodevelopmental factors. Several studies conducted on animal models have highlighted the potential efficacy of nutraceuticals in ameliorating symptoms associated with ASD, thus providing important insights into their therapeutic potential.

**Table 1: Animal models in ASD with references mentioned in the text**

| S.No. | Animal Model | Prenatal expo -sure of drug | Period of Exposure | Dosage of drug | Nutraceutical compound | Nutraceutical dosage | Period of treatment |
|---|---|---|---|---|---|---|---|
| 1 | Wistar Laboratory rats | Valproic acid | 12.5th day of gestation | 500mg/bw/kg, i.p., | Antibiotic and probiotic mixture (*Lactobacillus, Bifidobacterium* spp.) | Vancomycin (500mg/L), ciprofloxacin(20mg/L), imipenem (250mg/L), and metronidazole (1g/L), as antibiotic cocktail mixed with drinking water | 17 Weeks |
| 2 | Wistar rats | Valproic acid | E12.5 | 600mg/kg, i.p., | Resveratrol | 3.6mg/kg, s.c., | E 6.5 to E18.5 |
| 3 | Wistar rats | Valproic acid | E 12.5 | 600mg/kg, i.p., | Resveratrol | 3.6mg/kg s.c., | E 6.5 to E 18.5 |
| 4 | BTBR T+ Itpr3tf/J and C57BL/6 male mice, 6-8 weeks aged | - | - | - | Resveratrol | 20, 40mg/kg, i.p., once a week | (7days) |
| 5 | Male BTBR mice and C57BL/6 mice | - | - | - | Resveratrol | 40mg/kg i.p., once a week | (7 days) |
| 6 | Sprague Dawley rats | Progestins, norethindrone | Prenatal (E1) & postnatal exposure | 20mg/kg s.c., | Resveratrol | 20mg/kg – p.o., | 28 days after induction of ASD |
| 7 | Wistar rats[46] | Valproic acid | E12.5 | 600mg/kg i.p. | mTOR inhibitor (NVP-BEZ235) and Sesame oil | mTOR inhibitor (400 µg/kg), sesame oil (400µg/kg), p.o., | Everyday till weaning period |
| 8 | ICR mice | triclosan | 7$^{th}$ day of | Intragastric | Probiotic | *Lactobacillus plantarum* | 6$^{th}$ weeks to 9$^{th}$ |

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| | | | pregnancy | gavage 50mg/kg | | ST-III (5*108 CFU/mL), intragastric gavage daily | weeks after birth |
| 9 | Sprague Dawley rats | Sodium Valproic acid | E12.5 | 600mg/kg i.p. | Melatonin | 1.0 or 5.0mg/kg, p.o., | After PND22, for 28 days treatment |
| 10 | BALB/c mice | Post natal exposure of sodium valproate | PND 14 | 400mg/kg s.c. | Piperine | 20mg/kg via p.o., | PND 13 to PND 40 |
| 11 | BALB/c mice | Postnatal exposure of Sodium valproate | PND 14 | 400mg/kg | *Withania somnifera* | 100 & 200mg/kg, p.o., | PND 14 - 40 |
| 12 | Male Sprague Dawley rats | PPA | 3-4 old month pups | 1M of PPA, Intracerebrov -entricular injection | curcumin | 50, 100 & 200mg/ kg/day; p.o., | After 3rd day of surgery till 28th day |
| 13 | BTBR and C57 mouse pups (male) [47] | BrdU (bromodeo-xyuridine) to study cell proliferation | PND 8 | 50mg/kg | curcumin | 20mg/kg i.p., | PND 6 to 8 |
| 14 | Male Wistar rats | Sodium valproic acid s.c., | PND 14 | 400mg/kg | Ginkgo biloba | 100mg/kg i.p., | PND 13 to 40 |
| 15 | Swiss albino mice | Valproic acid i.p., | PND 14 | 400mg/kg | Curcumin, rosemary acid and eugenol | Curcumin – 50mg/kg, curcumin + eugenol – 50mg/kg+5mg/kg and curcumin + rosemary acid – 50mg/kg + 5mg/kg p.o., | PND 14 to 40 |
| 16 | 33-week-old male Sprague Dawley rats | PPA for the first five days, s.c., | After one week of acclim -atization | 500mg/kg | Lycopene | 5, 10 & 25 mg/kg p.o., | 35 days |

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| 17 | Oxytocin receptor gene knockout (Oxtr-KO mice) and wild type C7BL6/J (WT) mice ASD model induced by VPA | VPA – i.p., | E 13.5 | 600mg/kg | Resveratrol | 30mg/kg i.p., | Single i.p., before 24 hrs of 3 chamber test |
| 18 | 2 weeks old Swiss albino mice pups | VPA s.c., | PND 14 | 400mg/kg | Resveratrol & pterostilbene | I - Resveratrol (20mg /kg), II – pterostilbene (10mg/kg) and III – resveratrol (10mg/kg) + pterostilbene (5mg/kg) p.o., | PND 14 - 40 |
| 19 | Wistar rats | Valproic acid by intragastric administration | E12.5 | 800mg/kg | Quercetin | 50mg/kg – p.o., | Gestation day 6.5 – 18.5 |
| 20 | 3 weeks old male Wistar Albino rat pups | Neurotoxic dose of (PPA) propionic acid | After 7 days of acclimatization | 250mg/kg | Omega 3 fatty acids c omplex (from fatty fish - Lethrinus *nebuloses, Epinephelus marginatus, Scaridae fish*) | Fished are mixed with nor diet about 12.5% | For 36 days |
| 21 | Wistar rats | VPA i.p., | PND 21 | 600mg/kg | EGCC - epigallocatechin | 1, 2 & 5mg/kg p.o., | PND 21 - 90 |
| 22 | Wistar rats | VPA i.p., | E 12.5 | 500mg/kg/2ml | Pure red saffron powder and crocin | Saffron 30mg/kg/2ml, crocin – 15mg/kg/2ml i.p., | PND 34 – 61 |
| 23 | BALB/c and BTBR mice | Genetic alteration of the Oxt systems (Oxt, Oxt receptor | - | - | Beta - carotene | 1.0 – 5.0 mg/kg p.o., | (1, 4 & 7th day from the birth) |

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| | | and CD38) knoc kout mice | | | | | |
| 24 | 3 months of Sprague Dawley rats | Intracerebrovent -ricular infusion of 1 M propanoic acid | After 7 days of acclimati-zation (day 1) | 4 µl | Catechin hydrate N-omega-nitro-L-arginine methyl ester (L-NAME) and L – Arginine | Catechin hydrate – 25, 50 & 100mg/kg, L-NAME – 50mg/kg, L-arginine – 800mg /kg, L-NAME + catechin hydrate (50mg/kg + 50mg/kg) and L-arginine + catechin hydrate (800mg/kg+50mg/kg) p.o., | Day 3 – day 29 |
| 25 | Golden syrian male hamsters | Clindamycin and PPA p.o., | Day 27 of after treatment period and were killed next day | Single dose of clindamycin 30mg/kg on the 27th day, 250mg/kg of PPA | Probiotic (Protexin $^{R}$) | 0.2g/kg p.o., | 26 days |

For instance, probiotics have a great deal of evidence that links the gut to the brain through what is often termed the "gut-brain axis." There is evidence showing that certain strains of probiotics can improve socialization and reduce repetitive behaviors in ASD models. Compounds such as resveratrol have been shown to have neuroprotective properties and improve social behaviors through the modulation of inflammatory pathways and promotion of neuronal health. Other nutraceuticals, including curcumin and piperine, have shown antioxidant effects of combating oxidative stress that contributes to neurodevelopmental disorders.

The interplay of such nutraceuticals with prevailing pharmacological treatments opens the exciting frontier in ASD management. The ability of nutraceuticals to enhance bioavailability and synergistically amplify therapeutic effects may open ways to more effective treatment plans with fewer side effects, but challenges remain, for example, in standard dosages, comprehensive human clinical trials, and deeper understanding of individual variability in response to these compounds.

Overall, the emerging evidence highlights the potential of nutraceuticals in treating ASD. A more sophisticated analysis of these compounds will not only have the potential for alleviation of symptoms but may also provide preventive interventions for high-risk populations, emphasizing nutrition in the developing brain. Further research is therefore essential to optimize the therapeutic approaches and ultimately provide personalized interventions that are tailored to the individual needs of individuals with ASD.

We accept that we did not do metanalyses of the results which may be the limitation.

**Conclusion**

Food and drugs are not different things when it matters for the treatment of diseases and disorders. Nutrition-based therapy is our ultimate aim—to get the benefit without side effects. Likewise, modified foods become a centre of attraction for researchers and people. From the perspective of ASD, treatment is the most challenging thing for researchers due to its complexity in causes and variation in genetic mechanisms for every ASD-affected individual. Environmental factors like radiation, toxic drugs, pollution, prenatal exposure like chitosan, VPA, PPA, inflammatory cytokines like IL-6, IL-17, TNF-α, IL-6, IFN-ɣ, NF-κB, gene mutations by free radicals, and oxidative stress are the major causes of ASD. In the view of genetic mutations, there are multiple numbers of genes responsible for our normal homeostatic condition, but in the case of ASD, gene mutations occur at varied genes that differ from person to person with long-term treatment, so this is a critical task for the researchers to develop a therapeutic drug for the affected patients. Modified foods truly play a beneficial role in ameliorating behavioural, nutritional, and metabolic processes via scavenging free radicals, inhibiting oxidative stress, lipid peroxidation, inflammatory cytokines, gene mutations, regulation of miRNA, genes, and gene regulators by exhibiting antioxidant activity, increasing the level of mitochondrial antioxidant enzymes, prevention of alterations in brain structure, blocking of unwanted protein plaque formation in the brain, etc. Based on the meta-analysis of nutraceuticals given a clear-cut point in the treatment of ASD, there is a positive result in prevention and treatment not only in ASD but in other diseases too.

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**Ethics Statement**

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**Informed Consent Statement**

This study did not involve human participants, and therefore, informed consent was not required.

**Clinical Trial Registration**

This research does not involve any clinical trials.

**Author Contributions**

- **Palanivelrajan Sumathi Yogitha:** concept and design,
- **Melapalayam Rengarajan Suchitra:** manuscript preparation and supervision.
- **Srinivasan Parthasarathy:** manuscript preparation and supervision

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