



Review Article

Phytochemicals And Nutraceuticals as A Promising Drug Candidate in Autism Spectrum Disorder

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ABSTRACT

Autism is a wide range of neurological illnesses with an unknown etiology that are solely diagnosed based on behavioral testing. The prevalence and frequency of autism spectrum disorder (ASD) have increased during the past twenty years. This condition has been linked to increased oxidative stress and decreased antioxidant capacity. Furthermore, oxidative stress vulnerability in autism may increase due to genetic and environmental factors. ASD develops this disorder in terms of both clinical symptoms and pathological process due to elevated oxidative stress. Changes in complex human behaviors, such as social interaction, communication, and stereotypes, are features of autism. Additionally, autistic children may not be able to handle anxiety and behave inappropriately even in the presence of stimuli that are generally benign. Growing data suggests that epigenetic pathways contribute to the etiology of autism. Many research have tried to find epigenetic biomarkers for ASD up till now. Children with autism spectrum disorder (ASD) typically exhibit pronounced behavioral challenges coupled with social connection problems.

INTRODUCTION

Autism paves a spectrum of neurodevelopmental diseases which start in the initial childhood and have potential to remain till adolescence and adulthood. According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), people suffering from Autism spectrum disorder (ASD) have compromised social skills, impediments in speech and communication and repetitive behaviors at some level [1]. ASD is a framework applied to demonstrate individuals having particular integration of deterioration in social interaction, speech and obsessive behaviors, immensely confined concerns and/or neurological behaviors occurring at initial stages of life [2]. The loss in two major domains, first, constraints in social relationships, communication and stereotyped, constant

patterns of behaviors are the characteristics of autism which is a common neuropsychiatric problem [3]. Autism is a highly inherited and diversified group of neurological development phenotype identified in greater than 1% of children [4]. The prevalence of autism is fairly less than 1% globally but in high-earning countries, estimates are greater [2]. 1 in 59 children (almost 1.7%) has been reported its prevalence in Unites States of America (USA) [5]. It is a growth phase classified by compromised social interaction, speech and repetitive behavior affecting 1 in 59 children. By 2020, ASD is predicted to affect 1 in almost forty (40) children [6]. Autism is complex neurological development impairment and the symptoms vary from absence of social relations and loss of communication to

inflexible, stereotypic and repetitive behaviors. This disorder has also been linked with comorbidities like, epilepsy, aggression, loss in sensory processing, anxiety and also with Attention-deficit/hyperactivity disorder (ADHD) [7]. Pre-natal stress has also been related with greater risk to develop autism in the child. Elevated levels of oxidative stress and reduced levels of antioxidant like glutathione peroxidase, catalase and superoxide dismutase thereby increasing inflammation, malfunctioning of immune system and mitochondria leading cause of ASD [8]. Adults suffering from post-traumatic stress disorder (PTSD) face complicated retarding impulses and has been linked to Autism in children [9]. Autism can be diagnosed at the juvenile age of eighteen (18) months, so it is recommended that typical inspection of ASD at the age of 18-24 months with proceeding developmental surveillance in the primary care to be intervened [10].

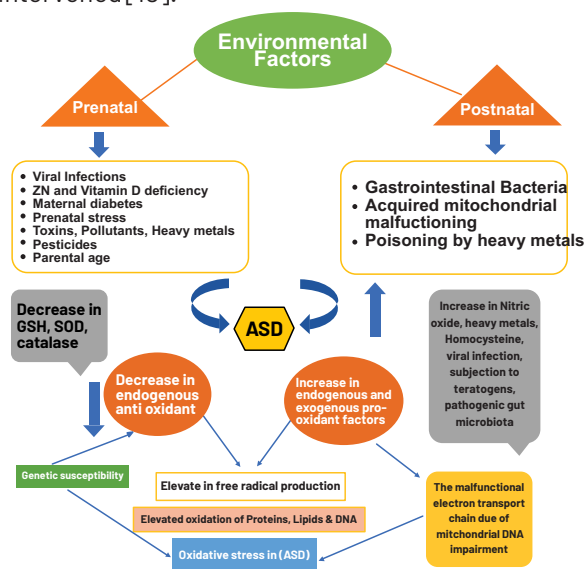


Figure 1: Different environmental predisposing factors which could be important for development of ASD by influencing genetic marks

Pathophysiology: In autism spectrum disorder (ASD), imbalance in the pathway of PI3K/Akt/mTOR has become the center of attention identify a curative role for tau depletion in down regulating this pathway and ameliorating the symptoms related with autism [10]. The distinct immune cells, mast cells, are provoked by stress and environmental stimuli that might then provoke microglia resulting in aberrant synaptic pruning as well as malfunctioning of neural connection. The “fear threshold” in the amygdala might be changed by this process and prompt a heightened “fight or flight” response. The integration of environmental stimuli together with corticotropin releasing hormone (CRH) which is secreted under the condition of stress, might be the main

contributors to the pathological process of autism [7]. Alterations in the sequence of DNA is DNA methylation which is linked to autism causation [11]. In ASD, the prevalence range of gastrointestinal complications is nine percent (9%) to seventy percent (70%) and it correlates with attitudes and behaviors compatible with the autistic endophenotype suggesting that these might be considered the main complications related with autism. A robust link of gut to brain cross-communication takes place due to gut dysbiosis which is responsible for abundant amount of propanoic acid (PPA) production, a short-chain fatty acid (SCFA), by impaired intestinal microflora in patients with autism. This aggravates impairment in neurochemical, mitochondrial as well as behavioral function taking place in autism [7].

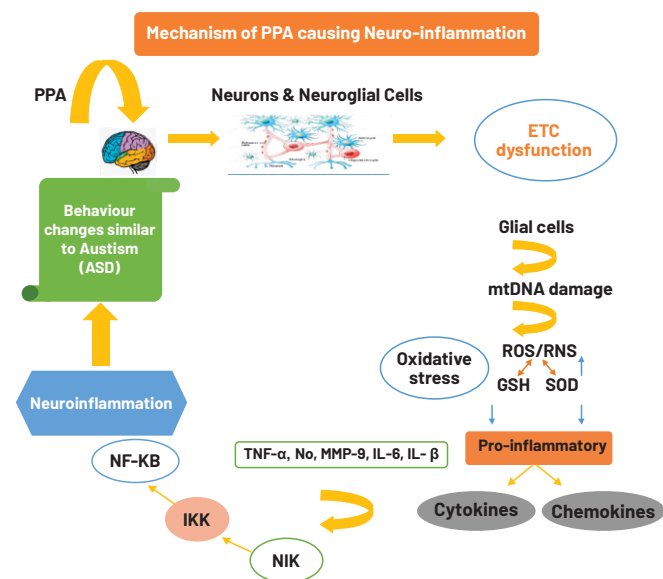


Figure 1: In Autism, the mechanism of oxidative stress

It is considered that autism appear during the course of initial cortical development. But, the definite stages of development and related molecular system which prime disease tendency are evasive. Schafer *et al.*, studied subject-acquired induced pluripotent stem cells (iPSCs) during the recapitulation of cortical development in order to figure out initial neurodevelopmental modifications in ASD with macrocephaly. ASD-related alterations in the growth pattern of initial development of neuron, which involved temporal downregulation of certain gene systems and structural growth escalation were revealed by our study. It is indicated by changed chromatin accessibility that observed alterations return back to a pathologically central phase in (NSC's). Concerted disproportionately represented network components in neural stem cells of control group was adequate to provoke autism-like properties, and bypassing the neural stem cells (NSC's) stage through direct conversion of autism induced

pluripotent stem cells (iPSCs) into induced neurons terminated autism-related phenotypes. It is recognized by our findings that heterochronic fluctuations of a gene network which organized initially in development, cause subsequent neurodevelopmental aberrations in autism [12]. Autism is a complex, diversified group of neurodevelopmental disorders occurring due to interaction between genes of environmental factors. ASD is closely linked with behavior alterations and loss of social interaction and communication. It has been suggested by existing research on pathophysiology that there is an association between severity of ASD symptoms and gastrointestinal problems. The intestinal permeability, mucosal immune function might be affected by downregulation of gut micro flora and intestinal inflammation. It has also been suggested by several studies that dietary components (food allergens/toxins) and metabolic activity of the gut microflora role might be related with behavioural modifications in neurodevelopmental disorders including ASD [13]. Sleep related problems are very common in young children suffering from autism (ASD) and are related with evidence of aggressiveness, anxiety or depression and attention problems [14]. The brain bases of autism (ASD) remain unknown despite its growing prevalence. It is indicated by aberrant levels of *N*-acetyl compounds, creatine + phosphocreatine, glutamate+glutamine or choline compounds computed by proton magnetic resonance spectroscopy which energetic metabolism of mitochondria, glial or neuron density and/or inflammation may add up to neuropathogenesis of ASD. The neuroanatomic distribution of these metabolites might assist analyze key theories of autism [14]. The gut microflora varies among typically developing (TD) and individuals with autism, although leaving it uncertain either the microflora contributes to symptoms besides from genetic risks. We transplanted gut microflora into disease free mice, taken from patients having autism or typically developing control group which showed that colonization of ASD gut flora is adequate for the induction of distinctive autism related behaviors. The mice brains having colonization of autism gut flora exhibit substitute grafting of autism-related genes. The particular species of bacteria as well as their metabolites take part in regulation of behaviors related to autism. It is anticipated by microbiome and metabolome profiles of mice fostering the gut flora of human. In fact, the treatment with metabolite of candidate microbe of an autism mouse model improved and regulated respectively behavioral abnormalities and excitability of neurons in the brain. We suggest that gut microflora, through formation of neuroactive metabolites, modulate the mice behaviors. This indicate that gut and brain

relations add up the pathophysiology of autism spectrum disorder [15].

Natural Products to Combat Autism Spectrum Disorder - A Mechanistic Approach: Dietary phytochemicals, as a substitute neurotherapeutic moiety, are considered to be secure and beneficial. By regulating signaling pathways like NF- κ B, Nrf2, MAPK cascade or Sirtuin-FoxO cascade, these compounds give neuroprotection. In scientific literature, there has been current evidence that dietary phytochemicals like curcumin, sulforaphane, naringenin and resveratrol regulate gut-brain debate responsible for behavioral, mitochondrial and biochemical malfunctioning and also cellular and behavioral sensory modifications. These dietary phytochemicals may be composed of novel brain-centered supply systems that control their constraints of reduced oral bioavailability and short half-life resulting in elongated action. The work on the formation of brain-centered potential therapeutic agents for neurological disorders like autism is still insufficient. In this chapter, we explore credible mechanisms and proof from scientific research studies as well as from our personal research for the usage of sulforaphane, resveratrol, naringenin and curcumin as neurotherapeutic agents for ASD [6].

Polyphenols: To fight against neurological (brain) disorders, dietary polyphenols are identified as auspicious nutraceuticals. These are the distinctive compounds which have indicated to be very beneficial to neutralize the neurodegeneration among other morbid conditions, oxidative stress, reduce inflammation, helpful in the prevention as well as treatment of numerous chronic diseases. In order to prevent and treatment of neurological disorders, the ability of these dietary polyphenols has not only been linked with their potential to arrive up the brain which rely upon their chemical composition and interaction promptly with cells in brain, but also on their capacity to regulate the cross-talk among gut and brain, interfering with various branches of this axis [16]. In order to prevent from or treat psychological or neurological disorders, one or more cannabinoids and/or terpenes together with psilocybin and/or psilocin can be used [17]. The compositions cannabinoid is depicted including minimum one (1) particular quantity of cannabinoid, particular quantity of a primary terpene, non-cannabinoid minimum 5% in terms of weight, carrier, non-terpene, optionally minimum three (3) secondary terpenes, glycol <5% in terms of weight and water <20% in terms of weight, where said non-terpene, non-cannabinoid carrier contains cellulose and terpenes to cannabinoids is about 0.1 to almost 1.0. In terms of weight-to-weight ratio in said composition. Also depicted are the above compositions where said non-cannabinoid, non-terpene carrier contains

<5% by weight cellulose and almost 0.05-1.0 is the terpenes to cannabinoids weight-to-weight ratio in said compositions, making terpene-enriched cannabinoid compositions with improved therapeutic effect compared with that of a composition consisting the similar quantities of cannabinoids and one half the amount of said primary terpene [18].

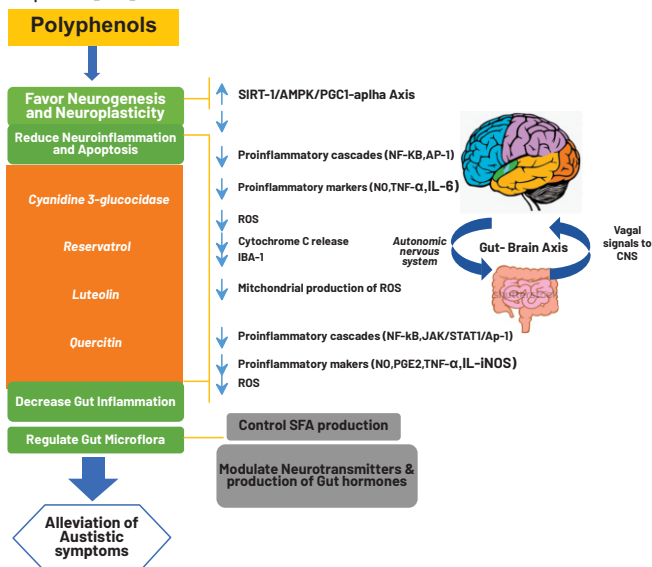


Figure 3 : Flow chart representing the major targets of polyphenols in ASD

Alkaloids: The aromatic oils, terpenoids, naturally occurring in numerous plants and greater than 200 have been described. Phytol, pinene, linalool, limonene, myrcene, caryophyllene oxide, nerolidol and β -caryophyllene all are the examples of terpenoids. The regulatory bodies such as the Food and Extract Manufacturers Association and the United States Food and Drug Administration (FDA) recommend that these terpenoids are generally Recognized as Safe as food additives [19].

Flavonoids: here has been a revival of attraction in pseudo and plant-based flavonoids as regulator of ($GABA_A$) receptor activity which affect restriction controlled by the main repressive neurotransmitter gamma-amino butyric acid-A ($GABA_A$) in the brain. The captivating domain comprise (i) flavonoids which *in vitro* studies exhibit subtype selectivity in recombinant receptor persistent with their behavior related impacts *in vivo*, (ii) by flavonoids, flumazenil-insensitive regulation of $GABA_A$ receptor action, (iii) by benzodiazepines the capacity of a few flavonoids to function as second-order regulators of first-order regulation and (iv) on $GABA_A$ receptor complexes, the recognition of the various active sites of flavonoids. In the unavailability of $GABA_A$, a growing and captivating domain is the triggering of $GABA_A$ receptors through flavonoids. For the formation of latest therapeutic agents, the flavonoids

are beneficial scaffolds which is implied by comparatively their hard configuration. Flavonoids have broad spectrum influences on several biological marks as similar to steroids. The confront is to perceive the structural components of flavonoid influences on certain marks and formulation of agents which are particular for these marks [20]. Natural flavonoids such as quercetin and luteolin display strong anti-inflammatory as well as anti-oxidant functions and restrict the secretion of inflammatory mediators from human Mast Cells (MCs). Luteolin and its structurally related quercetin inhibit allergic inflammation as well as the release of interleukin-6 and interleukin-8 (IL-6), (IL-8), histamine, leukotrienes and TNF-alpha from cultured mast cells of humans. It is indicated by brain expression, microglia activation and also by elevated levels of IL-6 and TNF-alpha in plasma that there is a close link between autism spectrum disorders (ASDs) brain inflammation [21].

Naphthoquinones: To aggregate neuroactive compounds, fermentation is considered as a beneficial procedure. The alterations in the quantities of neuroactive substances which are present in food are permitted by food processing. Food components may influence the production of neuroactive compounds by gut microflora. There is an association between probiotics, prebiotics and psychological health of humans. Specific plants and microbes manufacture the neuroactive compounds through playing various roles, particularly as a stress response. In foods, the well-known neuroactive compounds are dopamine, serotonin, melatonin, norepinephrine, tyramine, histamine, tryptamine, kynurenic acid, kynurenine, gamma-aminobutyric acid (GABA) and β -phenylethylamine. A few of these compounds are present in fermented foods that may affect mood or behavior as well as on overall human health [22].

CONCLUSIONS

Autism is broad spectrum disorder associated with behavioral abnormalities and elevated stress and anxiety levels. Environmental pollutants, poor maternal diet, gut microbiome anomalies are major etiological factors of ASD. Diet comprising of bioactive components plays a pivotal role in combating neurological disorders as Autism and Alzheimer. Gut microflora is associated with good brain health so, neuroactive substances in foods possesses health benefits; these substances can also be manufactured by gut flora that is very appealing subject to evaluate the relationship of gut microflora with brain health.

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