UNDERSTANDING AUTISM: A COMPREHENSIVE REVIEW OF UNDERLYING MECHANISMS AND THE PHYTO-THERAPEUTIC INTERVENTIONS

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ABSTRACT

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by significant deficits in social interaction, communication, and the presence of repetitive behaviors. First described by Leo Kanner in 1943, the modern understanding of ASD has evolved, and it is now formally classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The global prevalence of ASD is increasing, with estimates suggesting that 1 in 100 children worldwide are affected, although some researchers believe the true number may be higher. The etiology of ASD is multifactorial, involving a combination of genetic, epigenetic, and environmental factors. Genetic studies have identified numerous mutations and gene complexes associated with neurogenesis, synaptogenesis, and neuronal connectivity. Brain imaging studies have revealed structural and functional abnormalities, including altered Wnt signaling, dysregulated neurotransmitter systems, and impaired synaptic function, all of which contribute to the complex neuropathology of ASD.

Current conventional treatments for ASD are limited, with only a few FDA-approved drugs, such as risperidone and aripiprazole, which primarily manage symptomatic behaviors. This scarcity of effective treatments highlights a critical need for new therapeutic avenues. This review provides a comprehensive overview of the mechanisms underlying ASD, including altered signaling pathways like Wnt signaling, activity-dependent gene transcription, and synaptic dysfunction. Additionally, it explores the potential of complementary and alternative therapies, particularly phytochemicals and plant-derived compounds, for their anti-autistic properties. The review observes the therapeutic potential of nutraceuticals such as Omega-3 fatty acids, polyphenols, and carotenoids, and researches into specific plants like *Ginkgo biloba, Zingiber officinale, Astragalus membranaceus, Centella asiatica*, and *Acorus calamus*. By integrating the neurobiological mechanisms with the properties of these plant-based interventions, this review aims to expand the knowledge base on ASD and identify promising new horizons for treatment, while acknowledging the need for further research to substantiate their efficacy and safety.

KEYWORDS

Autism Spectrum Disorder (ASD), Neurodevelopmental Disorders, Wnt Signaling, Synaptic Dysfunction, Neurotransmitters, Phytochemicals, Complementary and Alternative Medicine.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome characterized by substantial socialization, communication problems, and stereotyped or repetitive behavior. It commonly occurs throughout the baby's developing stage. In 1943, Leo Kanner, an Austrian-American child psychiatrist, first described autism (Rodas, 2018) by studying 11 kids who had "a strong need for loneliness and isolation" as well as "an intense demand on continuous separateness"(Fisch, 2012). Kanner called the disorder "early infantile autism," which was later recognized as typical autism (Leo Kanner - Wikipedia, n.d.). The modern definition of "autism" is generally attributed to Leo Kanner. The term autism spectrum disorder (ASD) was most officially included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) with a relational description of key symptoms: based on developing social interaction and communication obstacles, as well as repeated, constrained habits, hobbies, or activities (Park & Park, 2020).

According to WHO, one in every 100 children worldwide has autism, although researchers believe the true prevalence is far higher (Autism, n.d., 2023). According to a 2020 CDC estimate, ASD affects around one of every 39 children. However, researchers predict that by 2025, nearly one out of every two children in the United States will receive an ASD diagnosis. There are an estimated 18 million persons with autism. In India.

According to investigations, the great majority of instances of autism are due to genetics. The likelihood of developing autism is increased among babies born to an older father and mother. As per the research, the probability that identical twins would experience autism ranges from 37 to 95 percent. In non-identical siblings, autism affects the other kid by approximately 31 percent if one exhibits the disorder (Autism and Health: A Special Report by Autism Speaks | Autism Speaks, n.d., 2023).

Overall brain development among individuals with ASD is significantly influenced by a range of environmental and familial components, along with their interconnections. Phylogenetic analysis of ASD has revealed mutations that prevent proper neurogenesis from the embryo until infancy. Several genetic complexes have been associated with synaptogenesis as well as axonal mobility. Moreover, due to the microstructural, macrostructural, and functional abnormalities that occur, a sequence of imbalanced neural nets involved in social and emotional functioning appears across the developing brain. ASD sufferers have complex neurodevelopment that is influenced by a wide range of hereditary and environmental variables. In MRI research assessing brain structure in individuals with ASD, cortical as well as subcortical nerve fibers increase throughout the initial stages of brain growth, which has frequently been observed. fMRI study proves reduced stimulation of pathways associated with emotional and social perception; resting-state fMRI study revealed widespread global underconnectivity in socioemotional circuits. Moreover, electrophysiological studies reveal that people with ASD exhibit modifications in both their resting state and stimulus-induced oscillatory behavior (Sinha et al., 2015). The well-preserved gene as well as genomic channel groups were connected with ASD. It is essential to integrate these genetic

components with a detailed phenotypic analysis of the cellular and behavioral features to comprehend the pathogenesis of ASD. There is optimism that new treatment modalities will be created using the plethora of ASD-related alleles that have previously been discovered.

Antipsychotics like Risperidone as well as aripiprazole, both manage Autism manifestations and constitute the sole medications FDA-approved in the present era in autism spectrum disorders. It must be suggested that one begin with modest dosages and cautiously taper down prescriptions because kids and teens with autism spectrum disorder appear to be particularly susceptible to pharmacological complications. Some complementary and alternative therapies have already been examined as possible remedies for autism, even though the information for several of these approaches is extremely scant (Vismara et al., 2010).

Furthermore, fundamental research using animal models is giving vital details regarding several facets of human autistic behavior. Yet further study is needed to completely understand the anomalies of ASD at the genetic and molecular levels (Banerjee et al., 2014). As already stated, ASD has been related to the genome and genomic routes that have endured well, and several of which have provided significant perspectives into the pathological changes in ASD sufferers' brains.

METHODOLOGY

An exhaustive literature search was conducted using several databases (PUBMED-MeSH, PMC, Web of Science, Google Scholar, and Research Gate). The above-mentioned databases were searched with no time constraints. The PRISMA procedure was followed.

RESULT AND DISCUSSION:

TYPES OF AUTISM SPECTRUM DISORDER

ASD generalization encompasses 5 distinct symptomatic groups. Autism may also be classified as syndromal and non-syndromal autism. Syndromal autism is connected with significant mental impairment or hereditary characteristics. Autism can potentially be of the regressive kind. Among such autistic kids, the identification of autism is established primarily based on a lack of speech or interpersonal abilities.

Autistic Disorder

In Autism Disorder, the anomalies in the interpersonal and verbal domains are persistent and apparent well before the age of three. The sufferer is likely to engage in only a few things. Autism is characterized by delayed communication. People with Autism Spectrum Disorder may also have cognitive impairment (Cosgrove et al., 2007).

Typical Characteristics (Mythili & Shanavas, 2014)

- Difficulty forming friends.
- Looking for friendship but unable to communicate in two-way interpersonal relationships
- Learning to accept social advances but being socially disengaged.
- Eye contact that is unnatural, non-directive, or disinterested.

- Poor comprehension of the intentions, views, or emotions of other

Asperger's Disorder

Some may be persistent social deficits, although they are less common in the area of interaction domain because speaking usually emerges at a regular age. Yet, some people might continue to have trouble with it. At a younger age, the anomalies look less prominent, but when that individual is in school, it becomes more noticeable. An ordinary or above-average IQ might be present in those who have the condition Asperger's syndrome. Males are more likely than females (13:1) to have this condition, while females might experience less severe cases(Ahuja & Kaur, 2014).

Typical Characteristics of Asperger's

- Intelligence is average or marginal
- No normal common sense
- Standard as well as early speech formation
- Inability to accept change
- Anxious

Pervasive Development Disorder

A determination of PDD can be made when a kid does not match the requirements for a specific disorder but has a significant and widespread disability in some behaviors. It is commonly known as atypical autism (Hendrix & Hopkins-Staten, 2011).

RETT's Syndrome

It is not exactly under the classification of autism, but the DSM-IV classifies it into the category of ASD. For two reasons, PDD is not included under the ASD classification. The first reason is that Rett's disorder is due to a single gene mutation, but others are due to multiple gene mutations. The second reason is that the progression of Rett is different from ASD (Ahuja & Kaur, 2014).

Childhood Disintegrative Disorder

Frequently, ASD is used to describe Childhood Disintegrative Disorder (CDD), which is a different condition. It is occasionally linked to different medical neurological problems, but none have been identified that fully explain all cases and signs of Childhood Disintegrative Disorder (CDD) (National Autism Center, 2011). During an average of 2-4 years of ordinary growth and development, but often around the age of 10, children with CDD begin to lose talents and show indicators of ASD. Kids with CDD may find it difficult to initiate discussions with others or communicate non-verbally by gestures, smiling, or nodding. The kids can perform repetitive actions like waving their hands, whirling their bodies, moving back and forth, or doing other sorts of continuous motor movements (National Autism Center, 2011).

SOME SIGNALLING PATHWAYS IN ASD

Altered WNT signaling in ASD

WNT signaling is essential for methods like Central nervous system regional integration, neural progenitor differentiation, neuronal migration, axon guidance, dendritic spines development, synapse formation, adult neurogenesis, and neuroplasticity as well as post-neurodevelopmental procedures(Komiya & Habas, 2008) As a result, any disruption in WNT signaling may lead to the emergence of disorder which affects the internal and external functioning of the Central nervous system(Mulligan & Cheyette, 2016; Okerlund & Cheyette, 2011). Over the past several years, research using genetically modified laboratory animals, hiPSC models, and large-scale human new genetic research in several neurodevelopmental disorders has highlighted the significance of spatial and temporal regulation of WNT signaling during an individual's life expectancy (Okerlund & Cheyette, 2011).

Even though WNT signaling is heterogeneous, it may be roughly divided into either "canonical" (β-catenin-dependent) or "non-canonical" (β-catenin-independent) pathways. These are essential for brain growth and neurons associated with developmental disabilities (Fu et al., 2004; Rosso & Inestrosa, 2013). Interestingly, several essential proteins of both signal transduction pathways are found at synapses, which are crucial for the development of synapses. Canonical Wnt communication causes β-β-catenin to travel from the surface of the cell toward the nucleus, which links exogenous signals to nuclear regulation of gene expression by downstream transcriptional mechanisms (Mullins et al., 2016). From one perspective, β-β-catenin is released by MET tyrosine kinases, which are linked to autism spectrum disorders (like CDH8), to attach calcium on the surface of cells (Judson et al., 2011). On the reverse perspective, GSK3 phosphorylates free cytoplasmic β-β-catenin to indicate the degree of proteasomal breakdown (Kwan et al., 2016). Several Wnt molecules, particularly Wnt2, connect LRP5/6 coreceptors and crinkled receptors to transfer messages at the apical membrane (MacDonald & He, 2012). Notably, the β-β-catenin-encoding gene CTNNB1 has already been linked to ASD risk variance (de Ligt et al., 2012). CDH8 is a prime example of a chromatin modulator that affects the expression of certain other autism genetic factors. CDH8 functions as a downregulator in the canonical Wnt signaling cascade (Cotney et al., 2015).

Activity-dependent gene transcription and translation of messenger RNA

The activation of neurons periodically controls mRNA interpretation and genetic factor control (Buffington et al., 2014; Greer & Greenberg, 2008) It is thought that several specific genes, such as CHD8 and CTNNB1, as well as de novo alterations connected to autism regulation or connect with conventional signaling pathways. Dysregulation in a variety of upstream signaling molecules of translation, such as the mammalian domain of rapamycin and Mitogen-activated protein kinase, leads to increased protein biosynthesis and, consequently, altered neuroplasticity. (Buffington et al., 2014).

Activity-dependent transcription of genes

Neural impulses modulate genomic patterns, and alteration of activity-dependent transcription factors or their substrates is linked to ASD. (Amir et al., 1999; Moretti et al., 2005) ADNP (Helsmoortel et al., 2014), engrailed 2 (EN2) (Hnoonual et al., 2016) (Paşca et al., 2011),TBR1 (Chuang et al., 2014) (Findling et al., 1997), MEF2C, de novo mutations in Ub15q11-q13 (Moretti et al., 2006) are examples of such interruptions.

Rett syndrome, a debilitating disorder with symptoms similar to autism, is a catastrophic neurodegenerative condition that affects females who have MeCP2 alterations on the X-linked genomic factor (Amir et al., 1999). MeCP2, a regulatory repressor that covers almost the whole chromosome, boosts overall regulatory activity and modifies chromatin condensation (Guy et al., 2011; Moretti et al., 2005). MeCP2 gets phosphorylated, as the NCOR subunit dissociates due to its induction by BDNF or drugs that increase intracellular cAMP levels, enabling transcription to take place. (Ebert et al., 2013).

Importantly, several investigations have shown that MeCP2 may bind to genetic material and transcriptional stimulators at the operator of an effective location to boost the production of genes, serving as both a regulatory activator and a repressor. (McGraw et al., 2011).

Most prevalent genetic mutations and unusual problems involving genes making calcineurin subunits have a major impact on the prevalence of ASD. Timothy syndrome, a monogenic disorder that raises the probability of ASD and is brought on by alterations in the L-type Calcium channel. (Guy et al., 2011; Paşca et al., 2011)

Synaptic function

A variety of genes that are linked to ASD are thought to affect synapse formation and functioning. Alterations in synaptic proteins may be one of the factors that lead to the rise of ASD. Among the potential factors that raise the possibility of getting ASD are aberrant synaptic molecules (Lord et al., n.d.), synaptic peptides, such as NLGNs (Vaags et al., 2012), NRXNs postsynaptic scaffolding proteins SH3, SHANK (Monteiro & Feng, 2017), glutamate receptors NMDAR (Yang et al., 2011), inhibitory GABA-A receptor (Chevaleyre & Castillo, 2004)

Synaptic structure and homeostasis.

The brain requires cellular homeostasis as well as functional synapse structure to operate normally. Enhanced dendritic spine density and abnormal nerve fiber shape were both found in neuropathological examinations of people with ASD(Lo & Lai, 2020). In autism pathophysiology, NRXNs, as well as NLGNs, which are presynaptic and postsynaptic binding associates, work together to create transsynaptic compounds that effectively regulate synapse growth and maintenance (Grabrucker et al., 2011). NLGN-2 is predominantly found on GABA synapses, as opposed to NLGN-1, NLGN-3, and NLGN-4, which are found on the glutamate postsynaptic membrane of the neuron.

Activity-dependently, NLGNs may take a role in the development of glutamatergic as well as GABAergic junctions. In particular, restriction of NLGN1 activation inhibits the development of glutamatergic junctions through the activation of NMDARs or even the downstream molecule CaMKII (Südhof, 2008), while reduction of NLGN2 activities inhibits the development of GABAergic connections.

Neurotransmitter system

Several neurotransmitters as well as neuromodulators work together to regulate the function of brain regions and neural circuits (Fernández et al., 2017). Cyclic variations in neurotransmitter level, discharge, and receptor distribution may have an immediate influence on the operation of brain circuits and, therefore, behavior.

The proportion of excitability to inhibitory neurons and their activity regulates the excitation and inhibition equilibrium. Individuals with autism have altered plasma concentrations of GABA as well as glutamate, with notably higher concentrations

of GABA and lower glutamate concentrations (Al-otaish et al., 2018). An earlier study has emphasized the significance of glutamate disruption in the cause of autism (Chao et al., 2007; Siegel-Ramsay et al., 2021; Zheng et al., 2016). Several studies showed a decreased amount of GABA receptors in the brains of ASD patients. ASD animal models also show a decrease in inhibitory neurons as well as disruption of regulatory neurological communication due to abnormalities in genes (Vogt et al., 2015), which could trigger changes in the proportion of excitation to inhibition.

5-HT has traditionally been considered to be linked to emotional behavior. Early studies revealed that autistic youngsters had higher amounts of serotonin in their blood (Muller et al., 2016). Brain scans and neurobiochemical studies showed that up to 45% of people with autism exhibit higher amounts of serotonin. In SERT and MAOA transgenic model organisms, impaired 5-HT neurological communication and interpersonal cognitive impairments were documented (Muller et al., 2016).

The dopamine (DA) function has been implicated in autism spectrum disorders, and a previous study found that patients' CSF levels have elevated DA metabolites. Mesolimbic dopaminergic transmission abnormalities in autistic children include reduced levels of dopamine within the frontal brain (Gillberg, 1993).

Nutraceuticals in asd

OMEGA-3

The metabolism of humans depends on omega-3 fatty acids in their diets. (Pangrazzi et al., 2020) As omega-3 fatty acids compounds have anti-inflammatory properties, they are essential for controlling the inflammatory response (Calder, 2010). Healthy brain activity is impacted by the defective metabolism of fatty acids. Moreover, omega-3 fatty acids are crucial for the myelin sheath's growth and for the architecture of cortical cellular membrane (van Elst et al., 2014). Studies show a connection between the pathogenesis of ASD and aberrant lipid oxidation. (James et al., 2004) Omega-3 fatty acids supplementation may enhance ASD-like behaviors in autistic persons, most probably through lowering brain inflammation and promoting the gastrointestinal system axis's proper functioning (Pangrazzi et al., 2020).

POLYPHENOLS

Polyphenolic compounds may be potential compounds to reduce the symptoms of ASD, according to the latest research. According to several investigations, certain polyphenols, like resveratrol, control mitochondrial respiration and guard against the malfunction that seems to be commonly present in individuals with an autism spectrum disorder. (Jardim et al., 2018). The first and most prevalent category of bioactive compounds generated by plants is phenolic acids, a type of nutraceutical chemical. Several foods, such as veggies, berries, and grains, contain these compounds (Pangrazzi et al., 2020). Phenols can donate electrons to oxidized atoms because they have one or more hydroxyl groups connected to an aromatic ring. Due to this, phenolic compounds are regarded as potent antioxidant compounds. The category of phenolics is exceedingly diverse and exhibits a variety of chemical characteristics. Flavonoids, which belong to the polyphenol group and include quercetin and luteolin, have anti-inflammatory and antioxidant characteristics. (Li et al., 2016) The delivery of polyphenols can reduce neuroinflammation and, as a consequence, encourage a diminution in ASD-related manifestations in kids. Moreover, a recent

study found that a 10-year-old ASD child's ASD-like behaviors improved after receiving microgranules containing luteolin and palmitoylethanolamide twice daily for a year. (Bertolino et al., 2017)

CAROTENOIDS

Carotenoids are a group of naturally occurring, fat-soluble, red, orange, and yellow tints that were already created by microbes, fungi, and plants. Carrots, tomatoes, and pumpkins all contain these molecules, which are also responsible for their distinctive hue. Significantly, several carotenoids have anti-inflammatory and antioxidant effects. (Skibsted, 2012). According to multiple studies, persons who consume higher carotenoids in their diet have a lower chance of developing chronic illnesses such as age-related macular degeneration, blindness, photosensitivity disorders, and heart problems (Susan Taylor, 1996). Moreover, carotenoids have been demonstrated to enhance cognitive abilities in middle-aged individuals, indicating that these substances may be useful in promoting brain and mental health (Kesse-Guyot et al., 2014). The terpenoid family member astaxanthin, a member of carotenoids, demonstrated potential benefits in the setting of neurological illnesses.

PLANTS WITH ANTI-AUTISM PROPERTIES

Ginkgo Biloba

Ginkgo extract, derived from the leaves of the Ginkgo biloba plant, is a medicinal compound that has shown promise in the treatment of a wide range of circulatory, nervous system, and brain disorders (T. C. Smith et al., 2007). The majority of the research studies on ginkgo's impact on psychological issues have focused more on memory enhancement, dementia, Alzheimer's, antioxidant capabilities, and using it in conjunction with other psychiatric medications to increase the impact or lessen unusual adverse reactions (Silva et al., 2011). Ginkgo biloba is effective in treating individuals with memory and attention issues resulting from brain anomalies, according to an analysis of 40 randomized clinical studies (T. C. Smith et al., 2007).

Additionally, Ginkgo biloba controls blood flow in the brain's arteries and may aid in reducing hyperactivity brought on by weariness and inattention (T. C. Smith et al., 2007). The CNS's various neurotransmitter systems respond favorably to ginkgo biloba extract. One study showed that Ginkgo prevented aged rats from having fewer brain 5HT1A receptors (HUGUET et al., 1994). In recent times, it was determined that ginkgo extract can reversibly block the MAOA and MAOB enzymes. This method highlights the ginkgo's modest anti-depressive and anxiety-relieving properties, which may be useful in the management of ADHD. The nervous system's function of dopamine has also been elevated by ginkgo. Ginkgo's therapeutic benefits have also been linked to its ability to inhibit platelet-activating factors, inhibit reactive oxygen species, and control serotonergic, noradrenergic, and dopaminergic systems (Burns et al., 2006). According to one study, GB extract can protect retinal neurons from glutamate-induced excitotoxicity (Gertz & Kiefer, 2004).

Even though there are numerous differences of opinion among studies on the benefits of Ginkgo biloba on dementia, most of them concur that Ginkgo is more helpful than placebos at moderate to intermediate levels. The impact of ginkgo on patients receiving risperidone treatment was assessed in research on 40 autistic children (Ernst & Pittler, 2000). The Aberrant Behavior Checklist was used to gauge the severity of the disease. The Adverse Effect Checklist was used to evaluate the adverse effects of medications. Subjects were observed for 10 weeks at two-week intervals. Risperidone dose ranged from 1-3.5 mg per day

(about equivalent to 0.08 mg/kg), while ginkgo T.D. dosage was 80 mg per day for individuals under 30 kg and 120 mg per day for those above 30 kg. The dose of ginkgo throughout the healing process remained unchanged. According to the findings of this study, adding ginkgo at dosages of 80 mg per day for people under 30 kg and 120 mg per day for people over 30 kg was not successful in any additional improvements in any of the symptoms of autism according to each of the five subscales of the ABC criteria (inappropriate speech, stereotype hyperactivity, irritability) (Ernst & Pittler, 2000).

Zingiber Officinale

Ginger is a natural medication primarily used for the treatment of feelings of nausea, vomiting, gastrointestinal spasms, and digestive problems. It promotes saliva and bile production in the gastrointestinal tract and removes toxins. By accelerating stomach emptying and promoting more food movement through the intestine, ginger may assist with digestion. In situations of gas and pain in the abdomen, it produces a positive sensation. It is perfectly safe to consume up to 3 grams of ginger daily or even more. It improves blood flow to the brain and is also now advised for autism (Hori K, Wada A, 1970)

Astragalus Membranaceus

In addition to being utilized as a cure for chronic conditions other than autism spectrum disorder, astragalus membranaceus is an energizing and immune-boosting plant. Astragalus membranaceus raises energy, improves the effectiveness of various types of immunological functions, and has antibacterial and antiviral effects. It also helps the body cope with stress. It is also used for water retention, feeling numb, persistent ulcerations, and sweating during the night. It is utilized as an immune booster in kids who frequently get illnesses (Jiao et al., 2014).

Centella asiatica

Centella asiatica is utilized to enhance mental clarity, overall mental performance, memory, and focus. It is also used to treat neurological problems as well as to help nerve cells recover from traumas such as spinal injuries. Epilepsy, hair loss, psoriasis, and senility are among the conditions it is used to treat. For the treatment of Alzheimer's disease, Centella asiatica has been a promising medicament (Pradhan, 1970; Stoeckel, 1981).

Acorus calamus

In Asian cultural medicine, Calamus, also known as the Acorus calamus, is a significant herb for mind rejuvenation. It strengthens our capacity for expressing ourselves. The root improves cognition and alertness, boosts blood flow to the brain's cerebral cortex, and fosters connection and self-expression. It has a bitter flavor and functions as an intestinal tonic. It effectively reduces the signs of autism. Calamus has a relaxing pulmonary action as well. A combination of calamus with other herbs is used to treat epilepsy, particularly absence seizures, and to take the place of anticonvulsant drugs (Balakumbahan et al., 2010).

CONCLUSION

In conclusion, autism spectrum disorders are complex neurodevelopmental disorders and are common among children. ASD is a spectrum of disorders, so it can manifest differently in each person. Autism has many etiologies involving genetic and

environmental factors. From the literature search for this review, it is identified that its estimates are higher but the treatments are still limited, most available therapies only provide symptomatic relief. So, there is a need to determine a new horizon of treatments. And our review may help to know more about autism disorder but further research is needed to expand the knowledge and understanding of ASD

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