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Exploring pathological targets and advancing pharmacotherapy in autism spectrum disorder: Contributions of glial cells and heavy metals

Dhrita Chatterjee, Kousik Maparu and Shamsher Singh

Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India

Summary. Autism spectrum disorder (ASD) is a globally recognized neurodevelopmental condition characterized by repetitive and restrictive behavior, persistent deficits in social interaction and communication, mental disturbances, etc., affecting approximately 1 in 100 children worldwide. A combination of genetic and environmental factors is involved in the etiopathogenesis of the disease, but specific biomarkers have not yet been identified. Due to the lack of clinical evidence, fluctuations in symptoms, and difficulties in *in-vitro* and *in-vivo* modeling, developing medications for ASD is quite difficult. Although several drugs are used to treat autism, only risperidone and aripiprazole have received FDA approval in the United States. Epidemiological studies have suggested that maternal exposure to valproic acid (VPA), acetaminophen, propionic acid, and metals, such as cadmium (Cd), lead (Pb), arsenic (As), and mercury (Hg), may contribute to the development of various neurodevelopmental disorders. Pathological targets directly implicated in the disease include excitatory-inhibitory (E/A) imbalance, hyperserotonemia, GSK-3 inhibition, and Akt pathway activation. However, while a combination of pharmacotherapy, behavioral, and nutritional/dietary interventions has been found to be the most effective conventional therapy to date, many patients have chosen to implement particular dietary supplements for reducing ASD symptoms. In this review, we briefly describe various pathological targets and their roles in the pathophysiology of ASD and treatment strategies, including some future research directions.

Key words: ASD, E/A imbalance, Glial cells, GSK-3β, Akt/mTOR pathway, Nutritional and dietary therapy

Corresponding Author: Prof. (Dr.) Shamsher Singh [M. Pharm, h.D.], Professor and Head, Neuropharmacology division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, 142001, India. e-mail: shamshersinghbajwa@gmail.com

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Introduction

Autism spectrum disorder (ASD) is a complicated neurodevelopmental condition that mostly affects an individual's capability to learn and interact with other people (Hirota and King, 2023). According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the key characteristics of ASD include repetitive and restricted activities, interests, behavior, as well as various cognitive challenges (Posar et al., 2015). ASD can range from mild to severe, profoundly impacting a person's quality of life, including social relationships, physical and mental health, daily activities, etc. The National Autistic Society reports that autism is more prevalent in males than in females by a ratio of 4:1, and it is typically diagnosed at the age of 2-4 years when the brain is developing (Goyal, 2016). As people with autism experience a wide variation in symptom type and intensity, it is termed a 'spectrum' disorder. Furthermore, psychological

Abbreviations. 5HT, 5 hydroxytryptamine; ABA, Applied behavioral analysis; ADHD, Attention deficit hyperactivity disorder; ASD, Autism spectrum disorder; BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; CCL4, C- motif chemokine ligand 4; CDC, Centers for disease control and prevention; CHD8, Chromodomain helicase DNA binding protein 8; CNS, Central nervous system; CNTNAP2, Contactin-associated protein-like 2; COX2, Cyclooxygenase 2; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, edition 5; FDA, Food and Drug Administration; FMR1, Fragile X messenger ribonucleoprotein; GFCF, Gluten-free casein-free; GSK 3, Glycogen synthesis kinase 3; GST, Glutathione S transferase; IL6, Interleukin 6; JAK-STAT, Janus kinase/ signal transducers and activators of transcription; LTP, Long term potential; MECP2, Megadalton protein complex 2; MECP2, Methyl CpG binding protein 2; mPGES-1, Microsomal prostaglandin E synthase-1; MRI, Magnetic resonance imaging; mTOR, mammalian target of rapamycin; NMDA, N-methyl D-aspartate; PGE2, Prostaglandin E2; PTEN, Phosphatase and TENsin homolog; RTT, Rett syndrome; SHANK3, SH3 and multiple ankyrin repeat domain 3; SSRI, Selective serotonin reuptake inhibitor; TNFα, Tumer necrosis factor α; TSC, Tuberous sclerosis complex; VPA, Valproic acid; Wnt/β catenin, Wingless/ β catenin.

disorders such as anxiety, obsessive-compulsive disorder, and depression are more common in ASD (Hodges et al., 2020). Notably, there are some physiological and pathological connections between attention deficit hyperactivity disorder (ADHD) and ASD, as both conditions exhibit similar symptoms (van Steijn et al., 2012). Over the past few decades, the prevalence of autism has increased significantly (Chiarotti and Venerosi, 2020). In the year 2021, the Indian Journal of Paediatrics published a study where the estimated prevalence of autism in India was about 1 in 68 children (Salari et al., 2022). Recently, in 2024, the US Centers for Disease Control and Prevention (CDC) suggested a prevalence of 1 in 34 children diagnosed with ASD in the US. Asian and Pacific Islander Children are more likely to be diagnosed with autism as a few research studies have reported that ASD more frequently affects Black rather than White children, however, the reason is not clear (Maenner et al., 2023).

The brains of children with autism involve alterations in the structure and function of a non-autistic brain. Researchers use Magnetic resonance imaging (MRI) to help identify the brain parts with anatomical dissimilarities among autistic people. Multiple investigations demonstrated that children and adolescents diagnosed with autism have a larger hippocampus, a smaller amygdala, reduced brain tissue in specific parts of the cerebellum, and a thicker cortex (Schumann et al., 2004). A 2020 study found that the amygdala is larger in girls diagnosed with the disease than in boys (Lee et al., 2022). An individual with autism also has atypical frontal, temporal, and parietal cortical growth and connection anomalies in the corpus callosum, a structure that promotes communication between the two hemispheres (Just et al., 2012). Figure 1 describes various etiological and pathological factors involved in autism. ASD is also termed "developmental disconnection syndrome" as it is a 'neural system' disorder driven by abnormalities in widely distributed cortical circuits.

A combination of numerous genetic and environmental variables significantly contributes to the occurrence of autism, described as a polygenic inherited brain disorder involving mutations in specific genes or chromosomal abnormalities (Chaste and Leboyer, 2012). The specificity of all the associated genes is described in Table 1. Additionally, autism is also influenced by some environmental factors involving (a) greater parenteral

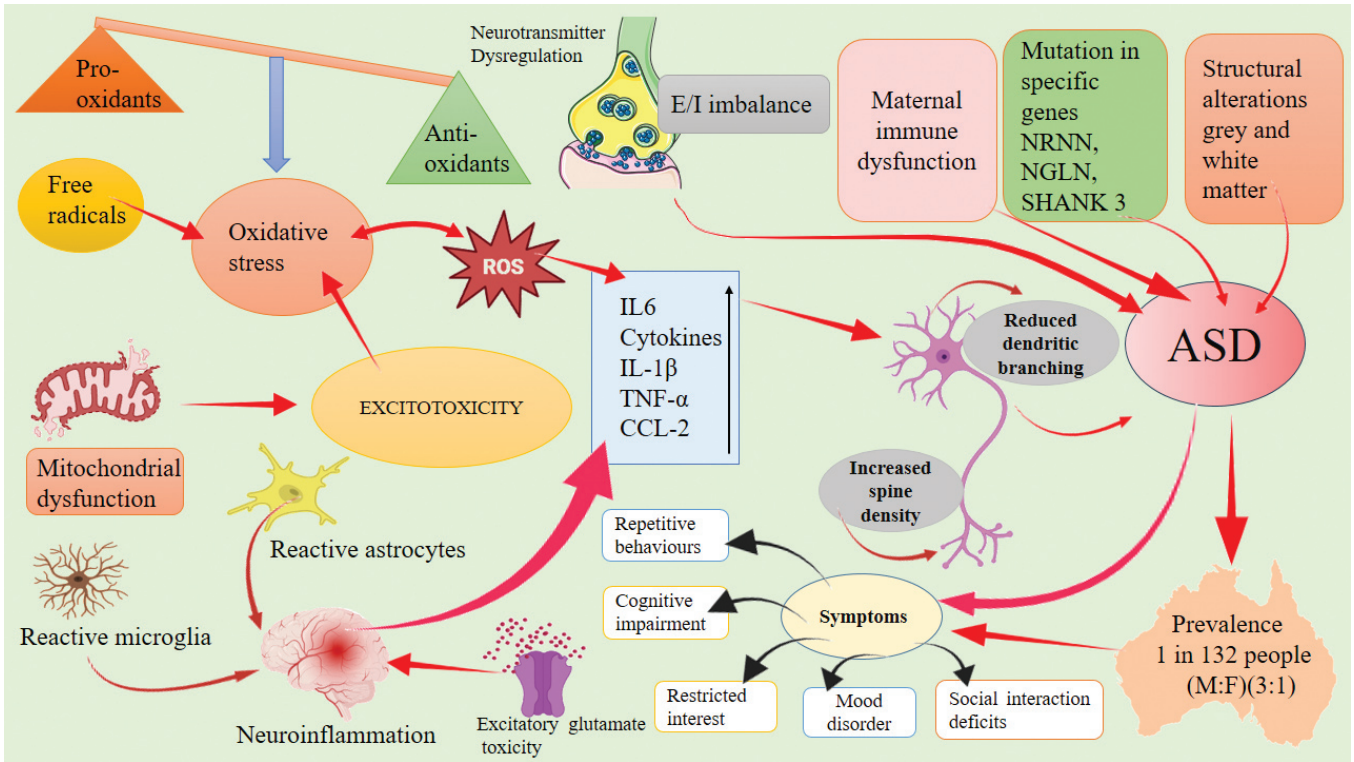

Fig. 1. Etiology and pathology involved in ASD. Increased prooxidants (Nitric oxide, xanthine oxidase, heavy metals) and decreased antioxidants (SOD, Catalase) enhance oxidative stress through mitochondrial dysfunction. Additionally, reactive astrocytes and microglia can trigger neuroinflammation by increasing the release of inflammatory mediators. This inflammatory response may interfere with synaptic maintenance, resulting in hyperconnectivity in specific brain regions, reduced neuronal dendritic branching, and increased spine density. These changes lead to the occurrence of ASD. This figure also shows the etiological factors and symptoms of autism. However, the combination of immune dysregulation, specific mutated genes, E/I imbalance, and neuroanatomical changes may underlie the pathogenesis of ASD.

age at conception, (b) prenatal exposure to air pollutants and pesticides, and (c) social factors, maternal stress, obesity, etc. (Lyall et al., 2014). However, ongoing research is focused on identifying the genetic and environmental variables primarily involved in the onset of ASD.

Heavy metal exposure and risk of autism

Over the years, researchers have raised questions about the relationship between heavy metals and the risk of autism, providing evidence that increasing in-utero exposure to toxic heavy metals may contribute to the development of autism in individuals. Toxicants, including lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), aluminum (Al), manganese (Mn), and nickel (Ni), are naturally present in the environment. Additionally, research conducted in Saudi Arabia demonstrated that autistic children had significantly lower levels of selenium as well as higher levels of lead and mercury than non-autistic children (Al-Ayadhi, 2005) (Fig. 2).

Table 1. Vulnerable Genes Causing ASD.

Sl.no	Gene Name	Symbol	Chromosome Location	References
1	SH3 and multiple ankyrin repeat domain 3	*SHANK3*	22q13	Shah, 2017
2	Methyl CpG binding protein 2	*MECP2*	Xq28	Pejhan and Rastegar, 2021
3	Phosphatase and TENsin homolog	*PTEN*	10q28	Stiles, 2009
4	Contactin-associated protein-like 2	*CNTNAP2*	7q35	Bakkaloglu et al., 2008
5	Chromodomain helicase DNA binding protein 8	*CHD8*	14q112	Yasin and Zahir, 2020

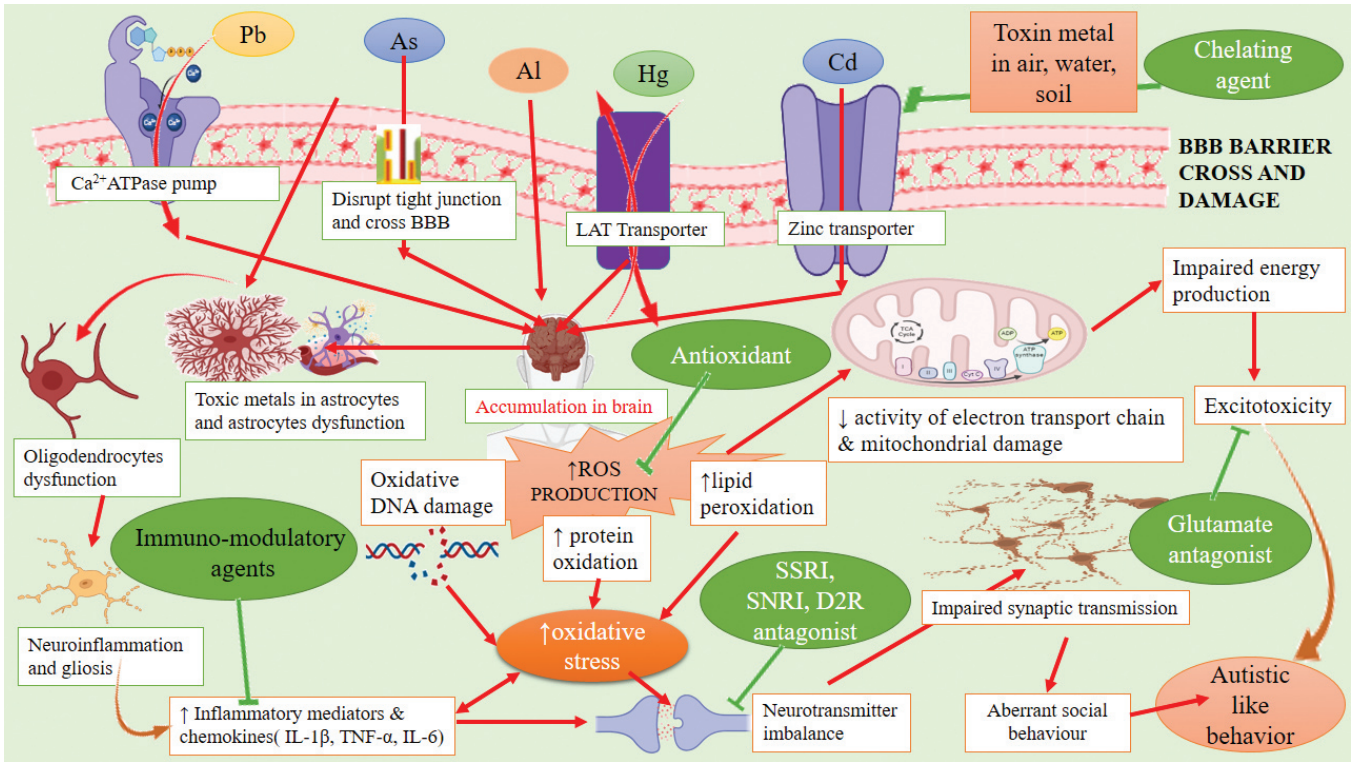

Fig. 2. Pathological mechanisms of heavy metal exposure in autism and different therapeutic approaches. Toxic heavy metals such as lead (Pb), arsenic (As), aluminum (Al), mercury (Hg), and cadmium (Cd) can cross the blood-brain barrier (BBB) through specific transport mechanisms, leading to their accumulation in designated areas of the brain. This accumulation damages astrocytes, resulting in neuroinflammation and increasing the release of pro-inflammatory cytokines. Furthermore, the presence of these metals raises the production of reactive oxygen species (ROS), which inflicts oxidative damage on DNA, proteins, and lipids. This oxidative stress ultimately enhances the activity of the electron transport chain (ETC), causing mitochondrial dysfunction that disrupts energy production and contributes to excitotoxicity. Consequently, this cascade of events leads to heightened oxidative stress, resulting in neurotransmitter imbalances and impaired synaptic transmission, which can manifest as atypical social behaviors and symptoms resembling autism.

Mercury

Mercury is a well-known neurotoxin with devastating consequences for human health, especially neuronal development. Accumulating evidence has focused on the relationship between Hg exposure and neurodevelopmental problems such as autism (Kern et al., 2016). Hg sourced from fish and other contaminated foods underscores the importance of glutathione-S-transferase (GST), an enzyme crucial for preventing the accumulation of harmful toxicants in organs (Gasmi et al., 2022). Prolonged exposure may lead to the accumulation of Hg in different parts of the brain, mainly the cerebellum and cerebral cortex, by crossing the blood-brain barrier (BBB) (Fernandes Azevedo et al., 2012).

Lead

Lead, a widely available non-essential metal found within the carbon group, is mainly exposed to the body via consumption or inhalation through the digestive and respiratory systems (Sanders et al., 2009). Excessive Pb exposure, especially in early life, may be harmful to brain development and result in ASD or cognitive impairment in the adult stage (Gundacker et al., 2021). Lead-induced alterations in the central dopaminergic, cholinergic, and glutaminergic systems, along with modification of many enzymes, including protein kinase C (PKC) and choline acetyltransferase, specifically trigger the appearance of autism (Gasiorowska et al., 2021).

Cadmium

Cadmium, a popular heavy metal, might trigger multiple cellular dysfunctions and has direct as well as indirect effects on brain development (Wang and Du, 2013) by inducing oxidative stress, cell proliferation, enhanced lipid peroxidation, and infertility. Several studies have documented that Cd levels are low in both the hair and urine of people with autism (Ding et al., 2023). Compared with Pb and methyl mercury, Cd overexposure is more harmful and is still a topic of controversy, which is why researchers continue to investigate and validate this hypothesis (Gorini et al., 2014).

Arsenic

Arsenic, an established environmental toxin, is present in the air, water, and soil and can enter the body through inhalation and ingestion (Chung et al., 2014). Overexposure to As induces oxidative stress, neuroinflammation, and neurotransmitter imbalance. It also increases the risk of skin, lung, and bladder cancers (Zhang et al., 2022). Ingesting As through contaminated water, tobacco products, or rice-based foods, particularly during the prenatal period, may lead to neuro-developmental anomalies and increase the risk of neurological disorders, including ASD (Ijomone et al., 2020).

Different drugs, toxins, and risk of autism

The relationship between drug consumption and the risk of developing autism is a complicated issue that has been thoroughly investigated. Prenatal exposure to various antiepileptic drugs and antidepressants may be a potential risk factor for developing autism in offspring (Sato et al., 2022).

Valproic acid

Valproic acid (VPA) is a clinically approved antiepileptic drug that is considered a potent teratogen. Valproate exposure in the first trimester may increase the risk of cognitive abnormalities, particularly neural tube defects in children (Saeed et al., 2020). Additionally, VPA exposure in utero increases synaptic plasticity controlled by N-methyl D-aspartate (NMDA) receptors and interferes with the GABAergic system by inhibiting GABA transaminase throughout postnatal development (Sui and Chen, 2012).

It is believed that the Wnt/β-catenin pathway performs a significant role in the initiation of autism through exposure to VPA (Mony et al., 2016). Investigations have discovered that VPA alters the transcription levels of ASD-associated genes in fetuses by disrupting signaling pathways, anomalies in synaptic functioning, and neurogenesis (Guerra et al., 2023). In 2015, a cohort study revealed that at age 6, children whose mothers used high-dose VPA (>800 mg/day) had a lower IQ; low-dose VPA (≤800 mg/day) caused verbal deficits but had no major impact on offspring IQ (Baker et al., 2015).

Acetaminophen

Acetaminophen, an analgesic and antipyretic drug, although some current investigations have not established a significant relationship, others have demonstrated a possible connection between prenatal paracetamol exposure and the risk of ASD (Khan et al., 2022). Additionally, it has been hypothesized that acetaminophen causes neurodevelopmental disorders, including ADHD and ASD, by inducing oxidative stress (Masarwa et al., 2018). It has been suggested that acetaminophen exposure in the second trimester decreases brain-derived neurotrophic factor (BDNF) levels in the striatum and alters dopamine metabolism in offspring (Woodbury et al., 2024).

Propionic acid

Propionic acid (PPA) causes neuroinflammation and behavioral alterations in rats (Alonazi et al., 2022). Studies have confirmed that excitatory-inhibitory (E/A)

imbalance serves as an etiological factor for ASD, and PPA causes E/A dysfunction, which results in autism (Doğan et al., 2023).

Pathological targets and drug therapy for autism

Autism can be categorized into syndromic and non-syndromic forms based on clinical characteristics. Although the exact pathological mechanisms of the disease are still unclear, research has identified potential therapeutic targets (Sztainberg and Zoghbi 2016). The most common genetic disorder related to autism, known as Fragile X Syndrome, is caused by suppression of the *FMR1* gene, while other diseases, including mutations in the X-linked *MECP2* gene, trigger Rett syndrome (RTT) and Tuberous sclerosis complex (TSC) caused by a mutation in either of the two genes, *TSC1* and *TSC2* (Salcedo-Arellano et al., 2021). Key literature from previous studies has suggested that many pathological signaling pathways are involved in the progression of the disease, including the central neurotransmitter system, Wnt/ β-catenin pathway, PI3/AKT/mTOR pathway, reactive astrocytes and microglia, which lead to neuroinflammation. Elevated glutamate levels in the synaptic cleft can lead to the overactivation of NMDA receptors, resulting in increased sodium and calcium influx into neurons, which heightens oxidative stress and disrupts synapse function. Additionally, interleukin (IL)-6 affects synapse formation and plasticity, whereas PI3K-AKT activation promotes a pro-inflammatory response in astrocytes.

Neurotransmitter system

Disbalance of neurotransmitter levels may lead to the development of autism, which is implicated in the pathophysiology of the serotonergic, dopaminergic, glutaminergic, and GABAergic systems.

Serotonergic system, including serotonin

The serotonergic system, including serotonin (5-hydroxytryptamine; 5-HT), helps regulate mood, hunger, sleep patterns, and social behaviors. Increased serotonin levels in the blood of autistic people considered 5-HT as a potential biomarker for identifying the disease (Muller et al., 2016). For instance, it has been proposed that hyperserotonemia during pregnancy may be a contributing environmental factor to the increased prevalence of ASD (Harrington et al., 2013). Brain imaging investigations indicate that a subset of autistic children experience lower serotonin levels in the brain, with serotonin receptor subtypes such as 5HT1R, 5HT2R, 5HT6R, and 5HT7R identified as therapeutic targets for autism (Lee et al., 2021). Selective serotonin reuptake inhibitors (SSRIs), which increase serotonin levels in the brain, are commonly used to treat depression and anxiety-type behavior in individuals with ASD. Examples include sertraline and fluoxetine, which are prescribed to treat core symptoms of autism (Nanjappa et al., 2022). However, the use of SSRIs in autism remains controversial, and further research is needed to understand their advantages and drawbacks.

Dopaminergic system

The dopaminergic system plays a crucial role in regulating movement, social behavior, and cognition, and its dysregulation, particularly in the striatum and prefrontal cortex, may contribute to the behavioral symptoms of ASD, such as repetitive and restrictive behavior (Blum et al., 2024). Understanding the significance of dopamine imbalance and receptor function in autism, medications that alter dopamine levels, such as atypical antipsychotics. Brexpriprazole, cariprazine, and aripiprazole are notable examples that have been used to treat autistic symptoms in individuals (Goes, 2023).

Glutaminergic system

The glutaminergic system, the primary excitatory neurotransmitter system, plays a crucial role in synaptic plasticity, memory, and cognition. Its dysfunction has been linked to several ASD characteristics, including social interactions and cognitive difficulties (Moretto et al., 2018). Clinical investigations have demonstrated that women tend to have higher glutamate (Glu) levels in their frontal grey matter and basal ganglia, while men have higher Glu levels in the parietal grey matter (Van Cauter et al., 2020). NMDA Receptors (NMDARs) play a crucial role in synaptic plasticity and transmission. Memantine, an NMDAR antagonist, has shown promise in alleviating ASD-like symptoms in individuals (Yang and Chang 2015). In addition to pharmacological approaches, non-pharmacological approaches targeting the glutaminergic system, such as nutritional therapies and dietary supplements, contribute to potential interventions for treating autistic symptoms.

GABAergic system

The GABAergic system, considered the main inhibitory neurotransmitter, plays a major role in the etiology of autism. Research utilizing animal models of ASD has revealed that many autistic symptoms may stem from a malfunction in GABAergic signaling within certain neural circuits (Zhao et al., 2022). According to a widely accepted theory, the pathology of autism arises from an imbalance in E/I neurotransmitter levels in neural circuits caused by either a heightened glutamatergic system or a decrease in the GABAergic system. Furthermore, disruptions in GABAergic signaling, intimately related to glutaminergic neurotransmission, suggest that drugs modulating GABAergic activity, such as benzodiazepines and other antiepileptic medications, may improve social interaction capabilities in individuals with autism (Cellot

and Cherubini 2014).

Glycogen synthesis kinase

Glycogen Synthesis kinase (GSK3), a highly abundant serine/threonine kinase, functions as a suppressor of the Wnt/β-catenin signaling pathway, which is crucial for controlling cell proliferation, differentiation, apoptosis, and cellular growth during embryonic development. Additionally, multiple Wnt pathway-related genes are directly associated with autism, and hyperactivation of this pathway leads to autistic symptoms in individuals. ASD patients may have either upregulated or downregulated β-catenin contingent upon which gene is mutated in the pathway (Caracci et al., 2021). GSK-3 is also inhibited by lithium, a highly accepted mood-stabilizing agent that imitates the activation of the Wnt–β-catenin pathway. Additionally, sulindac, an FDA-approved anti-inflammatory drug that functions as a β-catenin inhibitor and has been tested in VPA-induced ASD models, also improves anxiety, stereotypical, and other ASD-like behaviors in autistic rats (Zhang et al., 2015).

PI3/Akt/mTOR pathway

The PI3/Akt/mTOR Pathway promotes neuronal long-term potentiation (LTP) and plays a significant role in learning and memory formation. Hyperactivation of this pathway under certain circumstances potentially leads to ASD in some patients (Enriquez-Barreto and Morales 2016). Dysregulation of the mTOR pathway is associated with various ASD-related disorders such as RTT, fragile X syndrome, and tuberous sclerosis are linked to mTOR pathway dysregulation (Thomas et al., 2023). The upstream signaling molecules of mTOR, PI3K, and protein kinase B (Akt/PKB) define the PI3K/Akt/mTOR pathway and help in regulating autophagy (Li et al., 2014). Multiple studies have demonstrated that autistic patients have altered cytokine expression. Cytokines stimulate the PI3K/Akt/mTOR and JAK-STAT pathways, which control various cellular responses. Rapamycin, an mTOR pathway inhibitor, has been found to promote social interaction in autistic

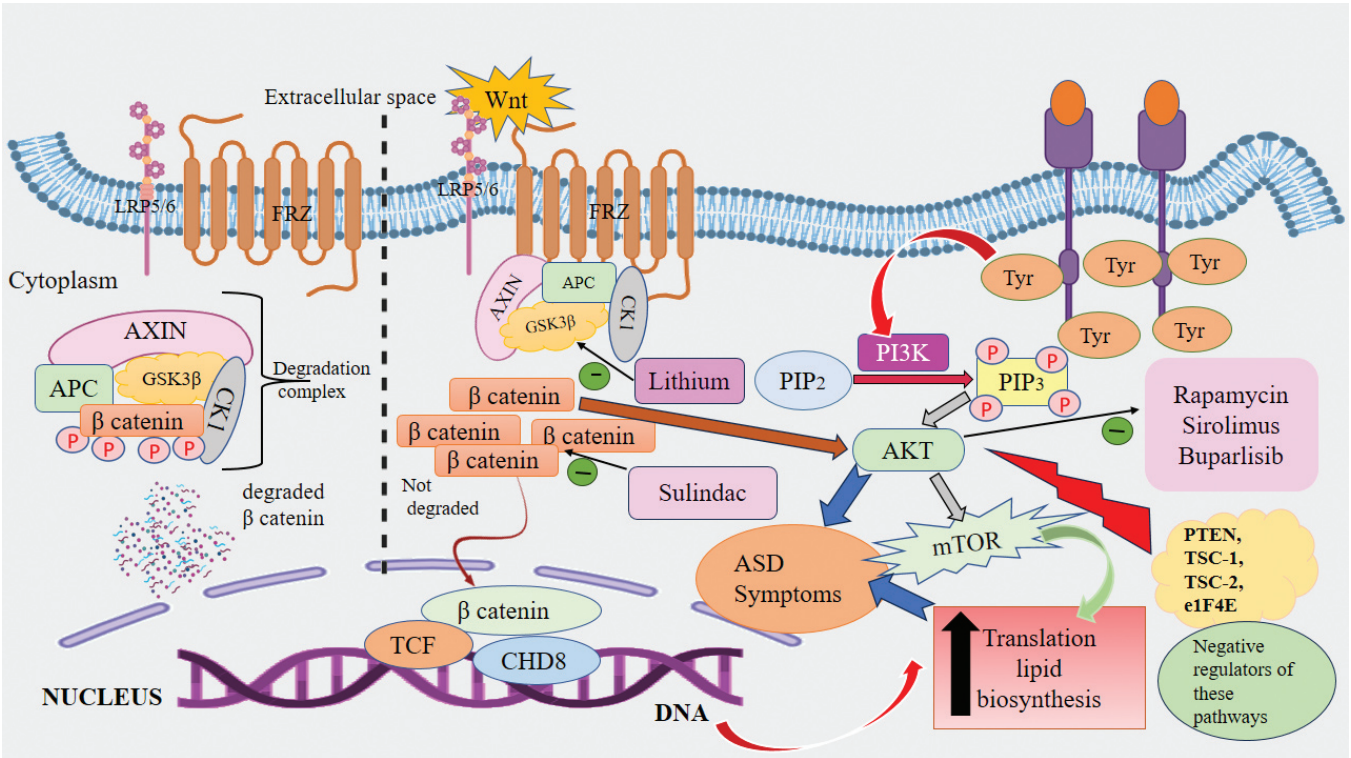

Fig. 3. Pathways directly involved in ASD. This figure depicts the pathological pathways, consisting of Wnt binding to both the FRZ and LRP5/6 receptor that blocks the disintegration of the destruction complex, which results in the accumulation of β-catenin in the cytoplasm. This β-catenin translocates to the nucleus and starts Wnt-dependent gene transcription. Various genes, including *CHD8*, *DDX3X*, and *TCF4* in the Wnt pathway, are highly linked to the risk of autism. Additionally, the PI3K/Akt/mTOR intracellular signaling pathway is also described in this diagram. Binding of stimuli to the Tyrosine kinase receptor leads to the activation of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), which converts phosphatidylinositol (3,4)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 phosphorylates and activates the Akt/mTOR pathway, which is involved in translation and lipid biosynthesis. Negative regulators of this pathway, PTEN, TSC-I, TSC-II, and eIF4E, lead to inhibition of this pathway, which causes autism in individuals. Pharmacological drugs involved in this pathway are also described in this figure.

patients by increasing the activity of the PI3/Akt/mTOR pathway (Fig. 3).

Role of axons, myelin, and exacerbated inflammation in the clinical severity of autism

Recent research suggests that alterations in axonal structures, the integrity of myelin, and increased inflammation play important roles in the severity of the disorder.

Axonal Integrity

Research has found that abnormalities in axonal structure can hinder neural communication. As axons are crucial for relaying signals between neurons, any dysfunction in this process can lead to cognitive and behavioral difficulties related to ASD. Studies have revealed that people with ASD frequently exhibit changes in axonal morphology, which may contribute to the atypical neural circuitry seen in the condition (Berth and Llyod, 2023).

Myelination

Myelin, a protective insulating layer that forms around nerve fibers, is essential for effective signal transmission in the nervous system. Myelination deficiencies are associated with reduced brain connectivity across different brain regions and slower neural processing speeds (Ravera et al., 2020). Recent research indicates that there may be disruptions in the function of oligodendrocytes, the cells responsible for myelination, resulting in diminished myelin integrity. This reduction can worsen symptoms associated with social communication and repetitive behaviors.

Role of glial cells and their contribution to the ASD phenotype

Recent transcriptomic analyses of autistic brains have underscored the significant role of glial cells in the pathogenesis of ASDs. These studies reveal a strong relationship between ASDs and genes involved in glial cell activation, as well as genes associated with immune and inflammatory processes.

Astrocytes

Astrocytes are star-shaped glial cells that enhance synaptic pruning through their ion channels and neurotransmitter release, while inflammatory cytokines and chemokines are released that can lead to neuroinflammation and synaptic changes (Xiong et al., 2023). Astrocytes are responsible for maintaining the balance of excitatory and inhibitory activities in the brain; their disturbed function can lead to increased glutamate or decreased GABA levels in the brain. Additionally, alterations in the morphology and number of astrocytes can affect their responses to inflammation and injury, with abnormal expression of astrocytic markers, such as aquaporin 4 and connexin 43, which has been observed in the brains of individuals with autism (Verkhratsky and Nedergaard 2018).

Microglia

Microglia, the immune cells of the brain, can be activated by various factors, such as inflammation or injury, leading to neuroinflammation, which has been associated with the development of autism. These cells contribute to synaptic pruning through intracellular methylation and modifications in mitochondrial function. Additionally, the cerebellum, pons, midbrain, anterior cingulate, fusiform gyri, and orbitofrontal cortices are the affected brain regions of young adults with autism where microglial activation has been shown in a recent positron emission tomography (PET) functional imaging study (Frick et al., 2013). Microglial activation leads to the release of reactive oxidative species (ROS) and pro-inflammatory cytokines, which can impair mitochondrial energy metabolism. Oxidative stress, resulting from microglial activation, is a critical factor in the development of neurodevelopmental disorders. Importantly, oxidative stress is recognized as a prevalent characteristic of ASD. The role of glial cells in the pathogenesis of autism and targeted pharmacotherapy is described in Figure 4.

Neuroinflammation

Neuroinflammation is mediated by neurons, microglia, macroglia, and astrocytes, which are the major central nervous system (CNS) cells and are actively involved in establishing a link between neuroinflammation and autism. Investigations have reported that higher levels of inflammatory mediators (cytokine, chemokines, CCL4, IL6, TNF-α) were found in the blood and brain samples of autistic patients (Matta et al., 2019). These elevated levels of TNF-α also have been associated with sleep disturbances in autistic patients, as they correlated with altered pineal melatonin release. Furthermore, studies have focused on the hypothesis that the PGE2 pathway and neuroinflammation may contribute to the occurrence of ASD by promoting the use of PGE2, COX-2, and mPGES-1 as potential biomarkers of the condition (Wong et al., 2016).

Pharmacotherapy involved in autism

Although there are no accepted medicines that can cure all the core symptoms of ASD, some drugs are used to reduce behavioral symptoms in autistic patients.

Available medications for ASD

Currently, only two FDA-approved antipsychotic drugs are available, namely risperidone (Risperdal) and

aripiprazole (Abilify), which are used in the treatment of irritability in autistic children at specific ages. Children aged 5-16 years were prescribed risperidone, and children aged 6-17 years were prescribed aripiprazole. There are also some drugs for treating several autistic behaviors, but these have not been approved by the FDA (Ichikawa et al., 2017) (Table 2).

Medications targeting glial cells

Research is increasingly focusing on pharmacotherapy that targets glial cells to tackle the neurobiological underpinnings of autism. As previously explained, astrocytes and microglia may play a role in neuroinflammation and brain connectivity, both of which are disrupted in ASD. Possible therapies aimed at correcting glial cell dysfunction in autism include:

Oxytocin

Oxytocin is a neuropeptide that interacts with oxytocin receptors. Recent clinical investigations have indicated that intranasal oxytocin delivery may ameliorate the fundamental social abnormalities linked to autism (Parker et al., 2017). It may diminish glial activation triggered by lipopolysaccharide (LPS) and lower the levels of proinflammatory mediators and cytokines.

Vitamin D

Vitamin D (VD) is a type of steroid derivative, and evidence indicates that VD supplementation can decrease the levels of pro-inflammatory cytokines, which may significantly improve clinical behavioral outcomes in children with autism (Jiang et al., 2023).

Sulforaphane

Sulforaphane (SFN) is a beneficial compound found in cruciferous vegetables, such as broccoli, Brussels sprouts, and cabbage. Research has shown that SFN can reduce neuroinflammation induced by reactive microglia, leading to decreased levels of iNOS and pro-inflammatory cytokines, including TNF-α and IL-6 (Cascajosa-Lira et al., 2024).

Cell replacement

Cell replacement is a potential treatment that involves employing stem cells or other cellular therapies

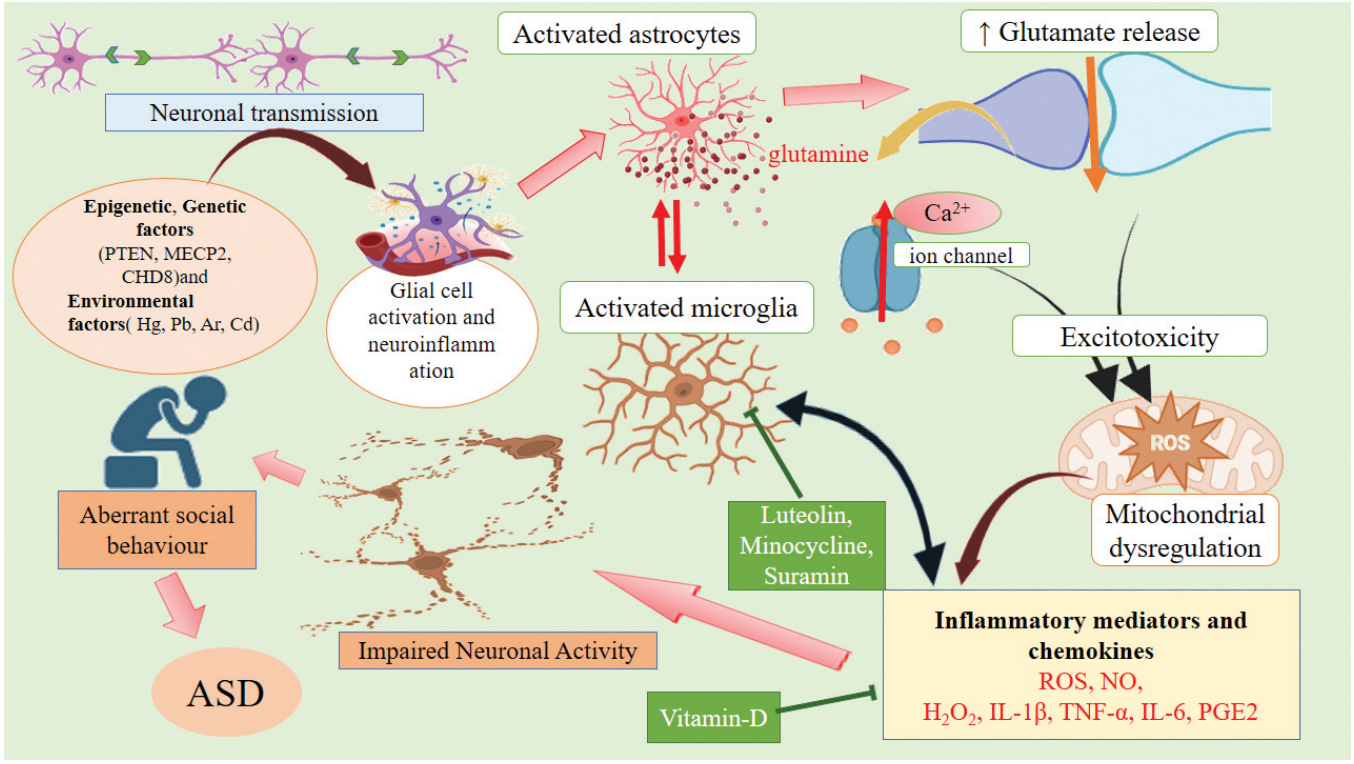

Fig. 4. Involvement of glial cells in the pathology of ASD along with their targeted medications. Epigenetic, genetic, and environmental factors lead to disruption of neuronal activation. They could trigger glial activation that disrupts normal physiological conditions i.e., increases the release of glutamate that leads to excitotoxicity that causes mitochondrial damage and releases proinflammatory cytokines. These releases lead to neuroinflammatory events and activate the microglia. Reactive microglia can further lead to the release of proinflammatory cytokines, including ROS. These interactions, together with mitochondrial dysfunctional release, could have an important role in the typical behaviors observed in autistic patients.

to enhance brain function by replacing dysfunctional or damaged glial cells and neurons and decreasing autism-like symptoms; however, more scientific evidence is needed to confirm that stem cell therapy changes autism characteristics (Siniscalco et al., 2018).

Natural products

Research on plant-derived psychopharmaceuticals has demonstrated their potential as a treatment for reducing ASD symptoms in individuals. Herbal medicines administered in combination with traditional medicines and several exercise activities may reduce the main symptoms, with fewer side effects. Natural compounds that have shown effectiveness in treating autism are listed in Table 3.

Recent advancements in autism treatment

Ongoing research on ASD has led to the develop-

Table 2. Available medicine for the treatment of ASD.

Sl.no	Target symptoms	Drug class	Drug name	References
1	Irritability, aggression, and self-injurious behavior	Atypical neuroleptics	Risperidone; Aripiprazole; Clozapine	Meza et al., 2022; Politte and McDougle, 2014
		Selective D2 Receptor antagonist	Haloperidol	Aman et al., 2008
		Selective serotonin reuptake inhibitor (SSRI)	Sertraline	Gallagher et al., 2004
2	Inattention and hyperactivity	CNS Stimulant	Methylphenidate	Ventura et al., 2020
		Serotonin and norepinephrine reuptake inhibitor (SNRI)	Venlafaxine	Hollander et al., 2000
3	Treatment of repetitive behavior	SSRI	Fluoxetine; Fluvoxamine	McDougle et al., 1990; Lucchelli and Bertschy, 2018
4	Insomnia	Oral antidepressant	Mirtazapine; Melatonin	Posey et al., 2001; Rossignol and Frye , 2014

Table 3. Natural products involved in the treatment of autism.

Sl.no	Drug Name	Model	Dose	Result	References
1	Luteolin and apigenin	VPA-induced rat model	20, 40, and 80 mg/kg (Oral)	↑ GSH, SOD, and CAT levels ↓ IL-1β, IL- 6, and TNF-α levels	Abhishek et al., 2022
2	Piperine	Sodium valproate-induced mice model	5 and 20mg/kg (Oral)	↓ Oxidative stress, ↑ serotonin level and Purkinje cell distribution	Pragnya et al., 2014
3	Resveratrol	VPA-induced rat model	20 and 40 mg/kg (Oral)	↓ IL-6, TNF-α and IL-17A, ↓ mitochondrial dysfunction, oxidative-nitrosative stress	Schwingel et al., 2023
4	Curcumin	Propionic acid-induced rat	Daily dose of 50/100/200 mg/kg	↓ MMP-9 and TNF-α in blood, plasma, CSF	Bhandari and Kuhad, 2015
5	Bacosides	VPA-induced female pregnant rat	0, 60, 300, 1,500, and 5,000 mg/kg	↓ oxidative stress, reduce glutamate accumulation	Sachdeva et al., 2022
6	Green tea extract	VPA-induced both male and female mice	75 and 200 mg/kg	Reduced behavioral symptoms	Banji et al., 2011

Table 4. Recent treatment strategies for autism.

Sl.no	Drug	Study conducted	Reference
1	Balovaptan	Vasopressin 1a Receptor antagonist modulates oxytocin receptors in the brain. Phase II research with 500 autistic adults and teenagers has revealed that it improves social interaction 15% more than placebo. This medicine also improves repetitive behavior. It entered a phase III clinical trial in 2018.	Schnider et al., 2020
2	Transcranial Magnetic Stimulation (TMS)	TMS is a non-invasive brain stimulation device to reduce symptoms associated with ASD. A study including 30 autistic patients aged 3-10 years suggested that repetitive TMS, along with traditional language treatment methods, can quickly cure language disabilities in autistic children.	Oberman et al., 2015
3	Suramin	Suramin, an antiparasitic drug, has been proven to reduce ASD core symptoms at a dose of 10 mg/kg (i.v. infusion) with fewer side effects. The duration of the study was 14 weeks.	Hough et al., 2023

ment of novel treatments with notable success; these breakthroughs are improving the social communication and interaction capabilities of autistic patients (Table 4).

Nutritional therapy in ASD

The development of autism may be linked to gut dysfunction, so autistic patients may suffer from serious nutritional deficiencies. Certain diets have been proposed, such as the GFCF (gluten-free, casein-free) diet, which may benefit autistic children and is commonly used as a treatment for ASD (Mulloy et al., 2010).

Gluten- and casein-free diet

Several investigations have demonstrated that the GFCF diet is an alternative therapy employed for ASD. This diet includes foods free from gluten and casein proteins, specifically excluding wheat, rye, barley, and dairy products (Quan et al., 2022). It is suggested that gluten and casein plus diet can alter brain functions, negatively affecting the CNS and resulting in behavioral disturbances. However, a study involving 15 children over 6 weeks revealed no significant improvement in their behavior (Hurwitz, 2013). As the GFCF diet may activate the opioid system, it is hypothesized that it will reduce ASD symptoms through this mechanism, but currently, there is no certain evidence to support this hypothesis.

Dietary supplements

Micronutrients, such as unsaturated fatty acids, magnesium, zinc, selenium, and vitamins A, C, B6, folic acid, B12, and D are associated with ASD (Indika et al., 2023). Studies have shown that autistic children have low omega-3 fatty acid levels in their blood. Recently, a review of dietary and nutritional interventions has provided evidence supporting the use of dietary supplements in the treatment of ASD (Mazahery et al., 2016).

Future perspectives

In recent years, an increasing amount of information regarding the targets involved in the pathogenesis of ASD has become available, and as the neural mechanisms of ASD have been established, specific medication therapies are now potentially possible. Although studies have been performed to understand the genetic and environmental conditions of ASD, there are still several important areas for future research and interventions that are crucial for enhancing the quality of life of people with ASD. Future research should focus on understanding targeted therapies and concentrate on genetic biomarkers involved in the disease. Applied Behavioral Analysis (ABA) is a behavioral treatment therapy recently employed to reduce autism-related symptoms in individuals, while technology-based interventions are also emerging as a novel approach for treating ASD. Nevertheless, additional investigation is needed focusing on drugs and treatment strategies for autism.

Conclusion

ASD is a hereditary neurological condition, and various complicated pathological mechanisms are involved in its pathology. Many treatment strategies have been to reduce ASD-like symptoms, but they have not yet been proven. As pointed out in the title, the main focus of this review paper lies on all the pathological pathways involved in autism, and drugs that mainly target these pathways. Multiple potential targets for pharmaceutical intervention, encompassing neurotransmitter systems, neuroinflammation, and neurodevelopmental pathways, have been discovered as a consequence of our knowledge of the neurobiological underpinnings of autism.

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