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Supplementary and Natural Remedy Involved in ASD Therapy

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ABSTRACT

Autism spectrum disorder (ASD) is a huge public health problem in children all over the world. Autism is characterized by impairments in communication and social interaction, limited interests in activities, repetitive behaviors, and a diminished ability to perform in school, the workplace, and other aspects of life. In recent years, the estimated prevalence of autism spectrum diseases has risen considerably. The condition necessitates long-term therapy and is typically regarded as incurable. Pharmacological intervention, which includes psychiatric medicines to treat behavioral issues, is accompanied by considerable side effects. Behavioral therapy, education, and nutritional therapies are the basis of traditional management. It has been reported that using natural compounds along with pharmacological medications has a positive effect in treating ASD youngsters, as well as diminishing the adverse effects of chemical medications. Unfortunately, data on the efficacy of natural remedies in ASD are scarce. The current review seeks to investigate studies of using natural remedies in ASD.

Key Words:
Autism spectrum disorder, Behavioral improvement, Herbs, Natural therapy.

1. INTRODUCTION

Autism is a neurodevelopmental disorder and a behaviorally defined syndrome marked by difficulties with social interaction and nonverbal communication [1]. Scientists call this condition autism spectrum disorder (ASD) involves all different symptoms such as limited socializing, diminished interaction, and repetitive behavior [2]. Parents start to notice these symptoms in their children in their second or third year [3].

Autism appearance varies a lot among children and its severity greatly differs too. Symptoms variety can range from communication disabilities to dysprosodic talkative [4]. In the last decade, there was a significant rise in ASD diagnosis [5]. The incidence rates of ASD have raised dramatically from rates of 1/2,500 in 1980 to rates of 1/150 [6]. Lately, researches show that one of every hundred children is a spectrum carrier [7]. It is noteworthy that ASD incidence rates differ by gender where about four boys affected by ASD to one girl. However, girls often suffer from worth cognitive problems [3]. The great rise in ASD prevalence may be attributed to several aspects, raised recognition may be the most affecting factor also early detection, and advanced age of parents in addition to environmental pollution [8].

Autism's early onset and chronic course have a severe impact on families, leading to substantial emotional and financial losses [9]. According to a previous study in the US, the average cost was $4.05

million, around 10% for medical costs, extra education accounting for 30%, and lost productivity accounting 60% [10].

2. AIMS AND METHODS

The main goal of the present review was to gather an overview of many research articles about the natural products that have been defined in the treatment of ASD rather than the chemical derived drugs which have a lot of undesirable side effects.

To this end, more than two hundred of published articles over the last years, were revised by accomplishment a search using the subsequent syntax (autism spectrum illness or ASD syndrome or persistent developmental disorders (Using title or abstract) and natural, alternative, or traditional treatment of ASD (Using title or abstract). References were recognized via electronic internet database web searching on different websites like Medline, Elsevier, Proquest, PubMed, and the Web of Science from 1970 to the present. The last searched database was run on December 2021.

3- ETIOLOGY

Several studies had been carried out, but no only one definite cause. Scientists attributed ASD incidence to many environmental factors [11]. Moreover, Hazard reasons during pregnancy comprise certain infections, like rubella, chemical toxicity with valproic acid, alcohol, narcotics, insecticides, lead poisons, air contamination, fetal growing constraint, and autoimmune diseases [12].

Recently, vast improvements in neurotransmitter, neuroimaging, and DNA studies have supported our recognition for the pathophysiology of ASD, however, the core origins of ASD are still unclear [13].

DNA study of families with autism have shown potential chromosomes 1, 2q, 7q, 9, 13, 15q, 16p, 17q, 19, 22, and X that may be accused in ASD incidence [14]. Particularly 6q21 is evidenced by many researchers. This region contains the glutamate receptor 6 (GluR6 or GRIK2) gene which has proven to be related to autism [15]. Breakpoints in 15 and X chromosomes also proved to be related to ASD [16].

ASD can be classified into syndromic and non-syndromic. The syndromic ASD is frequently accompanied by chromosomal aberrations or monogenic modifications. Examples of these alterations include Rett disorder, fragile X syndrome, and MECP2 duplication disorder [17], [18]. On the contrary, etiology of the non-syndromic ASD is quiet fairly undefined due to its genomic heterogeneity. So, cooperation of de novo genetic alterations and prenatal beside postnatal environmental influences are probable to play a role.

4- AUTISM PATHOLOGY

The pathophysiology of ASD is complicated and not entirely understood. In characterizing this complicated illness, research has discovered both genetic and environmental influences, particularly those impacting prenatal and early life developments. Although research in twins with ASD has shown a significant degree of heritability (38–54%), multiple meta-analyses studies have demonstrated that ASD has genetic-independent causes [19]. This section presents the anatomical and physiological changes related to pathological symptoms of ASD.

4.1 Neuroanatomy of autism: In comparison to controls, autistic individuals showed: 1) interrupted development of neurons in the forebrain limbic system; 2) cerebellum showed a reduced number of Purkinje cells; and 3) inappropriate count and cellular volume in the cerebellar nuclei and the inferior olivary nucleus of the brainstem [20]. Other brain regions such as the entorhinal cortex, amygdala, and mammillary body suffered from greater cell density and smaller cellular volume [21]. Researchers related these impairments in the limbic system to the emotional and mood manifestations in autistic patients [22]. Cerebral connectivity was described to be altered in persons with ASD. Decreased conductivity between distal brain areas and increased conductivity in proximal brain areas has been established [23].

4.1 Neuroinflammation: Despite some concerns regarding whether inflammation causes ASD development or modulates ASD pathogenesis and symptomatology, pieces of evidences imply that inflammation plays a role in the underlying mechanism of ASD [24], [25]. The immune system controls

an important portion of development of the central and the peripheral nervous system, this is done through regulating neural proliferation, forming synapses, and removing neurons that undergo apoptosis; furthermore, immune dysfunction has been linked to a variety of neurological disorders [26]. Recent research has found that people with ASD have different changed immune responses [27]. The levels of inflammation markers are higher in people with ASD, whereas the levels of anti-inflammatory markers are lower [28].

4.3 Oxidative stress: Several studies have found that the antioxidant capacity of autistic individuals is lower than normal level, their plasma levels of plasma reactive oxygen species (ROS) were elevated [29]. The grade of OS is determined through measuring the end products of lipid peroxidation and the levels of antioxidant parameters for example glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and other antioxidants which proved to be affected in ASD. Measurements of membrane phospholipids in autistic patients were disturbed, which usually are targeted by ROS [30].

4.4 Neurotransmitters: Serotonergic and dopaminergic systems are important pathogenic pathways sharing in ASD pathology. 33% of autistic individuals have been found to have high blood and urine serotonin levels, even though normal peripheral dopamine concentrations have been recorded [31]. Selective serotonin reuptake inhibitors (SSRIs) and dopamine receptor antagonists have been reported to reduce the main symptoms of ASD such as undesirable behavior, self-injury, and hostility [32]. A disturbed synthesis of serotonin has been explored in the temporal, frontal, and parietal cortex in patients. Altered dopaminergic activity in their cortex was also found [33].

5- MAIN MEDICATIONS PRESCRIBED FOR ASD

There is no known pharmaceutical therapy for the basic difficulties of ASD, which include chronic difficulties in socialization and repetitive, restricted behavior [34]; Pharmacotherapies for comorbid disruptive behaviors have low effectiveness and tolerability [25].

Several pharmacological and non-pharmacological treatments have been described to diminish and control ASD symptoms. Antipsychotics, antidepressants, and stimulants are the most common drug classes used in the therapy of this syndrome [35], which have been intended to relieve neurological and behavioral symptoms such as irritability, insomnia, and aggression. However, these medications adequately diminish these symptoms and side effects often cause discontinuation [36].

Clozapine and risperidone were the most common therapies in this field. Clozapine induces improvements in relationships, while risperidone improves social interactions and language [37]. Something should be noticed that the core symptoms of autism can’t be relieved by one drug, especially the communication and social impairments [38].

Risperidone (RISP) is a benzisoxazole derivative. It has been the most often used atypical antipsychotic in the treatment of autism, Leo Kanner described it for the first time in 1943 [39]. Risperidone's pharmacological development was based on its precursor, ritanserin, a 5-HT2A blocker, this development produced a drug with the major pharmacological activity of the D2-/5-HT2A receptor antagonism, with a higher impact on 5-HT2A receptors than on D2 receptors [40].

Risperidone has several adverse effects, including the extrapyramidal symptoms, hyperprolactinemia, weight gain, drowsiness, and the potential for type 2 diabetes [37] several studies proved motor effects such as dystonia [41]. Recently, clinical signs suggested that RISP may raise the risk of epileptic seizures [42]. Furthermore, treating with risperidone for a long time causes bone damage [43], which is connected to a drop in plasma vitamin D levels. It may lead to complications such as sleep disturbances, drowsiness, movement disorders, hyperprolactinemia, visual difficulties, and constipation [44]. RISP is metabolized in the liver and eliminated by the kidneys [45].

Other drugs are also prescribed for ASD children such as methylphenidate, clonidine, atomoxetine which unfortunately caused several side effects as shown in Table1.

Because of all of these issues, the demand for natural-based pharmaceuticals has increased; herbal remedies are always preferred by patients as a therapeutic option or as an addition to conventional treatment. [46]. In this review, we present the most medicinal plants and natural products effective in autism therapy which have neuroprotective effects and are considered potentials as remedy for treating the symptoms of autism.

Table 1: Side effects of main medications used to treat ASD symptoms.

Drug	Treated symptoms	Side effects	Ref.
Clozapine	Improvements in relationships	Tachycardia, sedation, seizures, cardiovascular/respiratory arrest, fever and hepatic effect.	[37] [47]
Risperidone	Social behavior and language problems	The extrapyramidal symptoms, weight gain, hyperprolactinemia, and the potential for type 2 diabetes, dystonia, epileptic seizures. Long-term risperidone therapy causes bone damage	[37], [41], [42], [43]
Methylphenidate	Hyperactivity, impulsivity, and inattention	Reduced appetite, inhibition of growth, delayed sleep onset, abdominal discomfort, hypertension, tachycardia, irritability, increased anxiety, and repetitive behaviors.	[48] [38]
Clonidine	Hyperactivity, irritability and outbursts, and repetitive behaviors	Drowsiness, sedation, decreased blood pressure, dizziness, constipation, and irritability	[49]
Atomoxetine	Attention-deficit/hyperactivity disorder–like symptoms	Reduced appetite, nausea, fatigue, mood changes, suicidal ideation, dizziness, and liver injury	[50]

6- ASD AND COMMON NATURAL THERAPY

Many researchers have focused on the role of natural medications in the treatment of autism in addition to other health problems [51]. They have been examined and demonstrated promising results in the treatment of a wide range of abnormalities, including neurological [52], cardiovascular [30], and diabetes mellitus problems [53]. These therapies were reported to have even fewer undesired effects and could be beneficial in diminishing the adverse effects once intake with the other chemical medications [41].

Several herbal and natural remedies, particularly with the exclusion or inclusion of special diets, have been used in the treatment of ASD [54]. Unfortunately, just a few have been confirmed by scientific research [35]. The preliminary outcomes of employing herbal medications for autism are hopeful in this regard [41], as shown in Table 2. The mechanisms of therapeutic plants are frequently unknown. It should be noted that these natural remedies are generally safe; however, for children, the safety profile has not been established [55].

Treatment with medicinal plants

6.1 *Zingiber officinale* (ginger): It is one of a family (Zingiberaceae), which contains gingerol, paradols, and shogaol. Ginger has been traditionally used in autism therapy due to its neural protective effect, antioxidant properties, and acetylcholinesterase inhibitory effect (AChEI), also it can improve memory [56]. *Z. officinale* was tested in a mouse model of age-related dementia, it showed effectiveness in memory enhancement and improving hippocampus neuronal density [57]. It was also shown to be effective in rats with localized cerebral ischemia and reduced brain infarct volume following unilateral middle cerebral artery occlusion and improved cognitive function [58].

A study was established in 2017 to investigate ginger extract as a protective and therapeutic herb in ASD using propionic acid (PPA) induced autistic animal models which suffered from severe behavioral

abnormalities. According to the results, ginger extract has a protective effect against PPA-induced social behavior deficits in rats, which might be related to its neuroprotective properties. There is no significant difference in PPA-induced neurotoxicity improvement between ginger extracts at 100 mg/kg and 200 mg/kg dosages. They concluded that ginger might be employed as an effective therapeutic regimen for diseases related to social function impairment, such as autism spectrum disorders [59].
Ginger is rich in a 6-gingerol fraction which has significant antioxidant properties, as well as a protective activity against the neurotoxic acrylonitrile-induced cerebral cortical damage. Consequently, 6-gingerol diminished acrylonitrile-induced depletion of central glutathione along with the activities of glutathione S-transferase (GST), glutathione peroxidase (GPX), and superoxide dismutase (SOD). It also decreased nitric oxide, malondialdehyde (MDA), interleukin-6, and tumor necrosis factor (TNF) levels that had been elevated due to the action of neurotoxins [60].

6.2 *Centella asiatica:* *Centella asiatica* (CA) is a traditional medicinal plant from the Apiaceae family [61]. C. asiatica lives in various tropical areas around the world, although it is indigenous to India, China, Sri Lanka, Madagascar, Indonesia, and Malaysia [3]. *C. asiatica* is used to improve memory, attention, mental capacity, neuromuscular problems, and nerve tissue healing after crushing traumas such as spinal injuries. It is also used to treat epilepsy and has shown promise in treating Alzheimer's disease [41]. This plant is rich in B-1, B-2, and B-6 vitamins, which are vital for the nervous system, it also possesses anti-inflammatory properties and antioxidant activity [62]. It increases circulation particularly to the skin blood vessels, and mucosal membranes [63]. These medicinal actions are strongly related to a varied set of active components including flavonoids, pentacyclic triterpene derivatives, polyphenols, alkaloids, and glycosides [64].

In vitro study, C. asiatica has a significant reducing impact on AChE activity [65]. *C. asiatica* has a powerful combination of flavonoids such as rutin, luteolin, and quercetin [66]. *C. asiatica* also enhances speech resumption in a study with young ASD individuals [67]. It protects from cognitive dysfunction, oxidative stress, AChE activity, and cytoarchitectural alterations induced by Aluminum chloride (AlCl3) [68]. The potential impact of *C. asiatica*'s on GABA production has been investigated, the plant extract was significantly increased glutamic acid decarboxylase (GAD) activity [69]. As a result, the possible effects of *C. asiatica* in improving ASD symptoms might be attributed to a rise in GAD activity [3].

6.3 *Acorus calamus:* *Acorus calamus* is a semiaquatic perennial herb that belongs to the Acoraceae family that grows in Asia, North America, and Europe [3]. The oils found in *A. calamus* possess a variety of beneficial properties that have been used to treat a variety of diseases. It is also utilized to help revive the brain and nervous system [70]
A study had been carried out in 2018 found that *A. calamus* was effective in reducing inflammation in a lipopolysaccharide (LPS) model. The highest dose of an *A. calamus* extract (600 mg/kg) improved the results in a passive avoidance memory test and reduced stress in the elevated maze model [71]. Furthermore, oxidative stress and antioxidant indicators were modulated in hippocampus samples of A. calamus-treated cells and the malondialdehyde (MDA) levels have been decreased [23].
A. calamus extract promotes neuroprotection in rats by lowering lipid peroxidation, glutathione levels, and superoxide dismutase (SOD) activity following middle cerebral artery occlusion-induced ischemia [72]. As well, it was beneficial in the treatment of attention and memory deficits, epilepsy, and convulsion when combined with *Centella asiatica, licorice, valerian*, and *shankpushpi* [41].

6.4 *Ginkgo biloba:* Extraction of *Ginkgo biloba* had been experimented with in therapy of several health issues such as nervous, circulatory, and cranial issues which resulting in promising effects. The most interesting abilities of *ginkgo biloba* appeared in the therapy of Alzheimer's disease, behavioral impartments, and vascular dementia. The use of *Ginkgo biloba* in conjunction with psychiatric medicines either improves their impact or reduces their side effect [73]. Flavonoids and terpenoids are the most effective medicinal components of *G. biloba* which give it the neuroprotective, anti-inflammatory, and

antioxidant properties. *Ginkgo* has also been shown to improve cognitive and neurological function, owing to its antioxidant action, arterial regulation, and platelet-activating factor antagonism, which protects the brain from ischemia injury. *Ginkgo biloba* can affect the central nervous system and neurotransmitter functions [3]. *G. biloba* extract coupled with risperidone has been tested in children aged 4 to 12 years but revealed no difference in their medical status, while more research is required [74]. However, in a previous short 4-week observational research, administration of 2 × 100 mg *G. biloba* extract for 4 weeks revealed a degree of improvement in autistic patients [75], indicating that the medicinal herb may have promising prospects in this disease.

6.5 Yokukansan: Yokukansan (YKS) is a Japanese mixture of seven plants, dried and mixed to form this combination. These plants are *Poria mushroom, Glycyrrhizae radix, Atractylodes lancea rhizoma, Uncariae ramulus et uncus, Cnidii rhizoma, Bupleuri radix, and Angelicae radix.* Wake *et al.* (2013) conducted a 12-week prospective open-label study of YKS in 20 autistic children and adolescents aged 6 to 17 years. For 12 weeks, the children and adolescents were given YKS at a dose of 2.5-7.5 g/day. Several studies indicated the possible efficacy of YKS in the therapy of hyperactivity/noncompliance and irritability/agitation in children. However, large-scale placebo-controlled trials are required to ensure the effectiveness and tolerability of this formulation [76].
Another study employed an experimental model based on the prenatal treatment of 5-bromo-2'-deoxyuridine (BrdU-rats) in rats. It showed that this experimental model generates hyper locomotor activity in rat pups, making it a suitable animal model for the study of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). The treatment with YKS was found to have a favourable effect on the cerebellar serotonin metabolism, resulting in a significant enhancement in cognitive ability and a reduction in locomotor agitation [77].

***6.6 Camellia sinensis* (Green tea):** Green tea is considered a great source of polyphenols, chiefly flavonoids, gallic acid, other phenolic acids like chlorogenic acid and caffeic acid. Green tea's major flavonoids are catechins (flavan-3-ols) which help in protecting the cells against damage caused by free radicals [78]. Correspondingly, green tea includes other flavonoids like kaempferol, myricetin, and quercetin [79]. Polyphenols of green tea can pass through the blood-brain barrier where they can normalize striatal dopamine depletion and treat the damage of neurons in the substantia nigra in N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine model animals [80]. These polyphenols have antioxidant activity [81], anti-inflammatory ability [82], anti-cancer abilities [78].
A study conducted by Banji *et al.,* (2011) aimed to explore the effect of green tea extract on mice postnatally exposed to valproic acid (VPA). They used a dose of 75mg/kg and 300mg/kg of green tea extract (GTE). In this study, GTE enhanced motor functions which could be credited to its capability to protect cerebellar tissues. In addition, experimental animals had a rise in the latency to fall from the rotating rod, and also deficits in muscular coordination were minimized in the GTE treated animals. Treatment with GTE had made a rise in time spent and a number of open arms entries; that may be evidence that fear and anxiety were reduced. Exploration activities and horizontal distance moved were measured in an open field after treatment with GTE suggest that stereotypic behavior was controlled, and exploratory activity was developed. GTE (300mg/kg) was retrieved the response elicited by VPA by maintaining neuronal circuitry in the amygdala, resulting in reduced anxiety symptoms [78]. GTE's neuroprotective potential might be attributed to catechins, which have higher antioxidant activity than vitamins C and E [83].

6.7 Cannabis sativa: Cannabis usage was reported to improve interpersonal communication [84]. The core constitutes of the cannabis (phytocannabinoids) are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC triggers the type-1 cannabinoid receptor (CB1R) in the brain; it is psychotropic and may cause anxiety and psychosis [85]. CBD is a regulator of the CB1R and reduces the effects of CB1R agonists such as THC. It has a rather high toxicity threshold and is not psychotropic [85]. While THC intake, particularly at a young age, can result in addiction, cognitive decline, motivational loss, and

psychosis, co-consumption of CBD may mitigate them [86]. CBD appears to have antipsychotic, antiepileptic, and neuroprotective characteristics [87].

A dose of 600 mg CBD has been decreased prefrontal GABA activity in ASD patients [88]. One of the most important CBD chemicals is epidiolex produced from cannabis which was approved in the USA for the treatment of two extreme types of epilepsy [89]. This may be significant for ASD patients because 10–30% of them also have epilepsy and numerous pathophysiological pathways are involved in both conditions [87]. The endocannabinoid system is a cell-signaling system that consists of cannabinoid receptors, their endogenous ligands (endocannabinoids, mostly anandamide and 2-AG), transporters, and enzymes that synthesize and breakdown endocannabinoids [90]. Animal studies assume that ASD has a lower endocannabinoid [91]. In many models, motivation of the endocannabinoid system and CBD supplementation [92] restored social impairments. Furthermore, children with ASD have decreased peripheral endocannabinoid levels [89].

6.8 *Asparagus racemosus:* *Asparagus racemosus* also called (Shatavari) and renowned as the "Queen of Herbs" in Ayurveda. This wonderful plant is used as a general tonic that enhances lifespan, improves mental performance, and boosts body's energy [93]. The roots of this plant are assumed to have anti-spasmodic, appetizer, aphrodisiac, anti-diarrheal, anti-dysenteric, laxative, cancer fighter, anti-inflammatory, anti-tubercular, neuro-protective, nootropic, anti-depressant, anti-anxiety, anti-epileptic, and have nephroprotective and neuroprotective properties [94]. *Asparagus racemosus* also aided in the reversal of autistic symptoms in rat pups [95]. Because of its antioxidant properties, *A. racemosus* dramatically corrected the altered oxidative stress indicators in autistic pups [96].

Likewise, a project was established in 2020 by Joon and Parle to investigate the roles of acetylcholine, catecholamines, and oxidative stress in the development of autistic symptoms, as well as their regulation by Shatavari. In this study, VPA was injected into pregnant female rats on the 13th day of gestation, resulting in dysfunctional pups with extremely low body weight at birth, poor olfactory discrimination, and delayed eye-opening. The autistic offspring pups suffered from elevated monoamine oxidase enzyme-A (MAO-A) activity in the brain. In this study, treatment with ethanolic extract of *Asparagus racemosus* roots at higher dosages (100 mg/kg and 200 mg/kg) was restored the increased MAO-A activity in the brains of autistic pups [97]. Monoamine oxidases (MAOs) catalyze the breakdown of monoamine neurotransmitters including serotonin, dopamine, and norepinephrine, which are important modulators of proper brain functioning. Serotonin has been proven to play a significant effect in autistic mood fluctuations [98]. The autistic offspring pups were having high levels of acetylcholinesterase (AchE) enzyme activity in the brain. Treatment of autistic rat pups with ethanolic extract of *Asparagus racemosus* roots lowered brain AchE activity and exhibited a neuroprotective effect. Finally, it was concluded that treatment with *A. racemosus* has anti-autistic potential could be due to its anti-oxidant impact [95].

6.9 *Curcuma longa*: Curcumin (diferuloyl methane) is the principal curcuminoid found in the Indian turmeric (*Curcuma longa*). Several studies have emphasized its numerous pharmacological possessions such as anti-inflammatory, antioxidant, anti-carcinogenic, and neuroprotective properties [99]. Curcumin's protective impact may be due to its high antioxidant capacity [100]. Nitrite levels elevation in PPA-rats is due to increased nitric oxide synthesis caused by an increase in inducible nitric oxide synthase activity [101]. Curcumin reduces elevated nitrite levels by NO scavenging and iNOS inhibitory action [102]. Curcumin treatment substantially and dosage dependently reduced the considerably elevated TNF and MMP-9 levels in the serum of PPA-treated rats and inhibits MMP-9 in blood mononuclear cells [103]. There are reported improvements in anxiety and depression-like behavior in the PPA-autistic mice following curcumin treatment which might be attributed to the activation of the anti-neuroinflammatory cascade [104]. Similarly, curcumin treatment was reported by Xu *et al.* (2005) to have anxiolytic and anti-depressant effects observable in open-field and forced swimming tests [105]. Curcumin has been shown in the literature to have an anti-anxiety impact through GABAergic and nitrergic regulation [106], as well as an antidepressant effect via serotonin, dopamine, and BDNF modulation [107].

Corresponding with these findings, a valuable study has been established to investigate the neuropsychopharmacotherapeutic potential of curcumin against PPA-induced autistic behavior in rats. Treatment with PPA altered the neurotransmitter levels of serotonin, dopamine, and glutamate, these neurotransmitter changes disrupted GAP junction coupling at the synapse and impacted numerous parts of the brain, including the pre-frontal cortex, which is important in social interaction. Curcumin therapy in (50, 100 and 200mg/kg) was improved numerous indices of sociability in PPA-treated rats due to its anti-inflammatory and antioxidant actions, as evidenced by biochemical and pro-inflammatory markers such as TNF-a and MMP-9. Curcumin treatment decreased self-grooming behavior and boosted marble burying activity in a dose-dependent manner through its anti-anxiety action that may be attributed to the ability of GABAergic and nitrergic systems regulation. Curcumin restored the memory as shown in the novel object recognition test [108].

6.10 *Panax ginseng Meyer* (Korean red ginseng): It is a common herb belongs the *Panax* genus. For many years, ginseng has received widespread attention for its anticarcinogenic [109], antioxidant [110], and anti-obesity properties [111]. KRG, in various preparations and extractions, has shown significant advantages in the central nervous system (CNS) issues specially Alzheimer's disease [112 - 113], cerebral blood flow, prevention of superoxide generation, ischemia damage [114], and learning and memory enhancement [115] in both human and animal investigations. Accordingly, it must be interesting to explore the influence of KRG on neurodevelopmental disorders like ASD and others.

A study demonstrated by Gonzales *et al*. (2016) indicates the possible therapeutic benefits of *Panax ginseng* when administered in a dose of (100 or 200 mg/kg) postnatally to ASD offspring of VPA-exposed mice. *Panax ginseng* therapy corrected behavioral deficits induced by VPA such as marble burying, sociability, locomotor activity, and spontaneous alternation, which also reversed the hyperactivity [46].

Other natural treatments

6.11 Bee venom: Bee venom (BV) has been investigated as a potential therapy for a variety of immune related disorders in both animals and humans [116]. Recently, BV injection has been recommended to be effective for the treatment of neurodegenerative disease models such as Alzheimer's disease [117], amyotrophic lateral sclerosis (ALS) [118], and Parkinson's disease (PD) in mice whereas BV have protected dopaminergic neurons in the substantia nigra and striatum [119].

In a line with these findings, a relevant study to evaluate the BV therapeutic action on the PPA autistic rat model has been created. PPA administration resulted in significant alterations in the enzymatic antioxidant capacity of rat brains, as evidenced by a marked able to decrease in CAT and SOD activity. Consequently, PPA exposure increased the MDA content of the rat pup brain, which is an indication of lipid peroxidation due to ROS accumulation. BV treatment with a dose of (0.5 mg/kg) considerably reduced PPA-induced oxidative stress and antioxidant parameters, including an increase in SOD and CAT activity. It was also shown that rat pups co-treated with BV had a reduced amount of carbonyl formation when compared to the PPA-treated group, indicating that BV administration had a protective impact on protein oxidation [120].

The role of BV in reducing PPA-induced oxidative stress might be attributed several strategies. First, melittin, a key component of BV, and phospholipase (PLA2) have been demonstrated to be capable of scavenging reactive oxygen species (ROS) and nitric oxide (NO) [121]. Second, melittin was found to strongly inhibit the human peripheral-blood leukocytic production of superoxide (O2-) and hydrogen peroxide (H_2O_2) in a nontoxic and dose-dependent manner, implying that melittin may work as a prototypic small, cationic, amphipathic, membrane-active, super-oxide-production-inhibiting peptide, providing a model peptide that may contribute to the downregulation of radical production [122]. Third, BV had an inhibitory impact on the LPS-induced production of ROS and calcium release. As a result, the modulatory action of BV may be connected to its numerous inhibitory effects on NO formation as well as ROS release in rat C6-glioma cells via protein kinase C-alpha (PKC-α) regulation [123].

6.12 Vitamin B6 and Magnesium: Vitamin B6 has been a common therapy for autism over the last 20 years [124]. This combination has been reviewed by several researchers [125]. Kuriyama, S. *et al.* (2002) found an increase in IQ and social quotient scores in autistic kids treated with vitamin B6 and Mg2 [126]. But this study had significant methodologic flaws, such as an insufficient explanation of the diagnosis, selection criteria, and results.

6.13 Omega-3: Omega-3 is a very well fatty acid, and the ration of omega-6 to omega-3 has been documented to affect immunological status; for example, omega-3 fatty acids are known to have anti-inflammatory qualities, whereas omega-6 fatty acids have pro-inflammatory features [127].
supplementing autistic children with Omega-3 has received much interest as a consequence of publications indicating the significance of omega-3 fatty acid abnormalities in ASD behaviors that can be corrected with treatment [128]. The mechanism through which omega-3 fatty acids ameliorate ASD symptoms is still yet unknown [129].

Following omega-3 treatment, children with ASD showed increases in overall health, sleeping patterns, cognitive capacity, motor skills, focus, eye contact, and sociability, as well as decreases in irritability, aggressiveness, and hyperactivity [130]. Amminger *et al.* (2007) conducted a randomized, double-blind, placebo-controlled 6-week trial in 13 children (aged 5–17 years) with ASD and revealed that omega-3 fatty acid supplementation at a dose of 0.84 g/d eicosapentaenoic acid (EPA) and 7 g/d (DHA) was associated with improvements in stereotypy and hyperactivity [131]. However, there is conflicting evidence about whether omega-3 fatty acids are an effective therapy for ASD [132].

6.14 Vitamin D: Several recent reviews on autism and vitamin D have been published. a brilliant investigation stated that we can consider that 25(OH)D supplementation is a potential therapy and preventative method for ASD [133]. Scientists found that autistic children often have low vitamin D blood concentrations [134].
An interesting study on a family reported that autistic children had diminished vitamin D levels than their first-degree relatives, indicating that reduced vitamin D may be implicated in abnormal brain progress leading to autism [135].
A study of Patrick and Ames (2014) concluded that 25(OH)D is crucial for normal brain progress. Many studies testified that fully supplement pregnant mothers and their children could preventing against ASD [136]. Therefore, pregnant and nursing women may need to take up to 10,000 IU daily [137]. A 300 IU/kg/daily of 25(OH)D is the minimum dose suggested by researchers to treat autistic people [138].

Table 2: Herbals and supplements used to treat the symptoms of autistic symptoms in human or animal models

Herb or Supplement	**Dose**	**Treated ASD Model or Human**	**Beneficial results**	**Ref.**
Zingiber officinale	100 mg/kg and 200 mg/kg	PPA autistic rat model	A protecting result against social behavior limitations induced by PPA in rats	[59]
6-Shogaol, bioactive compound of *Zingiber officinale*	10 mg/kg/day, orally for 5 days	Prenatal exposure to lipopolysaccharide (LPS)	Rescinded the grooming and the diminished rearing episodes. Enhanced the memory	[139]
Centella asiatica	150 and 300 mg/kg b.w./day, for 60 days	Alcl3-induced neurological conditions in rats	Saved the brain from alcl3-induced, oxidative stress, cognitive dysfunction, and cytoarchitectural alterations.	[68]

Acorus calamus	600 mg/kg	Lipopolysaccharide (LPS) model of neuroinflammation	Improved the passive avoidance memory test results and reserved anxiety through the elevated maze model	[23]
Ginkgo biloba	100 mg/kg/d i.p. Postnatal Days (PND) from 13 to 40	ASD induced by valproic acid in mice	Mitigated autistic changes caused by VPA	[140]
	4 weeks treatment (2 × 100 mg)	Autistic male patients (age 19.4–22.4)	Enhanced week speech, inadequate eye contact and hyperactivity.	[75]
	Ginkgo biloba extract (80 – 120 mg/day) + risperidone (2 – 3 mg/day)	Autistic patients (4 to 12) years of age	No noticeable effect on the treatment outcome of ASD patients	[74]
Yokukansan	1 g/kg through PND (1 – 21).	A Hyperactive Rat Model from Prenatal brdu (5-bromo-2′-deoxyuridine) Treatment	Diminished self-grooming Affected on metabolism of serotonin in cerebellum	[77]
	2.5 - 7.5 g/day	Autistic children and adolescents aged (6 - 17) years	Treatment of severe irritability/agitation and hyperactivity/noncompliance	[76]
	2.5 - 7.5 g/day	Patients diagnosed with PDD-NOS or Asperger's disorder	Reduced aggression, self-injury, irritability and tantrums. Improved results of the ABC-I tests.	[141]
***Camellia sinensis* (Green tea)**	300 mg/kg	ASD offspring of VPA-exposed mice	Improved motor jobs	[78]
Epigallocatechin gallate (EGCG), the most abundant and powerful flavonoid in green tea	2 mg/kg	ASD offspring of VPA-exposed mice	Rescinded VPA-induced basic behavioral changes EGCG had neuronal protective properties may be attributed to anti-oxidant activity	[142]
***Asparagus racemosus* (Shatavari)**	100 mg/kg and 200 mg/kg	ASD offspring of VPA-exposed rat	Returned the MAO-A activity in brain tissues Reduced nitrite concertation in plasma, raised GSH levels and improved catalase activity in brains of pups.	[97]
	100 mg/kg and 200 mg/kg	ASD offspring of VPA-exposed rat	Reduced anxiety, memory impairment, hyperlocomotion Amplified sensitivity to pain and depression-like behaviour	[95]

Curcumin, active component of ***Curcuma longa***	50, 100 and 200 mg/kg	PPA autistic rat model	Reversed PPA-induced changes happened in nervous system, behavior, biochemical markers	[108]
	10 and 20 mg/kg	Immobilization-induced restraint stress for 6h	The 20 mg dose showed anti-anxiety effect	[106]
	1 g/kg	ASD offspring of VPA-exposed mice	Enhanced the belated maturation and unusual body weight	[143]
	20 mg/kg	Black and Tan Brachyury (BTBR) mouse pups (model of autism)	Improved social activity, diminished repetitive manners, and corrected cognitive impairments. Saved the neurogenesis of hippocampus	[144]
	(25, 50, and 100 mg/kg, i.p.) or (50 and 100 mg/kg, i.p.)	Black and Tan Brachyury (BTBR) mouse pups (model of autism)	(25, 50, and 100 mg/kg) Upgraded social performance. (50 and 100 mg/kg) Moderated oxidative stress grade by riasing superoxide dismutase (SOD) and catalase (CAT) levels in the cerebellum and the hippocampus	[145]
***Panax ginseng Meyer* extract (Korean red ginseng)**	100 or 200 mg/kg	ASD offspring of VPA-exposed mice	Improved social performance, locomotion, marble burying, spontaneous alternation, and electroshock seizure threshold.	[46]
	250 mg	ASD male patients	Ameliorated inappropriate eye contact, irritability, hyperactivity and speech disabilities.	[146]
Bee venom (Apitoxin)	0.5 mg/kg	PPA autistic rat model	Diminished antioxidant markers, raised SOD and CAT activity	[120]
	0.5 mg/kg	PPA autistic rat model	Reversed the neurobehavioral impartments, social disabilities, raised repetitive/stereotypic behaviors, and hyperactivity	[147]
Vitamin B6 and Magnesium	30 mg/kg vit B6 and 10-15 mg/kg Mg	Autistic children	Reduced the autistic indicators significantly	[148]
	6 mg/kg Mg and 0.6 mg/kg vit B6	Autistic children	Enhanced social behavior, communicating, restricted behavior, and delayed functioning	[149]
Omega-3	1.5 g/d	Autistic children (aged 5–17 years)	Enhanced hyperactivity and stereotypic behaviour	[132]
	1.3 g/d	Autistic children (aged 3–8 years)	The results did not show a significant benefit for omega-3 supplementation	[130]
	1.5 g/d	Autistic children (aged 2-5 years)	The results did not show a significant effect for omega-3 supplementation	[150]

	1 g/d - for 12 weeks	Autistic children (aged 4-7 years)	Enhanced the Autism Treatment Evaluation Checklist (ATEC)	[151]
	1 g/d	Autistic children (aged 7-18 years)	Enhanced the Social behaviour and Attention difficulties	[152]
Vitamin D	400 ng/kg prenatal administration	(Maternal immune activation) MIA-ASD offspring	Diminished social impatments, stereotyped behavior Improved emotional learning and memory. Vitamin D had no effect on pro-inflammatory cytokine levels	[153]
	150 000 IU intramuscularly every month and 400 IU orally / day	A 32-month-old boy with ASD and vitamin D3 deficiency	Improved the behavioral issues. Increased serum 25(OH)D level.	[154]
	A dose started from 300 IU/kg/day	Autistic individuals	Reversed stereotypy and autistic behavior Improved eye contact, attention span.	[138] [155]

7. CONCLUSION

The purpose of this review was to view the trends in supplementary and natural remedies involved in autism spectrum disorder (ASD) studies and see how they aided in symptoms relief. It is clear from the research reviewed that autism is a complicated condition that needs more research and there is no known pharmaceutical therapy for the basic symptoms of this disorder. Routine drugs used in autism therapy always are associated with various side effects. There is urgent need to find novel and attentive potent medications to treat autism-related symptoms. Therefore, herbal plants and supplementary medications may offer a promising platform to find novel anti-autistic agents. Of the most promising herbals in this field were *Curcuma longa*, Yokukansan, *Ginkgo biloba*, and *Zingiber officinale*. More research is needed to prove the efficacy of *Centella asiatica*, *Acorus calamus*, *Asparagus racemosus* and *Camellia sinensis* in ASD treatment. Vitamins that may present as effective supplements for ASD patients are Vitamin D and the combination of vitamin B6 and magnesium. The results of Apitoxin showed noticeable improvement in the PPA autistic pups, which calls for more research for investigating its effectiveness. Several studies had carried out to examine the effect of omega -3 supplementation, but they had different results. Clinical trials using scientifically verified procedures may be conducted to be able to assess whether or not the usage of various natural medications may be an effective alternative to traditional pharmaceutical therapies used to alleviate the symptoms of ASD.

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