



A Narrative Review of Effective Herbal and Traditional Medicines on Management of Autism

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Abstract

Autism is a complex neurodegenerative disorder that affects people from birth. Through dietary approaches, sensory integration, rehabilitation training, education and finally medication management, the autistic disorder symptoms can be reduced. Of course, this does not mean that the main features of autism can be treated in general, but with medication control and education, these symptoms can be managed. In the last decade, treatment with herbal medicines has attracted special attention and promising results have been reported in the treatment of various diseases. In this review, it is tried to collect the plants that have been studied for the treatment of autism and herbal medicines with a possible effect on the symptoms of autism in the literature. The results show some few medicinal herbs and natural/ traditional formulations like *Gingko biloba*, *Centella asiatica*, *Humulus japonicus*, *Salvia leritifolia*, *Vitis vinifera*, Hazelnut, *Ukgansan* and Kwakhyangjungkisanhapyukmijihwangtang-gamibang have beneficial effects on different features of autism and could be helpful for the patients. More investigations are needed to prove their efficacy in more clinical studies in the future.

Keywords: Autism; Herbal medicines; Plants; Traditional medicine

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Introduction

Autism is a complex neurodegenerative disorder that affects people from birth. People with autism notice this disease in the first 2 years of life. Autism is often characterized by abnormal social behaviors, poor communication skills, communication problems, or in some cases, forced or repetitive behaviors [1]. These people usually have a different perceptual experience of the world, which is associated with changes in social cognition. [2]. Unusual sensitivities in hearing, sight, smell, taste and touch senses may be seen as symptoms of autism [3-7].

Also repeated thoughts, activities, and behaviors are other symptoms of autism, but impaired communication is the central core of impairments. These impairments are usually seen in the first three years of life and the incidence of these disorders is 10 in 10,000 people. The prevalence of this disease is higher in boys than girls and is reported to be 1 in 3 and 1 in 4, respectively [8]. About 1 in 68 children has been diagnosed with autism spectrum disorder (ASD) estimated from the Center for Disease Control and Prevention (CDC) data. According to the reported studies, 1 to 2 percent of people in Asia, Europe and North America were diagnosed with autism [9].

In autism disorder, several genetic and environmental factors interact and lead to the creation of a clinical chain. A multilocus model that controls epistatic interactions between several susceptibility genes explains the genetic aspect of this disorder. Over the past decade, many efforts have been made to characterize autism-related chromosomes. However, the transition from chromosomes to selected genes associated with autism is complex [10].

Neurological findings suggest that early genetic events occur in the brainstem, cerebellum, and cerebral cortex. Cellular mechanisms may include increased cell proliferation, altered cell migration, decreased cell death, or altered synapse elimination. Neurochemical disorders in autism may be associated with involvement of various neurotransmitter systems. So far, the role of the serotonergic system in autism has been well studied, and the cholinergic and GABAergic systems are also under further investigation [11].

The role of environmental factors in this disease is not yet clear. It is also not clear whether environmental factors are an aggravating factor along with genetic factors or cause the disease independently. Complex, non-deterministic interactions between genes in the brain development and developmental variability due to "random" factors such as small fluctuations of gene expression have a potential role in pathogenesis of autism. These considerations suggest that a non-deterministic perceptual framework is highly proper for autism research [12-15].

Through dietary approaches, sensory integration, re-

habilitation training, education and finally medication management, the autistic disorder symptoms can be reduced. Of course, this does not mean that the main features of autism can be treated in general, but with medication control and behavioral therapies, the seizures, inattention, depression and hyperactivity can be managed [16, 17]. Between pharmacological treatments, risperidone is the most common treatment for serious behavioral symptoms in children with autism [18]. Notwithstanding beneficial effects of risperidone on behavioral problems, the treatment results are ineffectual and have been associated with adverse effects, such as rhinorrhea, increased appetite, excessive weight gain and somnolence [19]. Accordingly, therapists seek treatment with higher efficacy and fewer side effects.

Traditional systems of medicine and medicinal herbs are considered as one of the sources to find natural therapeutic agents or methods, nowadays. In the last decade, treatment with herbal medicines has attracted special attention and promising results have been reported in the management of various disorders [20]. In this regard, treatment with herbal and traditional medicines to reduce the symptoms of autism has received special attention and many studies have been conducted [21].

Methods

The definition of autism is a new term and in traditional medicine, there is no diagnostic meaning of autism. In Chinese medicine, for example, there is a phrase called Phlegm in the heart orifice, which describes a condition like autism. In this review, some herbal medicines used for autism that have current investigation support for their efficacy would be introduced. The main purpose of this manuscript is to review and collect the most important and most referenced herbal and traditional medicines that studies have shown to be effective on autism, with the hope that these medicines can be a suitable alternative to treat autism symptoms with the least side effects. It should be noted that the materials collected in this review article have been selected from original articles indexed in various databases including Science Direct, Scopus and Google Scholar.

Results

Ginkgo biloba L.

Studies have shown that the extract prepared from the leaves of *Ginkgo biloba* is effective in treating many diseases related to the nerve and brain. Many studies have been done on this plant and it was used for the first time in the United States as an herbal medicine in the treatment of memory-related disorders [22,23].

The history of this medicinal plant dates back to two thousand years ago in China. Most studies have been done with this herbal medicine related to diseases such as dementia of arterial origin, memory improvement and cognitive disorders [22,23].

The results of studies show that *G. biloba* can be considered as an antidepressant and a neuroprotective agent in cerebral injury [24]. The results of 40 clinical trial studies show that **G. biloba** can improve concentration and memory problems in people with brain abnormalities. Also, *G. biloba* can reduce fatigue and lack of concentration by increasing blood flow in cerebral vessels [25]. The extract of this plant seems to be effective on central nervous system transmission systems. In one study, it was found that this plant reversed the reduction of cerebral 5HT_{1A} receptors in elderly rats [26]. It has recently been shown that ginkgo extract can reversibly inhibit monoamine oxidase (MAO)B and MAOA enzymes. This inhibition can explain the anti-anxiety and antidepressant effects of this extract in the management of attention deficit hyperactivity disorder [27].

One study investigated the effectiveness of *G. biloba* in patients with autism. The results showed that administration of *G. biloba* for 4 weeks at a dose of 100 mg per day improved the symptoms and signs of autism in patients with this disease. According to these results, it seems that *G. biloba* can at least be considered as an additional treatment [28]. In another study, the effectiveness of *G. biloba* extract as an adjunctive agent to risperidone in the treatment of autism was investigated in a double-blind placebo-controlled trial. In this study, 47 patients with an age range of 4 to 12 years with a diagnosis of autism were randomly divided into 2 groups. The first group received risperidone with Ginkgo extract and the second group received risperidone with placebo. Patients were monitored for changes in behavior and symptoms during this period. However, the results of this study revealed that the addition of *G. biloba* extract to the drug treatment of risperidone did not cause a considerable change in the rate of recovery. Although more studies are needed to confirm this claim [29].

***Centella asiatica* (L.) Urban**

Centella asiatica is an annual herbaceous plant of the Apiaceae family known as Gotu Kola. The active ingredients of this plant are pentacyclic triterpenes, which mainly include madecassoside asiaticoside, madecassic acid and asiatic acid [30]. Numerous therapeutic effects of this plant have been reported, some of which include wound healing, psoriasis, varicose wounds, eczema, lupus, diarrhea, amenorrhea, fever, urinary tract diseases of the female urinary tract, as well as to relieve anxiety and improve cognition [31]. As mentioned, studies show that this plant has seda-

tive and anti-anxiety effects. The main effects of this plant are due to the presence of brahmoside and brahminoside compounds. The anxiolytic effect is attributed to the binding to cholecystokinin receptors (a group of G protein-coupled receptors which bind the peptide hormones cholecystokinin (CCK) or gastrin), which appear in the process of modulating anxiety, nociception, hunger and memory in humans and animals [32]. Several studies have been implemented to investigate the antidepressant effect of this plant. One study found that total triterpenes had an effect on the immobility time of the animals in the forced swimming test. It seems imipramine and triterpenes have ameliorated the imbalance of amino acid levels and reduced immobility time, which confirms the antidepressant activity of *C. asiatica* [33].

In another study, corticosterone levels were measured in rat brains to evaluate the effect of triterpenes on depression. For this purpose, the contents of monoamine neurotransmitters and their metabolites in the rat cortex, hippocampus and thalamus were examined. The results showed a significant decrease in corticosterone and an increase in the content of serotonin (5-HT), norepinephrine (NE), dopamine (DA) and their metabolites 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) in rat brain [34]. It seems *C. asiatica* has revitalized the effect on the brain and nervous system, increase concentration, attention and combat aging. In this regard, aqueous extract of *C. asiatica* at doses of 100, 200 and 300 mg/kg was administered intracerebroventricularly to rats treated with streptozotocin (which causes cognitive impairment and oxidative stress) for 21 days. The result showed that the animals that received the aqueous extract exhibited an increase in cognitive behavior in elevated plus-maze and passive avoidance in a dose-dependent manner. Moreover, a considerable increase in catalase and glutathione levels and decrease in malondialdehyde (MDA) were seen in animals treated with 200 and 300 mg/kg extracts. [35]. Considering the mentioned effects of this plant, it seems that *C. asiatica* can be useful in the treatment of autism [36].

***Humulus japonicus* Siebold & Zucc.**

Humulus japonicus, known as Japanese hop, is an ornamental plant in the family Cannabaceae. Some authorities have it as a synonym of *Humulus scandens*. This plant is used as a traditional treatment and has anti-inflammatory, antitumor and antimicrobial effects. Also, this plant is used to treat hypertension, pulmonary disease and leprosy. Recent studies show that this plant can also affect Alzheimer's and Parkinson's diseases [37,38].

In a study, the effect of *H. japonicus* on the spectrum of autism disorder was investigated. BTBR T + Itpr3tf

/ J mouse model was used to evaluate the effect of *H. japonicus* on autism. The results of this study demonstrated that oral and gradual administration of *H. japonicus* ethanolic extract caused attenuated repetitive grooming behavior, increased social interaction and improved novel-object identification in BTBR mice. The anti-inflammatory effects of *H. japonicus* were investigated using immunohistochemistry and quantitative reverse transcription PCR analysis. The results showed that microglia activity in the hippocampus and striatum was significantly reduced and also pro-inflammatory cytokines such as C - C Motif Chemokine Ligand 2, interleukin (IL)-1 β and IL-6 were considerably reduced. On the other hand, *H. japonicus* administration balanced the levels of calcium/calmodulin-dependent protein kinase type II subunit α and N-methyl-D-aspartate receptor subtype 2B in the hippocampus of the studied mice [39].

Ukgansan

Ukgansan is an indigenous medicine or folk medicinal remedy used in China and Japan (Yokukansan in traditional Japanese medicine). It consists of *Atractylodes Rhizoma* White (*Atractylodes macrocephala* Koidz.), *Poria* (*Wolfiporia cocos*), *Angelicae Gigantis Radix* (*Angelica gigas* Nakai), *Cnidii Rhizoma* (*Cnidium officinale* Makino), *Uncariae Ramulus et Uncus*, *Bupleuri Radix* (*Bupleurum chinense* DC.) and *Glycyrrhizae Radix* (*Glycyrrhiza uralensis* Fisch. ex-DC.). It was first developed and used by Xue Ji in 1556 to treat contracture, convulsion, and epilepsy [40]. In addition, *Ukgansan* can be effective in the amelioration of autism through its anti-inflammatory effects, neurogenesis and upregulation of glutamate and serotonin [41]. Accordingly, studies were performed on this drug to determine its effectiveness on autism. A study conducted on an animal model of autism found that *Ukgansan* reduced grooming in the open field test [42]. *Ukgansan* also prevented behavioral disorders and improved neuroplastic signaling in a model of social isolation in mice [43]. The combination improves irritability in a 12-year-old child with autism, according to a case report. However, this condition had not improved with medication before [44].

In a 12-week study, the medicine was prescribed for 20 children in the age range of 6 to 17 years who were suffering from autism. Primary outcome measures included the Children's Global Assessment Score (CGAS), Clinical Global Impressions-Improvement of Illness Scale (CGI-I) and the Aberrant Behavior Checklist (ABC) irritability subscale. During this period, 20 participants received 2.5 to 7.5 g per day of this combination. The results showed that CGI-I improved significantly over 8 weeks. The mean CGAS was initially 31.92; while the mean final score at the end of the study was 54.52. After 8 and 12 weeks of prescrip-

tion, respectively, the ABC irritability/agitation subscale and the hyperactivity/noncompliance subscale were considerably improved. The combination was well tolerated. None of the participants dropped out of the study due to drug-induced side effects. [45].

In another study, 40 patients with pervasive developmental disorder (PDD) and Asperger's disorder were treated with Yokukansan for 12 weeks. Primary outcome measures included the CGI-S and ABC-I. Forty participants in the age group of 8 to 40 years received a dose of 2.5 to 7.5 g per day of Yokukansan. The results showed full-scale intelligence quotient (IQ) scores ranged from 70 to 110. About 90% of subjects exhibited fewer tantrums, self-injury and aggression as interfering symptoms of irritability. Also, CGI-S of participants was 1 or 2 (not at all ill, borderline mentally ill or normal) with 80% improvement on the ABC-I. It was also found that the drug did not have serious side effects and therefore none of the participants were excluded from the study [46].

As mentioned earlier, this combination used for treatment of ASD in unsettled, sensitive, nervous and angry children and has been used for management of malnutrition, night crying, insomnia and nervousness in Japan and South Korea. In order to elucidate the tolerability and efficacy of *Ukgansan*, large-scale placebo-controlled studies were needed. Accordingly, effectiveness, economic evaluation and safety of *Ukgansan* granule in children with autism spectrum disorder was designed during a study for a prospective, multicenter, randomized, double-blinded, placebo-controlled, parallel-group clinical trial. For this purpose, children with autism in the age range between 4 and 6 years were divided into two groups. 120 participants received *Ukgansan* granules with acupuncture and another 120 participants received placebo with acupuncture. The outcome measured in this trial at baseline and at 6, 12, and 24 weeks after the beginning of treatment, included behavior by the Aberrant Behavior Checklist, Autism Behavior Checklist and Childhood Autism Rating Scale; quality of life by the Child Health, Questionnaire social maturity by the Social Maturity Scale and EuroQoL Five-dimension Five-level Youth; and parental stress by the Parenting Stress Index. The results of this study showed that this combination has very few side effects and also has an acceptable effectiveness [44].

Salvia leriifolia Benth

Salvia leriifolia is a perennial herbaceous plant that grows exclusively in Semnan and South and tropical regions of Khorasan provinces, in Iran [47]. Studies show that *Salvia leriifolia* has therapeutic effects on autism [48,49]. The active ingredients in the leaves of this plant include borneol, cineole, pinene and 1,8-pinene [50]. Among the effective compounds of

this plant, borneol has been proven to increase brain function and improve brain disorders [51]. In indigenous medicine or folk medicine in China, borneol is a very common substance for enhancing the mind and thoughts due to targeting the brain, capability to direct drugs upward to the head, to increase drug distribution in brain tissue and to facilitate the permeation of drugs across the blood brain barrier (BBB) [52-54]. One study investigated the effect of borneol on improving the symptoms of autism in 15 children. Fifteen other children with autism were selected as the control group. The results of this study demonstrated that in the treated group, improvement in problem solving ability, increased attention and planning ability was seen [51]. It seems that additional studies on this plant and its effective compounds are needed to clarify the mechanism of the possible effect of the compounds in the control of autism.

Hazelnut (*Corylus spp.*)

Hazelnuts have a spherical or oval appearance and are 15-25 mm long and 10-15 mm in diameter and have a fibrous outer shell. Some species of hazelnut are larger than the common hazelnut and double the normal size at maximum growth. The hazelnut fruit falls out of the shell when it is ripe. The skin of the fruit is hard. The kernel (seed) of hazelnut is edible, which is called hazelnut kernel, and it can be consumed raw or cooked (roasted). The seed has a very thin, dark brown skin that is usually removed before consumption or cooking. Hazelnut is very nutritious and is full of useful fats, proteins and vitamins, hence its use for health is approved by the FDA [55]. On the other hand, studies have shown that problems related to ASD are related to the lack of fats such as omega-3 fatty acids, so fatty acid supplements may be effective in improving these symptoms [56]. Hazelnut oil contains significant amounts of omega-3 and omega-6 [57]. Hazelnut consumption may reduce the risk of neurological disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis and Huntington's disease due to its anti-inflammatory and antioxidant properties. Also, many documents present hazelnut as an excellent choice for neuroprotection against neurodegenerative disorders, and there is direct evidence of its neuroprotective effects. Therefore, it seems that a diet containing hazelnut or hazelnut oil can be effective in controlling the symptoms of autism. Of course, we require clinical studies to examine this claim in detail.

Grapes (*Vitis vinifera* L.)

Studies have determined that oxidative stress plays an undeniable role in autism. Numerous studies have also been performed on lipid peroxidation products and oxidative control agents (antioxidants) [58].

Studies point out that consumption of vegetables and fruits because of a variety of flavonoid compounds with anti-inflammatory and antioxidant properties is associated with better cognitive performance and lower risk of neurodegenerative disorders [59-61]. Flavonoids are polyphenols that have the potential to scavenge reactive oxygen species and free radicals [62]. Therefore, they are essential for the normal life of cells. Grapes are considered as a useful antioxidant due to their rich phenolic compounds, including flavonoids. Studies show that administration of grape juice for 12 weeks in elderly patients with memory impairment significantly improves verbal learning measurement and significantly increases verbal and spatial recall [63]. Grape seed extract has also been shown to improve memory in the animal learning impairment model induced by streptozotocin [64]. Accordingly, it seems that the consumption of grapes can help improve the symptoms of autism [65].

A patented herbal medicine

In a study by Chan et al., the effect of an intranasal herbal medicine on changes in brain function and neurophysiology was investigated. The results of this study demonstrated that this drug can reduce the symptoms associated with autism in children [51]. In the continuation of this study, the possible effect of herbal formula on executive function and neuroelectrophysiological activity related to autism was investigated. Accordingly, 30 children with autism were divided into two groups receiving herbal formula or placebo. At the beginning of the study and six months after treatment, patients' behavioral problems, executive function and electroencephalographic activity were measured. The treated group exhibited improvement in mental flexibility, planning and inhibitory control. Studies show that these changes may occur with increased activity in the peripheral and anterior cingulate cortices. These areas of the brain are directly related to executive control of behaviors. However, in the group that received the placebo, no improvement in neuronal function and executive function was seen [51].

Kwakhyangjungkisanhapyukmijihwang-tang-gamibang

In another study, seven patients with autism were treated with an Oriental medicine. This medicine, called Kwakhyangjungkisanhapyukmijihwang-tang-gamibang, contains a combination of several different medicinal plants, including *Acori Gramineae Rhizoma* (*Acorus gramineus* Soland), *Rehmanniae Radix Preparata* (*Rehmannia glutinosa* (Gaertn.) Steud.), *Agastachis Herba* (*Agastache rugosa* (Fischer et Meyer) O. Kuntze), *Hoelen Cum Radix* (*Poria cocos* (Schw.) Wolf), *Longanae Arillus* (*Dimocarpus*

longan Lour.), *Ziziphi Spinosae Semen* (*Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou), *Perillae Folium* (*Perilla frutescens* L.), *Polygalae Radix* (*Polygala tenuifolia* Willd.), *Dioscoreae Rhizoma* (*Dioscorea opposita* Thunb.), *Corni Fructus* (*Cornus officinalis* Sieb. et Zucc.), *Glycyrrhizae Radix* (*Glycyrrhiza glabra* L.), *Atractylodis Rhizoma Alba* (*Atractylodis japonica* Koidzumi), etc. The results of this study revealed that the administration of this herbal compound has improved cognitive abilities, motor function and communication skills in patients. In the conclusion of this study, it is mentioned that this Oriental medicine can be effective on autistic disorder; however, additional studies are needed to investigate the mechanism of this effect [66].

Conclusion

Studies show that treating autism with medicinal herbs is promising; however, the mechanism of action of most herbal remedies is unknown and their safety for children needs to be investigated [67]. In this review, we tried to collect the plants that have been studied for the treatment of autism. As mentioned earlier, autism is a complex disorder whose exact mechanism has not yet been determined. However, common drug treatment processes are controversial due to their ineffectiveness and side effects. As it is known, the main available strategies for obtaining compounds with medicinal properties are chemical synthesis, biotechnology and nature. Today, the use and extraction of effective compounds from plants have been considered by many scientists. As shown in table 1, different

herbal compounds and herbs are categorized according to treatment strategy and type of intervention. The results of these studies show that these compounds, at least partially, can be effective in reducing the symptoms of autism such as inattention, seizures or abnormal behaviors in autistic children. Of course, some of these studies have drawbacks in the field of study design. Since the quantity of active compounds in plants is different from each other, proper quality control and standardization of active ingredients can greatly help to provide a better effect and reduce the side effects of these compounds. Another necessity is the design and implementation of accurate animal experiments and clinical trials with standard sample size. Also, in table 2, there is a list of herbs that, based on the results of studies, are likely to be helpful in autism. Hazelnuts because of their omega-3s and grapes because of their flavonoids have the potential to improve the symptoms of autism. Of course, animal studies and clinical trials are needed to investigate this claim and determine the possible mechanism. Finally, it seems that using herbal and traditional medicines could play an undeniable role in management of autism in new future, by developing standard investigations and standardization of remedies. Comparing the data of these studies with each other has various limitations, among which we can point to the heterogeneity of the studied populations. Due to the selection of a specific scope on the topic and the limitation in the number of articles that specifically addressed this topic, we were faced with limitations in data collection. Also, it should be noted that due to the narrative nature of the upcoming article, probably not all studies have been reviewed.

Table 1. A Summary of plant-based drug studies used in the treatment of autism spectrum disorders

Intervention	Method	Results	Reference
<i>Ginkgo biloba</i>	Three patients received 2 × 100 mg <i>G. biloba</i> EGb 761 for 4 weeks	Some improvement on the Aberrant Behavior and Symptom Checklist	[28]
	Double-blind placebo-controlled trial, 47 patients with an age range of 4 to 12 years, the first group received risperidone with Ginkgo extract and the second group received risperidone with placebo	Addition of <i>G. biloba</i> extract to the drug treatment of risperidone did not cause a significant change in the rate of recovery	[29]
<i>Centella asiatica</i>	Aqueous extract of <i>C. asiatica</i> at doses of 100, 200 and 300 mg / kg was administered intracerebroventricularly to rats treated with streptozotocin for 21 days	In rats treated with aqueous extracts an improvement in cognitive behavior, passive avoidance, and elevated plus-maze was observed in a dose dependent manner. A significant decrease in MDA and an increase in glutathione and catalase levels were observed only in rats treated with 200 and 300 mg/kg extracts	[35]

<i>Humulus japonicus</i>	BTBR T + Itpr3tf / J mouse model was used to evaluate the effect of <i>H. japonicus</i> on autism	Oral and gradual administration of <i>H. japonicus</i> ethanolic extract caused attenuated repetitive grooming behavior, increased social interaction and improved novel-object recognition in BTBR mice	[39]
<i>Ukgansan</i>	Animal model of autism	<i>Ukgansan</i> reduced grooming in the open field test	[42]
	Animal model of autism	<i>Ukgansan</i> prevented behavioral abnormalities and improved neuroplastic signaling in a model of social isolation in mice	[43]
	12-week study, prescribed to 20 children with autism ranging in age from 6 to 17 years. Primary outcome measures included the Children's Global Assessment Score (CGAS), Clinical Global Impressions-Improvement of Illness Scale (CGI-I) and the Aberrant Behavior Checklist (ABC) irritability subscale.	CGI-I improved significantly over 8 weeks. The mean CGAS was initially 31.92; while the mean final score at 12 weeks was 54.52. The ABC irritability/agitation subscale (subscale 1) was significantly improved from 8 weeks, and the hyperactivity/non-compliance subscale (subscale 4) was significantly improved in 12 weeks. The combination was well tolerated. No subject left the study because of a drug-related adverse event	[45]
	40 patients with pervasive developmental disorder, treated with yokukansan for 12 weeks, Primary outcome measures included the CGI-S and ABC-I. Forty participants in the age group of 8 to 40 years received a dose of 2.5 to 7.5 g per day	Full-scale intelligence quotient (IQ) scores ranged from 70 to 110. 90% subjects showed fewer interfering symptoms of irritability, including aggression, self-injury, and tantrums, with a final CGI-S of 1 or 2 (normal, not at all ill or borderline mentally ill) and an 80% or greater improvement on the ABC-I. It was also found that the drug did not have serious side effects and therefore none of the participants were excluded from the study	[46]
	4- to 6-year-old children with were randomly assigned in two groups. 120 participants received <i>Ukgansan</i> granules with acupuncture and another 120 participants received placebo with acupuncture	Combination has very few side effects and also has an acceptable effectiveness in Childhood Autism Rating Scale, Autism Behavior Checklist, and Aberrant Behavior Checklist; social maturity by the Social Maturity Scale	[44]
Intranasal herbal medicine	The possible effect of herbal formula on executive function and neuroelectrophysiological activity related to autism, 30 children with autism were divided into two groups receiving herbal formula and placebo for 6 months	Improved inhibitory control, planning and mental flexibility, these changes may occur with increased activity in the peripheral and anterior cingulate cortices	[51]
Kwakhyangjungkisanhapyukmijihwangtang-gamibang	Seven patients with autism were treated with an Oriental medicine	Administration of this herbal compound has improved cognitive abilities, motor function and communication skills in patients	[66]

Table 2. Herbal medicines with a possible effect on the symptoms of autism.

	Effective ingredients	Possible effect	Reference
<i>Salvia leriifolia</i>	The active ingredients in the include borneol, cineole, pinene and 1,8-pinene	Improvement in problem solving ability, increased attention and planning ability was seen	[47,51]
Hazelnuts	Hazelnut oil contains significant amounts of omega-3 and omega-6	It has been suggested that difficulties associated with ASD may be explained in part by lack of omega-3 fatty acids, and that supplementation of these essential fatty acids may lead to improvement of symptoms	[56,57]
Grapes	Considered as a useful antioxidant due to their rich phenolic compounds, including flavonoids	Administration of grape juice for 12 weeks in elderly patients with memory impairment significantly improves verbal learning measurement and significantly increases verbal and spatial recall	[63]

A more detailed examination and the possible mechanisms involved in the control of autism symptoms and randomized controlled trials can be considered as suggestions for future studies.

Conflict of Interests

None.

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None.

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