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Autism: Pathophysiology and Promising Herbal Remedies

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Abstract: Autism is a comprehensive growth abnormality in which social skills, language, communication, and behavioral skills are developed with delay and as diversionary. The reasons for autism are unclear, but various theories of genetics, immunity, biological, and psychosocial factors have been proffered. In fact, autism is a complex disorder with distinct causes that usually co-occur. Although no medicine has been recognized to treat this disorder, pharmacological treatments can be effective in reducing its signs, such as self-mutilation, aggression, repetitive and stereotyped behaviors, inattention, hyperactivity, and sleeping disorders. Recently, complementary and alternative approaches have been considered to treat autism. Ginkgo biloba is one of the most effective plants with an old history of applications in neuropsychological disorders which recently is used for autism. The present review discusses the recent findings, pathophysiology, and etiology of autism and thereafter addresses the promising results of herbal remedies.

Keywords: Autism, Children, Herbal medicines, Ginkgo biloba.

INTRODUCTION

Autism is a highly heritable disorder with variable neurodevelopmental characteristics that generally appears in infancy and childhood and usually follows a steady course with no remission. Symptoms of autism usually begin after the age of six months, become established by age two years, and usually continue through adulthood [1]. Autism is a developmental disorder characterized by deficits in verbal and nonverbal communications, impaired social interaction, and stereotyped behaviors. The prevalence in the general population is about 0.06% and is four times higher in boys than in girls. Variations in autism prevalence are seen along ethnic, racial, and socioeconomic lines [2]. The emergence of autism early in life and its chronic course profoundly impact families, resulting in enormous emotional and financial costs [1]. Autism is characterized not by a single symptom, but by a triad of symptoms including repetitive behaviors, impaired and restricted interest in social interaction and communication [3].

The main aim in the treatment of autism is to increase the quality of life and reduce the associated deficits as well as family distress. Treatment is usually based on the child's needs; no single treatment is enough to control all symptoms [4]. In general, there is little evidence for the effectiveness of treatment options. Most interventions have not been effective, but, to some extent, treatment protocols are preferable to no treatment. Available approaches include social skill therapy, structured teaching, occupational therapy, developmental models, and speech and language therapy [4].

Many medications for the treatment of autism symptoms have been studied. Antipsychotics, antidepressants, and stimulants are the most common drug classes used to treat the disorder [5]. Risperidone and aripiprazole are the most common therapies for the irritability of patients; however, the safety of these drugs is in doubt. No known drug can relieve the core symptoms of autism, in particular the communication and social impairments [4].

Although many alternative therapies are available, few have been supported by scientific trials. Treatment is expensive and the indirect costs are also high [5]. A US investigation estimated an average lifetime cost of $4.05 million, with about 10% of costs being for medical expenses, 30% for extra education, and 60% for lost productivity [6].

Recently, herbal medicines have received more attention than before for the management of various diseases including psychoneurological disorders [7-9]. Some plants such as Ginkgo biloba have revealed promising results in the management of autism. In this paper, in addition to reviewing recent publications regarding the pathophysiology of autism, neurochemical substances and the effects of medicinal plants on autism are also discussed.

HISTORY

Historically, autism was included in the spectrum of schizophrenic disorders as schizophrenia disorder with premature beginning [10]. Canner first defined autism disorder by introducing 11 children who had been unable to communicate normally with people since the beginning of their lives, showed unusual reactions to their environment, and had problems in speaking such as pronoun reversal and echolalia. The word autism was first applied by Blouler to describe the status of schizophrenic patients. In 1978, Rutter presented a new definition that included the following signs [10]:

1. Social retardation not resulting from mental deficiency
2. Relationship problems not resulting from mental deficiency
3. Unusual behaviors including stereotyped and repetitive movements
4. Showing of symptoms before the age of 30 months

Currently, autism is known as a heterogeneous syndrome belonging to a group of neurodevelopmental disorders classified as pervasive developmental disorders (PDD). At first, the diagnosis of autism was based on clinical criteria that included a range of behavioral symptoms, such as a significant decrease in social relationships accompanied by stereotypic signs and limited behaviors and interests without the presence of an unnatural biologic marker [1]. Since studies proved that autism has an organic and not psychological base, different studies have tried to determine different causal aspects of the disorder [11].

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EPIDEMIOLOGY

In the first epidemiological study, the prevalence of autism was reported as 4-5 in each 10000 children in the age range of 8-10 years. Subsequent studies, however, showed a prevalence of 0.7-21.1 per 10000 . An even greater increase in prevalence has been reported in recent studies. In terms of gender, boys show prevalence four times as high as girls [2].

ETIOLOGY

The reasons for autism are uncertain. Genetics, immunity, biologic and psychosocial theories have been proffered to explain the etiology of autism [11]. In fact, it is presumed that autism is a complex disorder with distinct causes that usually co-occur [12, 13].

Genetic Causes of Autism

Evidences have been obtained concerning the role of genetic factors in the etiology of autism. Typically, however, it cannot be traced to a single-gene mutation or to a single chromosome abnormality. Numerous genes are candidates, but with a small number of effects attributable to each particular gene [14.15].

The prevalence of autism among patient siblings is much higher than that of the public population, but it is not as high as is expected for a monogenic disease [15]. The prevalence of autism in males creates the suspicion of a dependency to x, but the available evidence concerning transfer from father to son proves this inheritance model unlikely [16]. Regarding the complexity of autistic disorders and the variety of its clinical board, it is possible that polygene intervention and contact with environmental transformers are responsible for different expressions of this disorder [15]. Results of chromosomal studies have shown that several sites for intervention are resent, of which region 6q21 is supported by the highest number of articles. It is noteworthy that this region includes the 6-glotumat receptor gene that is considered a very good suspect in autism pathogenesis [17].

Neuropsychosocial Reasons for Autism

There are two categories of cognitive theories about the links between autistic brains and behavior. The first one focuses on deficits in social cognition. Autistic individuals can develop internal rules of operation to handle events inside the brain; however, they are less effective at empathizing and handling events created by other agents. It should be noted that most studies have not found evidence for this [18]. The second category focuses on general or nonsocial processing. It is clear that executive dysfunctions play a role in cognitive and social deficits [19].

It has been hypothesized that the limited ability of autistic individuals to see the big picture is related to central disturbances. The "enhanced perceptual functioning theory" focuses on the superiority of locally oriented operation in these patients [20, 21]. None of these theories is satisfactory on its own. The theories of social cognition poorly address the repetitive behaviors in autism, and the nonsocial theories have difficulty explaining the social communication problems. A combined theory based on multiple deficits in autism might be more useful [22].

Neurochemical Involvement in Autism

Numerous studies have addressed the extensive spectrum of neurochemical systems including monoamines, neuropeptides, stress-dependent hormones, oxytocin, cortisol, and neurotransmitter amino acids, the most important of which are discussed below [23]. It should be noted that many of these studies had inappropriate control groups and small sample size which make it difficult to draw conclusions with confidence.

Serotonin seems to play the most roles in autism; however, more investigation is needed before a reliable conclusion can be made. The possible dysfunction of oxytocin, amino acid neurotransmitters, and the cholinergic system has been proposed in recently published studies [24].

Serotonergic System

Most neurochemical studies have concentrated on serotonin(5-hydroxytrypamine or 5-HT). Serotonin is derived from the essential amino acid tryptophan. The first motivation to study serotonin in autism was the possible role of serotonin in understanding. The strong effect of serotonergic hallucinogens like LSD was the first core of serotonin studies in autism. Then, the observation that acute depletion of dietary tryptophan, a serotonin precursor, worsened the signs of autism became evidence of the role of serotonin in expressing the autistic symptoms. The role of serotonin in early neural development has recently caused it to be investigated as a possible factor in the development of autistic disorder [25].

Two important behavior clusters are presented in the dorsal and medial raphe nuclei [26]. The dorsal raphe nucleus sends projections to the basal ganglia which are considered as important areas for the regulation of motor performance. The median raphe nucleus innervates a part of the hippocampal formation(the dentate gyrus), which is an important site for the storage of memory [26]. High levels of serotonin during brain development can cause a loss of serotonergic terminals and secondary nerve growth. Interestingly, children who are exposed to drugs that increase serotonin develop higher levels of autistic disorder [27]. Primary studies of blood levels of serotonin in individuals with autism show that hyperserotonemia exists in one-third of patients; this is related to an increase of serotonin in the platelets of autistic individuals [28]. However, recent researchers have hypothesized that the central serotonergic function decreases in individuals with autism, and this hypothesis is supported by the good effects of SSRI drugs in treating violence and stereotypic motions of autistic patients. In fact, beyond the serotonin hypothesis, the presence of repeated and limited movements in patients with autism can justify the use of SSRI drugs [29].

Adrenergic System

Adrenergic system activity plays a main role in attention, filtering unrelated stimulants, responding to stresses, and memory. Since many of these performances are disturbed in patients with autism, researchers seek a relationship between this system and autism. Noradrenergic nerve cell bodies are located in the locus coeruleus and the activity of this system is crucial to attention, anxiety, and memory. Many of these functions are impaired in autistic patients. Noradrenergic activities have been evaluated in autistic patients by measuring noradrenaline and its metabolites in CSF, blood, and urine [30]. Studies have reported higher levels of noradrenaline in the blood of these patients compared with the control groups. Studies performed on the CSF of autistic patients, however, have shown no significant difference with those of the control group in terms of noradrenaline metabolite levels [31].

Overall, studies have shown that noradrenaline is not crucial in the symptoms and causes of autism disorder. Moreover, the application of agonist or antagonist noradrenergic drugs and their benefits have not been highly presented. The consumption of α -2 agonists like clonidine that lower noradrenaline activity has sometimes been effective in controlling hyperactivity in young patients with autism, yet these drugs have no effect on its core symptoms. B-Blockers have been effective in controlling aggression, self- mutilation, and febricity [32].

Cholinergic System

The role of cholinergic system in autism has recently been evidenced. Hence, a growing interest is emerging in the cholinergic modulation for targeting autistic symptoms. The cholinergic system is considered an ''action system'' which helps develop the capability of focusing on the environment and achieving a coherent behav-

ioral response. However, the role of defects in the cholinergic system in autism has not yet been fully studied. One report that showed abnormalities in cholinergic neurons of the frontal brain in patients with autism inspired interest in the study of acetylcholine in this disorder. Since the cholinergic system influences the completion and function of cognitive abilities, the hypothesis is that a disorder of this system may relate to cognitive impairments of autism patients, including attention and learning [33, 34]. In some studies conducted on the brain of patients with autism after their death, a significant decrease of muscarinic receptors in the cerebral cortex and potential abnormalities in nicotine receptors have been reported. However, how these differences are related to the causes of autism is not clear. Findings which have shown the decreased efficiency of nicotine receptors suggest potential medicinal interventions with agonists of nicotine receptors that increase attention [35]. Researchers have started using cholinesterase inhibitors like rivastigmine, galantamine, and donepezil in autism. Two double-blind, placebo-controlled studies have reported positive results which provide evidence for the role of acetylcholine and the use of drugs that inhibit cholinesterase enzyme in autism [36]. The augmentative therapy of galantamine(a potentiator of nicotinic receptors and an acetylcholinesterase inhibitor) was also shown in a double blind clinical trial and this drug was suggested for alleviating some of the autism-related symptoms [37].

Dopaminergic System

The dopaminergic system is involved in a wide variety of functions such as motor functions, cognition, eating and drinking behaviors, reward mechanisms, neuroendocrine regulation, and sexual behaviors [38,39]. Research into the role of dopamine in autism began with the observation that some dopamine blocker drugs, like antipsychotics, were effective in improving some aspects of autism disorder. These drugs were especially effective in decreasing hyperactivity, stereotypy, and aggression and self-mutilation behaviors [23]. Studies on animals have also shown that stereotypy and hyperactivity increase with dopaminergic activity stimulation. These findings may suggest that dopaminergic neurons are highly active in autism. Several studies that measured the dopamine metabolite homovanillic acid(HVA) levels showed a significant increase of HVA levels in CSF, and a higher level of HVA in CSF is accompanied by hyperactivity and more severe stereotype behaviors. Of course at the present time, it is doubtful that central dopamine increases in autism [40]. Clinically, using risperidone is accompanied by decreased scores in the Aberrant Behavior Check List scale, especially in the field of stereotypic behaviors, hyperactivity, and irritability. It has had some effects on both social isolation and inappropriate speech(especially echolalia). Studies have not shown a special effect on social interactions and communicative skills, but whether the longer consumption of risperidone or other atypical antipsychotics impose more stable effects on the core symptoms of autism is not clear [41].

Opioid System

Some studies have shown high levels of endogenous opioids in patients with autism, and some studies have reported unclear results. Making a conclusion from the available results is difficult. In clinical work, opioid antagonists such as naloxone and naltrexone are also used in patients with autism based on this hypothesis. In most of the studies where naltrexone was used, few effects in the main symptoms of autism have been achieved, but some studies have reported a decrease in self-mutilation behaviors that in turn are very valuable. Decreased signs of hyperactivity and impulsive behaviors in autistic patients were reported in another study [42, 43].

Glucocorticoids

The function of cortisol in autism has been studied, because it seems that some related behavioral disorders can result from high activity and chronic over-excitation which increase the levels of this stress hormone [44]. Some studies reported no differences in the levels of ACTH or cortisol in the blood of autistic or that of control individuals; however, a study of 48 autistic patients reported elevated levels of both cortisol and ACTH [45].

Amino Acid Neurotransmitters

Glutamate and gamma-aminobutyric acid(GABA) are two chemical transmitters related to extensive synaptic relationships in CNS. Glutamate is an excitatory neurotransmitter in the spinal cord, while GABA is responsible for the majority of inhibitory relationships in the brain. GABA in the brain is provided by the effect of Glutamic Acid Decarboxylase(GAD) on glutamate. Ionotropic receptors make up one group of glutamate receptors and play a role in the development of the cortex [46]. Glu86, Glu M8, and one of the NMDA receptors play a role in autism [47]. The over-expression of some genes like the excitatory amino acid 1 transmitter and AMPA 1 have been observed in autism [48]. Deficits in the glutamate system influence cortex growth [49]. GABA path is also important to brain growth, and the equilibrium of the GABAergic and glutamatergic systems facilitate modeling of the cerebral cortex by replacing main cells, pyramidal cells, and interneurons [50]. The establishment of the GABAergic system and the immigration of GABAergic interneurons are critical in the growth of the inhibitory part of the cortex that controls the excitatory glutamate system. It is believed that autism is a hypoglutamic disorder [51].

Several findings have suggested that in autism the GABAergic system is suppressed, which results in the excessive stimulation of the glutamate system. In this regard, postmortem studies have reported abnormalities of cellular development in the cerebellum and limbic system [52]. These areas have glutamate receptors, and the over-activity of glutamate receptors can result in excitotoxicity. In children two years of age, which is a critical development period as well as a time when symptoms of autism often emerge, the glutamate activity may cause brain damage [53]. Excessive stimulation of glutamatergic neurons is also associated with seizure, a common phenomenon among autistic patients [54]. Glutamic Acid Decarboxylase is considered the main rate-limiting factor in the synthesis of GABA. This enzyme has been shown to be reduced by 48-61% in cerebellar and parietal areas of the brains of autistic patients in comparison with non-autistic individuals. These differences may provide evidence for abnormalities in the glutamate/GABA of autistic patients [55]. How the imbalance in GABA and glutamate neurotransmitters contributes to the etiology of autism, however, is not yet clear and requires further research.

Immunologic Involvement in Autism

Recently, knowledge about the immune system and its close relationship with the central nervous system(CNS) has been developed, leading to the development of psychoneuroimmunology. One important theory about the etiology of autism disorder is that environmental immunity factors play a role. Extensive studies have been conducted on this theory. Common specifications are seen between autism and autoimmune disorders, like genetic capacity, relationship with viral infections, immunologic function disorders, and sexual differences [56]. General changes that are seen in the immune system as a result of autism disorder generally include immune deficiency resulting from T lymphocytes, changes in the performance of natural killer(NK) cells, an abnormal ratio of CD4-CD8, more activated T lymphocytes, increased monocytes, the relative increase of monocytes compared to total white globules, and an increase in immunoglobulin levels. Moreover, changes in the system of helper lymphocytes from Th1 to Th2 activity that simultaneously decrease IL-2 and IFNλ production and increase IL-4 production have been recorded [57]. Regulation of the immune system is affected by genetic mechanisms. Different studies have shown autoimmune antibodies against myelin basic protein, neurofilament proteins and 5HT1A receptors [55, 58]. Autoimmune anti-

bodies belonging to the two groups of IgM and IgG have been found against endothelial proteins of cerebral capillary. Anti-brain autoimmune antibodies in the plasma of 171 children with autism disorder, normal individuals, and their parents have been studied quantitatively. Results of the study showed a significant increase in these antibodies in children with autism [59]. In addition to immunogenic mechanisms, autism disorder has been studied in relation with viral or bacterial infections early in life and even prenatal infections [55]. Interest in this possibility was aroused by different reports of changes in the metabolism of serotonin and oxytocin in children with autism. Overall, reaching a final conclusion regarding this subject is not practical, since the possibility of a relationship between immunologic findings and the heterogeneity of this disorder should be considered.

CLINICAL DIAGNOSIS AND SYMPTOMS

The diagnosis of autism is based on the DMS-IV diagnosis criteria. Clinical symptoms of the disorder, as presented in diagnosis criteria, include disorders in relationships, social interaction, interests, and behavior. The patient cannot establish emotional relationships with others, does not like to be caressed or kissed, and does not seem to notice other children. The patient handles objects and humans similarly, avoids eye contact, and has some problems in language, dialect, and nonverbal communication. Some patients acquire verbal abilities, but then stop using them and regress. Patients that do learn language use reverse pronouns. Their speech is a set of repetitive words and is one-way rather than an interactive and mutual conversation. The patient does not play symbolic, fantastic, or imitative games and does not use toys appropriately. These children show unusual body movements including back-arching, hand-flapping, rotating around, turning hands, toe walking, and stereotyped movements. They have sudden attacks of fear and anger and may either have very low activity or be hyperactive, restless, and inattentive. They annoy themselves or others and also have many problems sleeping [60].

People with autism often present abnormal moods and emotions(for example laugh or fuss without an obvious reason), may not fear obvious risks or, vice versa, show extreme fear against safe objects [56, 60]. Complementary psychiatry has provided a better understanding of the social and communication deficiencies that are available in autism. Studies have shown that children with autism do not show common and continuous attention and theory of mind is not formed. Joint attention includes three types of cooperation of attention between child, another person, an object, or an event. Theory of mind is a concept that others have thoughts that don't agree with one's own thoughts, and one can be aware of another's emotional state and mood through facial signs, social signals, or by listening to other's speaking. Many children with autism have problems with sensory integration that is characterized by disorganized sensory inputs to the body. They may have either intensive or mild problems with interpreting environmental variables like smells, noises, touch, or vibration. They may show proportional or increased reaction to such stimulants that is accompanied by self-excitation behaviors. These behaviors are an extensive spectrum of obsession to self-mutilation(head banging and biting) [23, 60].

PROGNOSIS

The prognosis is not good in two-thirds of autism cases. Autism is a lifetime disability, and patients are not able to live independently [60].

TREATMENT

Therapeutic purposes in affected children are decreasing destructive behaviors, reinforcing language, communicational skills, and self-care. Main treatments are non-medicinal and include educational treatments like speech therapy, physical treatments, psychotherapy(to improve anxiety and depression signs and improve problem-solving skills in patients with high performance) [23].

Drug Treatment

No medicinal remedy has been recognized to treat the disorder, but signs like self-mutilation, aggression, repetitive and stereotyped behaviors, inattention, hyperactivity, and sleeping disorders can be treated using medications. Since these children are involved in educational remedies, drugs that do not disturb the education are more useful. Different drugs for this disorder that have been tested include antipsychotics, serotonin reuptake inhibitors, B-blocker, naltrexone, lithium, clonidine, thyroid hormones, and antidepressants [23, 62]. Of such drugs, the most important positive findings involved antipsychotics. Their consumption has been accompanied by decreases in signs and does not affect learning abilities. Evidence shows that, if consumed correctly, antipsychotics are effective long-term treatments for autism patients [23]. The most prevalent neurobiological disorder is increased serotonin in autistic patients. Medicinal interventions with SSRIs and atypical antipsychotics that are effective on both dopamine and serotonin receptors have therapeutic benefits [23, 62]. Different studies have reported the role of atypical antipsychotics like risperidone and olanzapine in controlling behavioral signs, aggression, self- mutilation, repetitive behavior, and irritability. Moreover, clozapine has been reported to induce improvements in relationships. Studies involving risperidone have reported improvements in social interactions and language [63]. Side effects reported in all studies have been related to risperidone and were mainly drowsiness and weight increase. Some studies also found motor effects like dystonia in patients treated with risperidone, but they were transient and could be treated by decreasing the drug dose [23]. The therapeutic dosage of risperidone for treating autism symptoms ranges from 1-3.5 mg per day(approximately equal to 0.08 mg/kg/day) [23].

The therapeutic effect of pentoxyphiline in cerebral hypoxia has been approved through increased blood flow, increased synaptic serotonergic in CNS, and inhibited TNF production [64]. Methylphenidate is a drug that stimulates the brain stem and cerebral cortex through the mechanism of norepinephrine reuptake inhibition and has been effective in treating hyperactivity accompanied by autism [65].

It is supposed that autism is a hypoglutamatergic disorder, and therefore, the glutamatergic system is also a target for therapeutic strategy. Drugs like piracetam(with the mechanism of AMPA receptors stimulation) have had useful effects in treating autism [66]. Other drugs including lamotrigine(with the glutamate synaptic inhibition mechanism) and dextromethorphan and amantadine(that are NMDA receptor antagonists) have also been effective [23, 67].

Recently some medicinal plants such as the Ginkgo biloba have revealed promising results, the most effective of which are presented below.

Medicinal Plants Effective Against Autism

Recently herbal medicines have been the focus of some researchers. They have been tested and have shown promising results in the treatment of a wide variety of complications such as neurological [68-70], cardiovascular [71-73] problems and in diabetes mellitus [74-76]. These remedies have low side effects and may also reduce the side effects of other drugs [77-79].

Defining autism is a new concept, and traditional medicine has no diagnosis called autism. Thus, traditional healing terms are hard to describe. For instance, there is a Chinese concept calling "Phlegm in the heart orifice" in which a condition identical to modern autism is described. So, despite vocabulary challenges and indications, we can find medicinal plants effective in autism.

Fortunately, the preliminary results of using herbal medicines for autism are promising. The mechanisms of medicinal plants are

often unknown, and science is at the beginning of herbal understanding. It should be noted that medicinal plants, in general, are remarkably safe, however, in most cases the safety profile especially for children, has not been established [80]. This paper presents here the medicinal plants most effective for autism.

Ginkgo Biloba

Ginkgo extract, extracted from of Ginkgo biloba leaves, is a remedy that has shown promising results in treating a large range of circulatory, brain, and nerve conditions. Ginkgo biloba is one of the most widely studied plants with more than 200 published papers about it. It was used in the United States for the first time to prevent or treat memory problems. Its use history dates back more than two thousand years in China. The most prevalent studies concerning the effects of ginkgo on neurologic problems have been more concerned with memory improvement, dementia with arterial origin, Alzheimer's, cognitive disorders, antioxidant effects, and along with other psychiatric drugs in reinforcing their effect or decreasing special side effects [81, 82]. In a recent trial performed on Ginkgo biloba, significant improvement in sexual function resulting from SSRI was found; this effect was more obvious in women(61). Other placebo-controlled studies performed on symptoms of PMS syndrome have shown improvement in neuropsychological symptoms [83]. There is evidence indicating that Ginkgo biloba can be used as an antidepressant, and it has had a neuro-protective effect on cerebral damage(61). A review of 40 controlled clinical trials showed that Ginkgo biloba was effective in treating people with memory and concentration problems resulting from cerebral abnormalities. In addition, Ginkgo biloba regulates blood flow in brain arteries and may help to decrease hyperactivity caused by fatigue and lack of attention [83]. Ginkgo biloba extract is effective on several neurotransmitter systems of the central nervous system. In one study, it reversed the decrease in cerebral 5HT1A receptors in old rats [84]. Recently, it has been approved that ginkgo extract can inhibit both MAOA and MAOB enzymes reversibly. This mechanism emphasizes the mild anti-anxiety and anti-depression effects of ginkgo and could help the treatment of ADHD [86]. Ginkgo has also increased the dopaminergic activity of the brain. The pharmacologic effects of ginkgo has also been attributed to a combination of the antagonism of platelet-activating factor, effects of anti-free radicals, and the regulation of serotonergic, noradrenergic, and dopaminergic systems [86]. One study reported the protective effect of GB extract against Glutamate Induced Excitotoxicity in retina neurons [87]. Although there are many disagreements in studies related to the effects of Ginkgo biloba in dementia, generally, the majority of them agree that ginkgo is more effective compared with placeboes in mild to intermediate ranges.

The main therapeutic components of Ginkgo biloba extract are flavonoids and terpenoids which have antioxidant, anti-inflammatory, and neuroprotective effects. Ginkgo also has positive effects on cognitive and neurologic performance; it imposes this effect through antioxidant activity, arterial regulation, and antagonism of platelet-activating factor that protects the brain against ischemic damages [84].

The most prevalent side effect of Ginkgo biloba is headache that can be inhibited by a gradual increase in dosage. The fact that Ginkgo biloba may increase anti-coagulation effects or bleeding time has not been yet confirmed. However, a recent study concluded that caution should be applied in combining Ginkgo biloba with anti-coagulant drugs like aspirin, especially when the bleeding risk is high, for example in patients with active gastric ulcer or subdural hematoma. Some cases of seizure have been observed in patients susceptible to seizure or people which lower seizure threshold who use drugs. Drug cease is suggested at least 36 hours before surgery. The safety of this drug use during pregnancy and lactation has not been established [84]. Generally ginkgo is tolerated well, and its side effects are rare and usually mild, including diarrhea, nausea, headache, vertigo, palpitation, eczema, or vomiting [85-88]. Poisoning signs include seizure, decreased consciousness level, and ultimately death. Intravenous products might be accompanied by anaphylactic shock. Its edible pill should not be chewed [89]. A study performed on 40 children affected with autism evaluated the effect of ginkgo on patients who were treated with risperidone [90]. The intensity of the disorder was evaluated using the Aberrant Behavior Check List(ABC). Medicinal side effects were measured using the Side Effect Check List. Patients were studied for 10 weeks in two-week intervals. Risperidone dosage was in the range of 1-3.5 mg daily(approximately equal to 0.08 mg/kg) and ginkgo T.D. dosage was 80 mg/d for patients weighing under 30 kg and 120 mg/d for patients weighing more than 30 kg. Ginkgo dosage was constant during the therapeutic period. Based on the results of this study, adding ginkgo in dosages of 80 m/d for individuals with a weight <30 kg and 120 m/d for individuals with a weight >30 kg did not provide more improvement in any of the autism signs based on the 5 subscales of ABC criterion(Inappropriate speech, Stereotype Hyperactivity, Irritability) [90].

Zingiber Officinale

Ginger is an herbal medicine used mostly to treat spasm, stomach distress, motion sickness, nausea, and vomiting. It increases digestive tract secretions, including saliva and bile, and neutralizes toxins. Ginger can aid digestion by speeding the emptying time of the stomach and by increasing the movement of food through the gut. It cause a good feeling in cases of bloating and abdominal discomfort.[4] Up to 3 grams of ginger per day or even more is very safe. It increases blood flow in the brain and has recently been recommended for autism [91, 92].

Astragalus Membranaceus

Astragalus membranaceus is an energizing and immune building herb which is mostly used as a stamina tonic or a healing remedy for chronic illnesses other than autism. *Astragalus membranaceus* increases stress adaptation, boosts energy, enhances the efficiency of many types of immune function, and has antibacterial and antiviral properties. It is also used for night sweats, chronic ulcerations, and edema and numbness. It is used as an immune enhancer in children who have frequent infections. *Astragalus membranaceus* is preferred for cold prevention; however, it might be used for acute cold and flu as well as for the Coxsackie virus, a flu-like virus that mainly affects children. Astragalus is frequently used for the prevention and treatment of respiratory infections [93, 94].

Centella asiatica

Centella asiatica or Gotu kola is a plant with a long history of brain building capacity. The plant grows in hot moist climates and is commonly eaten raw as a green vegetable with many different foods and salads, and no important toxicity for it has been reported. This plant is very high in B-complex vitamins, including in B-1, B-2, and B-6, which are important for the nervous system. *Centella asiatica* has high anti-inflammatory and antioxidant activity. It is a standout plant for the nervous system and is beneficial for cognition and neurological recovery. It is used to promote circulation, especially to the blood vessels of the skin and mucous membranes [95, 96].

Centella asiatica is used to increase memory, concentration, general brain function, mental acuity, neuromuscular disorders, and the repair of nerve tissues from crushing traumas, including spinal injuries. It is also used to treat epilepsy, hair loss, psoriasis, and senility. *Centella asiatica* shows potential for treating Alzheimer's disease. The active substances in Gotu kola are mostly triterpenes with steroid-like activity which improve the function and integrity of the collagen matrix, the basic glue that holds the cells of the body together [97, 98].

Acorus calamus

Acorus calamus or Calamus is a major plant for the mind in Asian traditional medicine. It increases the power of self-expression

and intelligence. The root increases the circulation to the brain, enhances memory and awareness, and increases self-expression and communication. It has a bitter taste and acts as a mucolytic and anti-gas digestive aid. It is effective in relieving autism symptoms. Calamus also possesses warming respiratory function. In attention or memory deficit, it is used in combination with *Centella asiatica*, licorice, valerian, and shankpushpi. This combination is also used to treat epilepsy, especially absence seizures, and as a replacement for anticonvulsant medications [99-101].

CONCLUSION

Autism is a lifelong developmental disability characterized by repetitive interests and behaviours, social interaction difficulties, impaired communication and restricted sensory sensitivities. More than 1 in 100 children have autism and its prevalent is increasing. The autism severity can be minimised by early diagnosis and with suitable interventions. With no debt, autism is a heritable developmental disorder [14-16]. It is unclear whether the real incidence of autism is increasing or the diagnosed prevalence. If real incidence is increasing, it may have a good implication in realizing the causes of autism. The increase in incidence of autism in recent years may point to environmental risk factors for some susceptible cases. There is no reliable evidence for environmental pathogens. There is a possibility that environmental factors act by interaction with genetic vulnerabilities [14].

Oxidative stress is involved in a wide variety of diseases [102-108] including neuropsychological complications [109-113]. However, the role of oxidative stress in autism is not clearly understood. Oxidative stress and antioxidant activity have been studied by measuring the detoxifying agents such as glutathione, lipid peroxidation and the antioxidants involved in the defense systems. Lipid peroxidation markers have been shown to increase in autism, which indicates that oxidative stress is increased in this disease. A correlation between reduced levels of antioxidant proteins and loss of previously acquired language skills has been shown in children with autism. The membrane phospholipids, the prime target of reactive oxygen sepsis, are altered, too [114]. Several studies have shown alterations in antioxidant activities such as catalase, glutathione peroxidase and superoxide dismutase in patient with autism. Furthermore, altered homocysteine/methionine metabolism and glutathione levels, as well as increased inflammation, excitotoxicity, immune and mitochondrial dysfunctions have been reported in autism. Genetic and environmental parameters may increase vulnerability to oxidative stress [115]. Hence, studies suggest enhanced oxidative stress in autism that may contribute to the development of this disease. More importantly, all medicinal plants effective in autism have high antioxidant activities. However, how much the antioxidant activity of these plants is important in their anti-autism effects is not clear. If the antioxidant activity of these plants play a crucial role in their anti-autism effects, other plants with antioxidant properties [116-120] should be effective in this disease, which worth examining.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Rapin I, Tuchman R. Autism: definition, neurobiology, screening, diagnosis. Pediatr Clin North Am 2008; 55(5): 1129-46.

[2] Newschaffer C, Croen L, Daniels J, *et al.* The epidemiology of autism spectrum disorders. Annu Rev Public Health 2007; 28: 235-58.

[3] National Dissemination Center for Children with Disabilities(NICHCY). Disability Info: Pervasive Developmental Disorders. Fact Sheet 20(FS20) October 2003.

[4] Myers S, Johnson C. Management of children with autism spectrum disorders". Pediatrics 2007; 120(5): 1162-82.

[5] Oswald D, Sonenklar N. Medication use among children with autism spectrum disorders. J Child Adolesc Psychopharmacol 2007; 17(3): 348-55.

[6] Ganz M. The lifetime distribution of the incremental societal costs of autism. Arch Pediatr Adolesc Med 2007; 161(4): 343-9.

[7] Saki K, Bahmani M, Rafieian-Kopaei M. The effect of most important medicinal plants on two important psychiatric disorders(anxiety and depression)-a review. Asian Pac J Trop Med 2014; 7(Suppl 1): 34-42.

[8] Rabiei Z, Rafieian-kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of *Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of meynert in rat. Neurochem Res 2014; 39(2): 353-60

[9] Delfan B, Bahmani M, Hassanzadazar H, Saki K, Rafieian-Kopaei M. Identification of medicinal plants affecting on headaches and migraines in Lorestan Province, West of Iran. Asian Pac J Trop Med 2014; 7(Suppl 1): 376-379.

[10] Michael G, Paul H, Philip C. Shorter Oxford Textbook of psychiatry. 5th ed. Oxford University Press. Newyork 2006; pp: 671- 8.

[11] Glebenzon BJ, Rosenberg AL. On Autism: its prevalence, diagnosis, causes & treatment. Top Clin Chiropr 2001; 8: 42-57.

[12] Happé F, Ronald A. The fractionable autism triad: a review of evidence from behavioural, genetic, cognitive and neural research. Neuropsychol Rev 2008; 18(4): 287-304.

[13] Happé F, Ronald A, Plomin R. Time to give up on a single explanation for autism. Nature Neurosci 2006; 9(10): 1218-20.

[14] Abrahams B, Geschwind D. Advances in autism genetics: on the threshold of a new neurobiology. Nature Rev Gen 2008; 9(5): 341-55.

[15] Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics 2004; 113: e472 - 86.

[16] Cheng Y, Qin G, Dai X, Zhao Y, NPY1. A BTB-NPH3-like protein plays a critical role in auxin-regulated organogenesis in Arabidopsis. Proc Natl Acad Sci 2007; 104: 18825-9.

[17] Jamain S, Betancur C, Quach H, *et al.* Paris Autism Research International Sibpair(PARIS) Study. Linkage and association of the glutamate receptor 6 gene with autism. Mol Psychiatry 2002; 7: 302-10.

[18] Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. Nature Rev Neurosci 2006; 7(12): 942-51.

[19] Kenworthy L, Yerys B, Anthony L, Wallace G. Understanding executive control in autism spectrum disorders in the lab and in the real world. Neuropsychol Rev 2008; 18(4): 320-38.

[20] Happé F, Frith U. The weak coherence account: detail-focused cognitive style in autism spectrum disorders. J Autism Dev Disord 2006; 36(1): 5-25.

[21] Mottron L, Dawson M, Soulières I, Hubert B, Burack J. Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. J Autism Dev Disord 2006; 36(1): 27-43.

[22] Rajendran G, Mitchell P. Cognitive theories of autism 2007; Dev Rev 27(2): 224-60.

[23] Sadok BJ, Sadok VA. Comprehensive textbook of psychiatry.8th ed. Williams & wilking. Philadelphia 2005; pp: 3164-75.

[24] Lam KSL, Aman MGL, Arnold E. Neurochemical correlates of autistic disorder: A review of the literature. Research in Developmental Disabilities 2006; 27: 254-289.

[25] Whitaker-Azimitia PM. Serotonin and brain development: Role in human developmental diseases. Brain Research Bulletin 2001; 56: 479-485.

[26] Carlson NR. Physiology of behavior 7th ed., Boston: Allyn and Bacon 2001; pp. 96-129.

[27] Adamsen D, Meili D, Blau N, Thony B, Ramaekers V. Autism associated with low 5-hydroxyindolacetic acid in CSF and the heterozygous SLC6A4 gene Gly56Ala plus 5-HTTLPR L/L promoter variants. Mol Genet Metab 2011; 102: 368-373.

[28] Adamsen D, Ramaekers V, Ho H, *et al.* Autism spectrum disorder associated with low serotonin in CSF and mutations in the SLC29A4 plasma membrane monoamine transporter(PMAT) gene. Autism Mol 2014; 5: 43.

[29] Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz P. Serotonin hypothesis of autism: implications for selective serotonin reuptake inhibitor use during pregnancy. Autism Res. 2013; 6(3): 149-68.

[30] Campbell HL, Tivarus ME, Hillier A, Beversdorf DQ. Increased task difficulty results in greater impact of noradrenergic modulation of cognitive flexibility. Pharmacol Biochem Behav 2008; 88: 222-9.

[31] Zhang, Sun Y, Wang F, Wang, Z, Peng Y, Li R. Downregulating the canonical Wnt/ß-catenin signaling pathway attenuates the susceptibility to autism-like phenotypes by decreasing oxidative stress. Neurochem Res 2012; 37: 1409-19

[32] Luong KVQ, Nguyễn LTH. The role of beta-adrenergic receptor blockers in autism. Am J Psychiatr Neurosci 2013; 1(1): 14-21.

[33] Baradaran A, Rabiei Z, Rafieian M, Shirzad H. A review study on medicinal plants affecting amnesia through cholinergic system. J Herbmed Plarmacol 2012; 1(1): 3-9.

[34] Rahnama S, Rabiei Z, Alibabaei Z, Mokhtari S, Rafieian-kopaei M, Deris F. Anti-amnesic activity of *Citrus aurantium* flowers extract against scopolamine-induced memory impairments in rats. Neurological Science 2014: 1-8.

[35] Lam KS, Aman MG, Arnold LE. Neurochemical correlates of autistic disorder: a review of the literature. Res Dev Disabil 2006; 27: 254-89.

[36] Polleux F, Lauder JM. Toward a developmental neurobiology of autism. Ment Retard Dev Disabil Res Rev 2004; 10: 303-17.

[36] Rafieian-Kopaei M, Gray AM, Spencer PS, Sewell RDE. Contrasting actions of acute or chronic paroxetine and fluvoxamine on morphine withdrawal-induced place conditioning. Eur J Pharmacol 1995; 6; 275(2): 185-9.

[37] Ghaleiha A, Ghyasvand G, Mohammadi MR, *et al.* Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial. J Psychopharmacol 2014; 28(7): 677-685.

[38] Saki K, Bahmani M, Rafieian-Kopaei M, *et al.* The most common native medicinal plants used for psychiatric and neurological disorders in Urmia city, northwest of Iran. Asian Pac J Trop Dis 2014; 4(Suppl 2): 895-901.

[39] Bahmani M, Shirzad HA, Majlesi M, Shahinfard N, Rafieian-Kopaei M. A review study on analgesic applications of Iranian medicinal plants. Asian Pac J Trop Med 2014; 7(Suppl 1): 43-53.

[40] Doyle CA, McDougle CJ. Dopamine. Encyclopedia of Autism Spectrum Disorders 2013; 988-994.

[41] Masi G, Cosenza A, Mucci M, De Vito G. Risperidone monotherapy in preschool children with pervasive developmental disorders. J Child Neurol 2001; 16: 395-400.

[42] Hunter LC, O'Hare A, Herron WJ, Fisher LA, Jones GE. Opioid peptides and dipeptidyl peptidase in autism. Dev Med Child Neurol 2003; 45(2): 121-8.

[43] Shirzad H, Shahrani M, Rafieian-Kopaei M. Comparison of morphine and tramadol effects on phagocytic activity of mice peritoneal phagocytes *in vivo*. Int Immunopharmacol 2009; 9(7-8): 968-70.

[44] Polleux F, Lauder JM. Toward a developmental neurobiology of autism. Ment Retard. Dev Disabil Res Rev 2004; 10: 303-17.

[45] Duffy FH, Shankardass A, McAnulty GB, *et al.* Corticosteroid therapy in regressive autism: a retrospective study of effects on the Frequency Modulated Auditory Evoked Response(FMAER), language, and behaviour. BMC Neurology 2014; 14: 70. http: //www.biomedcentral.com/1471-2377/14/70.

[46] Manent JB, Represa A. Neurotransmitters and brain maturation: early paracrine actions of GABA and glutamate modulate neuronal migration. Neuroscientist 2007; 13: 268-79.

[47] Barnby G, Abbott A, Sykes N, *et al*. Candidate-gene screening and association analysis at the autism-susceptibility locus on chromosome 16p: evidence of association atGRIN2A and ABAT. Am J Hum Genet 2005; 76: 950-66.

[48] Purcell AE, Jeon OH, Zimmerman AW, Blue ME, Pevsner J. Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. Neurol 2001; 57: 1618-8.

[49] Derkach VA, Oh MC, Guire ES, Soderling TR. Regulatory mechanisms of AMPA receptors in synaptic plasticity. Nat Rev 2007; 8: 101-13.

[50] Manent JB, Represa A. Neurotransmitters and brain maturation: early paracrine actions of GABA and glutamate modulate neuronal migration. Neuroscientist 2007; 13: 268-79.

[51] Evitt P, Eagleson KL, Powell EM. Regulation of neocortical interneuron development and the implications for neurodevelopmental disorders. Trends Neurosci 2004; 27: 400-6.

[52] Purcell AE, Jeon OH, Zimmerman AW, Blue ME, Pevsner J. Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. Neurology 2001; 57(9): 1618-1628.

[53] Kornhuber J, Mack-Burhardt F, Konradi C, Fritze J, Riderer P. Effect of antemortem and postmortem factors on [3H]MK-801 binding in the human brain: Transient elevation during early childhood. Life Science 1999; 45: 745-749.

[54] Hussman JP. Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. Journal of Autism and Developmental Disorders 2001; 31: 247-248.

[55] Fatemi SH, Halt AR, Stary JM, Kanodia R, Schulz SC, Realmuto GR. Glutamic acid decarboxylase 65 & 67 kDa proteins are reduced in autistic parietal & cerebellar cortices. Biological Psychiatry 2002; 52: 805-810.

[56] Kaplan HI, Sadok BJ. Synopsis of psychiatry. 10th ed. Lippincott. Williams and Wilkins. Philadelphia 2007 pp: 1208-22.

[57] Glebenzon BJ, Rosenberg AL. On Autism: its prevalence, diagnosis, causes & treatment. Top Clin Chiropr 2001; 8: 42-57.

[58] Gudarzi SS, Yasamy M, Akhondzadeh S. Cyproheptadine in treatment of autism. Eur Psychiatry 2002; 17(4): 230-1.

[59] Sperner-Unterweger B. Immunological aetiology of major psychiatric disorders: evidence and therapeutic implications. Drugs 2005; 65: 1493-520.

[60] Matson JL, Beighley J, Turygin N. Autism diagnosis and screening: Factors to consider in differential diagnosis. Research in Autism Spectrum Disorders 2012; 6(1): 19-24

[61] Silva LMT, Schalock M, Ayres R. A model and treatment for autism at the convergence of Chinese medicine and Western science: First 130 cases. Chinese Journal of Integrative Medicine 2011 17(6): 421-429.

[62] Buitelaar JK, Willemsen-Swinkels SH. Autism: current theories regarding its pathogenesis and implications for rational pharmacotherapy. Paediatr Drugs 2000; 2: 67-8.

[63] Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. J Am Acad Child Adolesc Psychiatry 2001; 40: 887- 94.

[64] Akhondzadeh S, Fallah J, Mohammadi MR, *et al*. Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. Prog Neuropsychopharmacol. Biol Psychiatry 2010; 34: 32-6.

[65] Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attentiondeficithyperactivity disorder. J Autism De Disord 2000; 30: 245-55.

[66] Akhondzadeh S, Tajdar H, Mohammadi MR, *et al.* A double-blind placebo controlled trial of piracetam added to risperidone in patients with autistic disorder. Child Psychiatry Hum Dev 2008; 39: 237-45.

[67] Rezaei V, Mohammadi MR, Ghanizadeh A, *et al.* Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34(7): 1269-72.

[68] Rabiei Z, Rafieian M. Effects of *Zizyphus jujuba* extract on motor coordination impairment induced by bilateral electric lesions of the nucleus basalis of meynert in rat. Physiology and Pharmacology 2014; 17(4): 469-77.

[69] Delfan B, Bahmani M, Rafieian-Kopaei M, Delfan M, Saki K. A review study on ethnobotanical study of medicinal plants used in relief of toothache in Lorestan province, Iran. Asian Pac J Trop Dis 2014; 4(Suppl 2): 879-884.

[70] Roohafza H, Sarrafzadegan N, Sadeghi M, Rafieian-Kopaei M, Sajjadi F, Khosravi-Boroujeni H. The association between stress levels and food consumption among Iranian population. Arch Iran Med 2013 Mar; 16(3): 145-8.

[71] Asgary S, Sahebkar A, Afshani, M, Keshvari M. Haghjooyjavanmard, Sh, Rafieian-Kopaei M. Clinical evaluation of blood pressure lowering, endothelial function improving, hypolipidemic and anti-inflammatory effects of pomegranate juice in hypertensive subjects. Phytother Res 2013; DOI: 10.1002/ptr.4977.

[72] Rafieian-Kopaei M, Shahinfard, N, Rouhi-Boroujeni H, Gharipour M, Darvishzadeh-Boroujeni P. Effects of Ferulago angulata extract on serum lipids and lipid peroxidation. Evid Based Complement

Alternat Med. 2014; 2014: 680856. doi: 10.1155/2014/680856. Epub 2014 Feb 24.

[73] Sarrafzadegan N, Khosravi-Boroujeni H, Esmaillzadeh A, Sadeghi M, Rafieian-Kopaei M, Asgary S. The association between hypertriglyceridemic waist phenotype, menopause, and cardiovascular risk factors. Arch Iran Med 2013; 16(3): 161-166.

[74] Bahmani M, Zargaran, A, Rafieian-Kopaei M, Saki M. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus in the Urmia, Northwest Iran. Asian Pac J Trop Med 2014; 7(Suppl 1): 348-354.

[75] Mirhoseini M, Baradaran A, Rafieian-Kopaei M. Medicinal plants, diabetes mellitus and urgent needs. J Herbmed Pharmacol 2013; 2(2): 53-54

[76] Asgary S, Rafieian-Kopaei M, Shamsi F, Najafi S, Sahebkar A. Biochemical and histopathological study of the anti-hyperglycemic and anti-hyperlipidemic effects of cornelian cherry(Cornus mas L.) in alloxan-induced diabetic rats. J Complement Integr Med. 2014; 11(2): 63-9. doi: 10.1515/jcim-2013-0022.

[77] Baradaran A, Nasri H, Nematbakhsh M, Rafieian-Kopaei M. Antioxidant activity and preventive effect of aqueous leaf extract of *Aloe vera* on gentamicin-induced nephrotoxicity in male Wistar rats. Clin Ter 2014; 165(1): 7-11. doi: 10.7471/CT.2014.1653

[78] Nasri H, Rafieian-Kopaei M. Tubular kidney protection by antioxidants. Iranian J Publ Health 2013; 42(10): 1194-1196.

[79] Ghaed F, Rafieian-Kopaei M, Nematbakhsh M, Baradaran A, Nasri H. Ameliorative effects of metformin on renal histologic and biochemical alterations of gentamicin-induced renal toxicity in Wistar rats. J Res Med Sci 2012; 17(7): 621-625.

[80] Nasri H, Shirzad H. Toxicity and safety of medicinal plants. J Herbmed Plarmacol 2013; 2(2): 21-22.

[81] Werneke U, Turner T, Priebe S. Complementary medicines in psychiatry: review of effectiveness and safety. Br J Psychiatry 2006; 188: 109-21.

[82] Smith TC, Ryan MA, Smith B, *et al.* Complementary and alternative medicine use among US Navy and Marine Corps personnel. BMC Complement Altern Med 2007; 7: 16.

[83] Noorbala AA, Akhondzadeh S. Attention deficit/hyperactivity disorder: etiology and pharmacotherapy. Arch Iran Med 2006; 9: 374-80.

[84] Hechtman L. Attention -deficit/Hyperactivity disorder. In: Sadock BJ, Sadock VA. Comprehensive text book of psychiatry. 8 ed. Lippincott Williams & Wilkins. Philadelphia 2005.

[84] Huguet F, Drieu K, Piriou A. Decreased cerebral 5-HT1A receptors during ageing: Reversal by *Ginkgo biloba* extracts(EGb 761). J Pharm Pharmacol 1994; 46: 316-8.

[85] White HL, Scates PW, Cooper BR. Extracts of Ginkgo biloba leaves inhibit monoamine oxidase. Life Sci 1996; 58: 1315-21.

[86] Burns NR, Bryan J, Nettelbeck T. *Ginkgo biloba*: no robust effect on cognitive abilities or mood in healthy young or older adults. Hum Psychopharmacol 2006; 21: 27-37.

[87] Wang YS, Xu L, Ma K, Wang S, Wang JJ. Protective effects of *Ginkgo biloba* extract against glutamate-induced neurotoxicity in cultured retinal neuron. Chin Med J(Engl) 2005; 118: 948-52.

[88] Sierpina VS, Wollschlaeger B, Blumenthal M. *Ginkgo biloba*. Am Fam Physician 2003; 68: 923-6.

[89] Chan E. The role of complementary and alternative medicine in attention-deficit hyperactivity disorder. J Dev Behav Pediatr 2002; 23: S37-45.

[90] Hasanzadeh E, Mohammadi MR, Ghanizadeh A, *et al.* A double-blind placebo controlled trial of ginkgo biloba added to risperidone in patients with autistic disorders. Child Psychiatry Hum Dev 2012; DOI: 10.1007/s10578-012-0292-3.

[91] Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. Br J Anaesth 2000; 84(3): 367-71.

[92] Rasool M, Malik A, Qureshi MS, *et al.* Recent updates in the treatment of neurodegenerative disorders using natural compounds. Evidence-Based Complementary and Alternative Medicine 2014(2014), Article ID 979730, 7 pages. http: //dx.doi.org/10.1155/2014/979730.

[93] Bedir E, Pugh N, Calis I, Pasco DS, Khan IA. Immunostimulatory effects of cycloartane-type triterpene glycosides from astragalus species. Biol Pharm Bull 2000; 23(7): 834-7.

[94] Zheng Z, Liu D, Song C, Cheng C, Hu Z. Studies on chemical constituents and immunological function activity of hairy root of Astragalus Chin J Biotechnol 1998; 14(2): 93-7.

[95] Chen YJ, Dai YS, Chen BF, *et al.* The effect of tetrandrine and extracts of Centella asiatica on acute radiation dermatitis in rats. Biol Pharm Bull 1999; 22(7): 703-6.

[96] Shukla A, Rasik AM, Jain GK, Shankar R, Kulshrestha DK, Dhawan BN. *In vitro* and *in vivo* wound healing activity of asiaticoside isolated from *Centella asiatica*. J Ethnopharmacol 1999; 65(1): 1-11.

[97] Mook-Jung I, Shin JE, Yun SMH. *et al*. Protective effects of asiaticoside derivatives against beta-amyloid neurotoxicity. J Neurosci Res 1999; 1; 58(3): 417-25.

[98] Veerendra-Kumar MH, Gupta YK. Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clin Exp Pharmacol Physiol 2003; 30(5-6): 336-42.

[99] Dhawan D. *In vitro* and *in vivo* wound healing activity of asiaticoside isolated from Centella asiatica. J Ethnopharmacol 1999; 65(1): 1-11.

[100] Balakumbahan R, Rajamani K, Kumanan K. Acorus calamus: An overview. J Med Plants Res 2011; 4(25): 2740-2745.

[101] Srikantha-Murthy KR. Vagbhata's Astanga Hrdayam. vol. 3. Varanasi: Krishnadas Academy 1995; p. 387.

[102] Bahmani M, Rafieian M, Baradaran A, Rafieian S, Rafieian-Kopaei M. Nephrotoxicity and hepatotoxicity evaluation of Crocus sativus stigmas in neonates of nursing mice. J Nephropathol. 2014; 3(2): 81-5. doi: 10.12860/jnp.2014.16. Epub 2014 Apr 1.

[103] Madihi Y, Merrikhi A, Baradaran A, Rafieian-kopaei M, Shahinfard N, Ansari R, Shirzad H, Mesripour A. Impact of Sumac on postprandial high-fat oxidative stress. Pak J Med Sci 2013; 29(1): 340-345 doi: http: //dx.doi.org/10.12669/pjms.291(Suppl).3529

[104] Hasanpour Z, Nasri H, Rafieian-Kopaei M, Ahmadi A, Baradaran A, Nasri P, Nematbakhsh M. Paradoxical effects of atorvastatin on renal tubular cells: an experimental investigation. Iran J Kidney Dis. 2015 May; 9(3): 215-20.

[105] Baradaran A, Nasri H, and Rafieian-Kopaei M. Protection of renal tubular cells by antioxidants: Current knowledge and new trends. Cell Journal(Yakhteh), Winter 2015; 16(4): 568- 568.

[106] Rabiei Z., Rafieian-Kopaei M, Mokhtari S, Alibabaei Z, Shahrani M. The effect of pretreatment with different doses of Lavandula officinalis ethanolic extract on memory, learning and nociception. Biomed Aging Pathol 2013; doi: 10.1016/j.biomag.2013.10.006.

[107] Rafieian-Kopaei M, Nasri H. Comment on: preventive effect of Teucrium polium on learning and memory deficits in diabetic rats. Med Sci Monit Basic Res. 2013 Jul 31; 19: 208-9. doi: 10.12659/MSMBR.889344.

[108] Alibabaei, Z., Rabiei, Z., Rahnama, S., Mokhtari, S., Rafieian-kopaei, M. Matricaria Chamomilla extract demonstrates antioxidant properties against elevated rat brain oxidative status induced by amnestic dose of scopolamine. Biomedicine & Aging Pathology 4(2014) 355-360. Doi : 10.1016/j.biomag.2014.07.003.

[109] Delfan B, Bahmani M, Rafieian-KopaeiM, Delfan M, Saki K. A review study on ethnobotanical study of medicinal plants used in relief of toothache in Lorestan province, Iran. Asian Pac J Trop Dis 2014; 4(Suppl 2): S879-S884.

[110] Rafieian-Kopaei M, Nasri H. Comment on: preventive effect of Teucrium polium on learning and memory deficits in diabetic rats. Med Sci Monit Basic Res 2013 Jul 31; 19: 208-9. doi: 10.12659/MSMBR.889344.

[111] Saki K, Bahmani M, Rafieian-Kopaei M, Hassanzadazar H, Dehghan K, Bahmani F, Asadzadeh J. The most common native medicinal plants used for psychiatric and neurological disorders in Urmia city, northwest of Iran. Asian Pac J Trop Dis 2014; 4(2): S895-S901. doi: 10.1016/S2222-1808(14)60754-4.

[112] Saki K, Bahmani M, Rafieian-Kopaei M. The effect of most important medicinal plants on two importnt psychiatric disorders(anxiety and depression)-a review. Asian Pac J Trop Med 2014; 7S1: S34-42. doi: 10.1016/S1995-7645(14)60201-7.

[113] Delfan B, Bahmani M, Hassanzadazar H, Saki K, Rafieian-Kopaei M. Identification of medicinal plants affecting on headaches and migraines in Lorestan province, West of Iran. Asian Pac J Trop Med 2014; 7S1: S376-9. doi: 10.1016/S1995-7645(14)60261-3.

[114] Chauhan A, Chauhan V. Oxidative stress in autism. Pathophysiology 2006; 13(3): 171-181.

[115] Ghanizadeh A, Akhondzadeh S, Hormozi M, Makarem A, Abotorabi-Zarchi M, Firoozabadi A. Glutathione-related factors

and oxidative stress in autism, a review. Curr Med Chem 2012; 19(23): 4000-5.

[116] Bahmani M, Rafieian-Kopaei M, Hassanzadazar H, Saki K, Karamati SA, Delfan B. A review on most important herbal and synthetic antihelmintic drugs. Asian Pac J Trop Med. 2014 Sep; 7S1: S29-33. doi: 10.1016/S1995-7645(14)60200-5.

[117] Akhlaghi M, Shabanian G, Rafieian-Kopaei M, Parvin N, Saadat M, Akhlaghi M. Citrus aurantium blossom and preoperative anxiety. Rev Bras Anestesiol. 2011 Nov-Dec; 61(6): 702-12. doi: 10.1016/S0034-7094(11)70079-4.

[118] Bahmani M, Rafieian-Kopaei M, Jeloudari M, Eftekhari Z, Delfan B, Zargaran A, Forouzan S. A review of the health effects and uses of drugs of plant licorice(Glycyrrhiza glabra L.) in Iran. Asian Pac J Trop Dis 2014; 4,(2): S847-S849 . Doi: DOI: 10.1016/S2222-1808(14)60742-8.

[119] Sharafati-Chaleshtori R, Rokni N, Rafieian-Kopaei M, Drees F, Sharafati-chaleshtori A and Salehi E. Use of Tarragon(Artemisia dracunculus) essential oil as a natural preservative in beef burger. Ital J Food Sci 2014, 26 -427-432.

[120] Bahmani M, Rafieian-Kopaei M, KaramatiA, Bahmani F, Bahmani F, Bahmani E, Asadzadeh J. Antiparasitic herbs used in west regions of Ilam province located in west of Iran. Asian Pac J Trop Dis 2014; 4(2) S764-S769. DOI: 10.1016/S2222-1808(14)60724-6

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