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Review Article

Role of Unani Neuroprotective Herbal Drugs in the Management of Autism

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ABSTRACT

Autism, a sub-type of pervasive developmental disorders, is characterized by difficulty in communication and social interaction, restricted interests in activities, repetitive behaviours and reduced ability to function at school, work place and other areas of life. The estimated prevalence of autism spectrum disorders has increased dramatically in the past several years. The disease requires long-term treatment and is generally considered incurable. Conventional management focuses on behavioural therapies, education and dietary therapies. Pharmacological intervention includes psychotropic drugs to reduce behavioural problems, but is associated with significant adverse effects. In Unani system of medicine a number of plant drugs have been used extensively in various neurological disorders because of their neuroprotective properties. Plant based Unani drugs have multiple bioactive compounds, which may work on multiple systems including oxidative stress, mitochondria, inflammatory cytokines and immune system. This review paper focuses on the neuroprotective potential of some Unani medicinal herbs which can be used in autism as a substitute of pharmacotherapy or can be an adjunct therapy.

Keywords: Unani, herbal, neuroprotective, autism, *Amla*, *Jadwar*, *Brahmi*, *Badam*, Autism and herbal drugs

INTRODUCTION

Autism, also called autism spectrum disorder (abbreviated as ASD), is a sub-type of pervasive developmental disorders that refer to a group of conditions characterized by qualitative deficits in social interaction, communication skills and by a restricted, stereotyped, repetitive repertoire of interests and activities. [(1,2)] Autism can be diagnosed at any age, but it is said to be a "developmental disorder" because its symptoms usually appear in the first two years of life.

As per the *5th Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*, people with ASD have difficulty in communication and social interaction, restricted interests in activities, repetitive behaviours and reduced ability to function at school, work place and other areas of life.

The characteristic social behaviours in autism include an avoidance of eye contact, problems with emotional control or understanding the emotions of others, and a markedly restricted range of activities and interests.

The estimated prevalence of ASD has increased dramatically in the past several years, rising from 1 in 150 children in 2002 to 1 in 68 in 2012. [(3)]

Autism spectrum disorder is generally not curable and hence, requires

long term management. The principal objectives of management are to curtail the core features and related symptoms, lessen functional dependence and maximise quality of life. [(4)] There are many different types of treatment for ASD, such as medical management, rehabilitation training, education and dietary approaches.

There are only a limited range of available interventions which primarily target the core features of autism, and their effectiveness is often poor. [(5)] Existing interventions for autism core features are (a) psychosocial interventions mainly focussed on improving social and communication skills and (b) pharmacological management to decrease rigid or repetitive behaviours which have a possible association with mental health problems. However, there is no psychosocial intervention that specifically focuses on understanding and managing stereotyped, repetitive or rigid behaviours. [(6)]

Medications are primarily used for treating associated symptoms of autism, like anxiety, irritability, hyperactivity aggression, inattention, self-injury and sleep disturbance or insomnia. Psychotropic medications are often prescribed for associated behavioural symptoms but may have significant side effects. [(7)] For serious behavioural symptoms in children with autism, risperidone is the most commonly used drug among the pharmacologic interventions.[(8)] Despite its beneficial effects on behavioural symptoms, risperidone treatment has been associated with adverse events, such as rhinorrhoea, increased appetite, excessive weight gain and excessive sleep. [(9)]

Because of the limitations and risks of conventional treatments and chronic nature of autism many parents of children with autism are therefore seeking alternative therapies with least side effects. Herbal drugs occupy an important niche in the treatment of diseases worldwide and are commonly used in traditional Unani system of medicine, which strengthen body defence without remarkable side effects. They have been extensively studied in many diseases including neurological and psychiatric disorders with promising results.

This review paper focuses on the neuroprotective potential of some Unani medicinal herbs which can be used in autism as a substitute of pharmacotherapy or can be an adjunct therapy.

METHODS

The information of this review were obtained from classical textbooks of Unani Medicine as well as electronic databases such as, Google Scholar, Scopus, PubMed, Science Direct and Web of Science and included articles from 2001 to 2018. The articles were searched with the keywords: "Autism" (with modern medical literature), "autism spectrum disorder", "Autism and Herbal drugs", "Anti-oxidant", "neuroprotective herbs" etc.

All human and animal studies investigating the pharmacology of herbal drugs with regard to neuroprotective activity and also the articles that reported the effects of plant drugs on neuropsychiatric disorders, were included in this review article.

Role of Unani Neuroprotective Herbal Drugs in the management of Autism:

Autism is believed to have genetic neurological and environmental origins, yet in only a modest fraction of individuals specific causes can be identified. [(10)] Genetic variations are detected in as many as 30 % of individuals with autism, including 5-7 % with single-gene disorders (such as tuberous sclerosis and fragile X syndrome), 5 % with disorders of metabolism, and 7-20 % with copy number variants (CNVs). [(11)] A number of studies suggest that the cytokine such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) levels are significantly elevated in different tissues like blood, brain, and cerebrospinal fluid (CSF) in autistic subjects.

Oxidative stress and several disturbances in biochemical and inflammatory factors have also been observed in the etiology of Autism. [(12)] Several authors imply that there is a link

between autism and irregularities in mitochondrial homeostasis and also produce genetic and biochemical evidence supporting a role for mitochondrial dysfunction in the pathogenesis of autism. [(13)] In Unani system of medicine a number of plant drugs have been used extensively in various neurological disorders because of their neuroprotective properties. The role of neuroprotective drugs involves a number of effects like prevention against oxidative stress, mitochondrial dysfunction, inflammation and immune dysregulation. Plant based Unani drugs have multiple bioactive compounds, which may work on multiple systems including oxidative stress, mitochondria, inflammatory cytokines and immune system. These drugs with properties of curing neurological disorder can be utilized in the management of autistic disorder. Some of these herbal Unani drugs with their neuropharmacological profile are described below:

Amla (Emblica officinalis* Gaertn*):

Amla (*Emblica officinalis* Gaertn) belonging to the Euphorbiaceae and is widely distributed in central and southern India, Bangladesh, Pakistan, Sri Lanka, Malaysia and Southern China. [(14)] It is a tree of small or moderate size with a greenish-grey bark and greenish-yellow flowers, formed in axillary clusters. The fruits are green, depressed, globose or oblate, indented at the base, smooth, fleshy and shining. *Amla* fruit as mentioned in Unani literature is haemostatic/styptic, astringent, anti diarrhoeal, brain tonic, cardiac tonic, hair tonic and tranquilizer. [(15)] Therapeutically it is used for Cardiac asthenia, palpitation, neurasthenia, cerebral asthenia, diminished vision and hair fall. [(15)]

(a) *Emblica officinalis* tree (b) *Emblica officinalis* fruit, dried (left), fresh (right)

Neuro-pharmacological Profile:

Cognitive and Memory Enhancing Effects:

- Administration of dried *Amla* (*E. officinalis*) powder (50, 100, and 200 mg/kg, p.o.) for 15 days resulted in a dose-dependent enhancement of memory scores in both exteroceptive and interoceptive behavioral models for testing memory in both young and aged rats. [(16)]
- Administration of *E. officinalis* tannoid principles orally for 60 days in aluminum chloride (AlCl3) induced Alzheimer's disease (AD) in rats, significantly revert back the AChE activity, Al concentration and molecules related to A-beta synthesis in the brain regions studied as compared to control group. [(17)]
- Hydro-alcoholic extract of *Emblica officinalis* reversed the amnesia, ameliorated the oxidative stress and markedly reduced the level of acetyl cholinesterase (AchE) in brain. [(18)]

Neuroprotective and Anti-oxidant Activity

- Pretreatment of *E. officinalis* hydroalcoholic extract in kainic acid-induced seizures in rats showed neuroprotective effect by improving the levels of Glutathione (GSH) and TNF-α in brain. [(19)]

- Treatment with hydroalcoholic extract of *E. officinalis* fruitat intraperitoneal dose of 300, 500 and 700 mg/kg in pentylenetetrazole (PTZ)-induced seizures prevented cognitive impairment via ameliorating oxidative stress markers like brain malondialdehyde (MDA) and Glutathione (GSH) in brain. [(20)]
- Aqueous extract of *E. officinalis* showed antidepressant-like activity possibly by inhibiting Monoamine oxidase-A (MAO-A) and Gamma Amino Butyric Acid (GABA), along with its antioxidant action. The active tannoid principles present in *E. officinalis* with its antioxidant as well as nitric oxide (NO) scavenging properties might have contributed to the observed protection against alcohol-induced brain mitochondrial dysfunction. [(21)]
- Pretreatment with aqueous fruit extract of *E. officinalis* in radiation induced biochemical lesions in the brain of mice produced radioprotective effect by decreasing lipid peroxidation via increasing the levels of GSH, protein and cholesterol in brain. [(22)]

Immunomodulatory activity

- *Emblica officinalis* extract showed immunomudulatory effect via enhancing the proliferation of lymphocytes and by restoration of IL-2 and gamma-IFN production in chromium (Cr)-induced immunosuppression (in vitro). [(23)]
- E*xtract* of *E. officinalis* in a dose of 100 mg/kg for 15 days produced immunomodulatory effect in BALB/c mice (infected with *Leishmania donovani*) by reducing parasite load via increasing levels of IgG2a and by lowering the level of IgG1. [(24)]
- *Emblica officinalis* extract in combination with *Ocimum sanctum, With ania somnifera, Emblica officinalis* and *Tinospora cordifolia* showed immunomodulatory activity through increased leukocyte proliferation by lipopolysaccharide (in vitro) and by increasing the activity of natural killer cells (NK cells) in mice. [(25)]

***Badam* (*Prunus amygdalus* Dulcis):**

Badam or almond (*Prunus amygdalus* dulcis) tree belonging to the Rosaceae family is a native to the Middle East and South Asia. It has been cultivated in Greece and China for centuries and is now cultivated mainly in the Mediterranean region and in California. In India, almond is mainly cultivated in Kashmir and is supposed to be one of the chief crops of this region. [(26)] Almond fruit consists of kernel, middle shell, outer green shell cover or almond hull and a thin leathery layer or seed coat. The nutritional importance of almond fruit is related to its kernel. [(27)] In Unani system of medicine, almond kernels are considered as brain tonic and are used in cerebral abnormalities such as loss of memory, insomnia, and headache. [(28)]

(a) *Prunus amygdalus* seeds (b) *Prunus amygdalus* kernels

Neuro-pharmacological Profile:

Memory Enhancing Activity:

- Administration of Almond (*P. amygdalus*) in different dosed significantly reversed scopolamine induced amnesia, also reduced the brain acetylcholinesterase (AChE) and exhibited a remarkable cholesterol and triglyceride lowering property in rats. [(29)]
- Almond supplementation prevented scopolamine-induced amnesia in mice and improved learning ability in HFD-fed rats. [(30)]

Anxiolytic Activity:

- *Prunus amygdalus* Dulcis in a dose 1600 mg/kg possess anxiolytic property equal to that of diazepam in mice when assessed by using open-field tests. [(31)]

Neuroprotective Activity:

Neuroprotective effect of *Prunus amygdalus* nut kernels was evaluated against aluminium chloride induced spatial memory deficits in rats. Pre-treatment with *Prunus amygdalus* extract prevented neurochemical, histopathological and behavioural changes to a significant extent. [(32)]

Immunostimulant Activity:

- Treatment with almonds stimulated the production of interferon-α (INF-α), interleukins (IL-12), INF-gamma and tumour necrosis factor (TNF-α). [(33)]
- Almonds improved the immune surveillance of the peripheral blood mono nuclear cells towards viral infections and also decrease Herpes simplex virus (HSV-2) replication. [(33)]

Antioxidant activity

Ali Jahanban Isfahlan *et al* inferred than methanolic extract of almond possesses anti-antioxidant and anti free-radical activities and their phenolic extract may be helpful in preventing various oxidative stress related diseases. [(27)]

***Brahmi* (*Centella asiatica* Linn.):**

Brahmi (*Centella asiatica* Linn.) is a small perennial creeping aromatic herb belonging to the family Apiaceae, indigenous to Southeast Asian countries like India, China, Indonesia, Sri Lanka, and Malaysia in addition to South Africa and Madagascar. [(34)] *Brahmi* is described in Unani system of medicine as a nerve tonic, stomachic, carminative and tonic to vital organs (liver, kidneys, brain) and is extensively used to enhance cognition and memory. [(35)]

Neuro-pharmacological Profile:

Cognitive and memory enhancing Activities:

- Several studies suggest that *Brahmi* has Cognitive and memory enhancing activities. Aqueous extract of *Brahmi* showed significant effect on learning and memory and significantly decreased the levels of norepinephrine, dopamine and 5-HT and their metabolites in the brain. [(35,36)] *Centella asiatica* Aqueous extract also demonstrated probable effectiveness in preventing cognitive deficits along with the oxidative stress. [(37)]

(a) *Centella asiatica* **dried** (b) *Centella asiatica* **fresh**

Neuroprotective Activity:

- Brahmi (*Centella asiatica*) aqueous extract has a protective effect on the brain in neurodegenerative disorders like Parkinson's disease. The hydroalcoholic extract of *Brahmi* was found to inhibit acetylcholinesterase (AChE), the principle enzyme having a significant function in pathogenesis of Alzheimer's disease. This neuroprotective effect of *Centella asiatica* extract could be due to its rich contents in triterpenes and polyphenols, which are useful detoxifying agents. [(38)]

Antiepileptic activity

- *Centella asiatica* has been traditionally used as anxiolytic and anticonvulsant as increases the cerebral levels of GABA. In pharmacological screening using various experimental models, the hydroalcoholic extract of *Brahmi* leaves showed protective role against rise in intracranial electric stimulation (ICES) and also chemo-convulsions when given orally. It also caused a decline in formation of products of lipid peroxidation, diminution in spontaneous

motor activity, enhancement in hyperactivity induced by diazepam withdrawal, hypothermia, and increase in sleeping time of pentobarbitone. In a dose of 200 mg/kg the pentylenetetrazol-induced convulsions were completely inhibited by the extract. In seizures induced by pentylenetetrazole and convulsions induced by strychnine, 100 mg/kg of the extract showed promising effect. These results suggested its promising anticonvulsant, antioxidant and CNS depressant action. [39,40]

Antioxidant activity

- Methanol extract of *Brahmi* significantly proved to increase the level of anti-oxidants such as glutathione peroxidase (GSHPx), superoxide dismutase (SOD) and catalase in mice having lymphoma.
- Asiatic acid derivatives of *Brahmi* demonstrated significant neuroprotective effects on cultured cortical cells by enhancing cellular defense mechanism against oxidative stress.
- The neuroprotective effects of asiaticoside derivatives of *Brahmi* against beta-amyloid induced neurotoxicity were also studied on B103 cell cultures and hippocampal slices. Of the twenty-eight asiaticoside derivatives, three components, including asiatic acid had a strong inhibitory effect on cell death induced by beta-amyloid and free radicals. [40]

Aqueous extract of *Brahmi* and its active constituent asiaticoside showed anti-inflammatory activity, brought about by inhibition of nitric oxide synthesis. Aqueous extract of *Centella asiatica* significantly decreased inflammation of prostaglandin E2-induced paw edema in rats. [36]

***Jadwar (Delphinium denudatum* Wall.)**

Jadwar (*Delphinium denudatum* Wall.) belonging to Ranunculaceae family is an annual perennial, glabrous or slightly downy herb found in Western Himalayas from Kumaon to Kashmir at altitudes of 3,000 to 4,500 m especially on grassy slopes. [41]

In Unani literature, *Jadwar* is referred as brain and nervine tonic, cardiotonic, general tonic and tonic for viscera, stomach, teeth, exhilarant, sedative and anti-inflammatory. Unani physicians have recommended it for the treatment of paralysis, insanity, epilepsy, migraine, mania, hysteria and also convulsions. [42]

(a) *Delphinium denudatum* plant (b) *Delphinium denudatum* dried root

Neuro-pharmacological Profile:

Neuroprotective Activity:

Delphinium denudatum extract treatment for three weeks significantly attenuated the activities of SOD and CAT when tested on the neuronal injury in 6-hydroxydopamine (6-OHDA) rat model of Parkinsonism. [43]

Anticonvulsant Activity:

Aqueous fraction isolated from the roots of *D. denudatum* produced anticonvulsant activities as investigated in the maximal electroshock test (MEST) and subcutaneous pentylenetetrazole (PTZ), bicuculline (BIC), picrotoxin (PIC)-induced seizures of the FS-1 subfraction (FS-1). [44]

Anxiolytic Activity:

A study was carried out to evaluate the anti-anxiety properties of the hydroalcoholic extract of *Delphinium denudatum* root produced good anxiolytic effects in Wistar albino rats in doses of 200 and 400 mg/kg using different anti-anxiety tests like Elevated Plus Maze, Staircase, Actophotometer, and Light and Dark tests. [45]

DISCUSSION

Autism, or autism spectrum disorder (ASD) is a complex neurological disorder which has a lifelong effect on

social interaction, communication skills and characterised by a restricted, stereotyped, repetitive repertoire of interests and activities. [(1)] Autism spectrum disorder is generally not curable and hence, requires long term management.

Many drugs like antipsychotics, serotonin reuptake inhibitors, B-blockers, naltrexone, and antidepressants have been tested for this disorder. Psychotropic medications are often prescribed for associated behavioural symptoms but may have significant side effects. [(7)] Unani herbal drugs have been extensively studied in many diseases including neurological and psychiatric disorders with promising results without producing adverse effects. Many Unani drugs like *Amla* (*Emblica officinalis*), *Badam* (*Prunus amygdalus*), *Brahmi* (*Centella asiatica*), *Jadwar* (*Delphinium denudatum*) with properties of curing neurological disorder can be utilized in the management of autistic disorder. The role of neuroprotective drugs involves a number of effects like prevention against oxidative stress, mitochondrial dysfunction, inflammation and immune dysregulation. The literature review in this paper revealed that *Amla* (*Emblica officinalis*), *Badam* (*Prunus amygdalus*), *Brahmi* (*Centella asiatica*), *Jadwar* (*Delphinium denudatum*) provide neuroprotection through various mechanisms/ activities. Since, Oxidative stress, disturbances in biochemical and inflammatory factors, abnormalities in mitochondrial homeostasis are considered to have important role in the pathogenesis of the autism phenotype. These Unani neuroprotective dugs can have a beneficial role in improving autism associated and core symptoms through their anti-oxidant, immunomodulatory, cognitive and memory enhancing, anti-inflammatory and anti-convulsant activities. The active tannoid principles present in *E. officinalis* with its antioxidant as well as nitric oxide (NO) scavenging properties provide protection against brain mitochondrial dysfunction in autism.

Conflict of Interest: None

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