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Sahiba
PG Scholar (MD), Department
of Moalajāt, Regional
Research Institute of Unani
Medicine, University of
Kashmir, Habak, Naseembagh
Campus, Hazratbal, Jammu
and Kashmir, India

**Mohammed Sheeraz Mushtaque
Ahmed**
Research Officer Level II &
Reader, Department of
Moalajāt, Regional Research
Institute of Unani Medicine,
University of Kashmir,
Habak, Naseembagh Campus,
Hazratbal, Jammu and
Kashmir, India

Ahtesham Ahamad
PG Scholar (MD), Department
of Moalajāt, Regional
Research Institute of Unani
Medicine, University of
Kashmir, Habak, Naseembagh
Campus, Hazratbal, Jammu
and Kashmir, India

Shugufta Hamid
PG Scholar (MD), Department
of Moalajāt, Regional
Research Institute of Unani
Medicine, University of
Kashmir, Habak, Naseembagh
Campus, Hazratbal, Jammu
and Kashmir, India

Corresponding Author:
Sahiba
PG Scholar (MD), Department
of Moalajāt, Regional
Research Institute of Unani
Medicine, University of
Kashmir, Habak, Naseembagh
Campus, Hazratbal, Jammu
and Kashmir, India

Neuroprotective strategies in Unani medicine for managing autism spectrum disorders: A holistic approach

**Sahiba, Mohammed Sheeraz Mushtaque Ahmed, Ahtesham Ahamad
and Shugufta Hamid**

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and interaction, as well as restricted interests and repetitive behaviors. ASD encompasses a broad range of symptom severities and associated features, leading to variability in presentation and challenges in diagnosis and treatment. Although the exact causes are unknown, both genetic and environmental factors contribute to its development. Its prevalence has increased significantly in recent decades. Unani medicine offers a holistic approach to managing ASD, focusing on restoring balance through individualized dietary and lifestyle modifications, pharmacotherapy, and regimenal therapies. It also addresses comorbidities such as gastrointestinal disturbances, immune dysregulation, and metabolic imbalances. Early identification and intervention are essential for improving the quality of life of individuals with ASD. Integrating Unani medicine with conventional approaches may provide a comprehensive treatment strategy, addressing both physical and psychological aspects of the disorder. This review focuses on the neuroprotective potential of Unani drugs as alternatives to pharmacotherapy in autism.

Keywords: Autism, *Ihtirāq*, *Akhlāt*, Neuroprotective, Unani drugs

Introduction

ASDs are complex neurodevelopmental disorders typically manifesting in childhood with challenges in social interaction, communication, and repetitive behaviors^[1, 2]. The term "autism" was first used by Leo Kanner in 1943 to describe children with diminished social interest. Since 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM) has included autism, Asperger syndrome, pervasive developmental disorder-not otherwise specified, and childhood disintegrative disorder under the umbrella term "Autism Spectrum Disorder (ASD)"^[2].

ASDs are highly heritable, with monozygotic twin concordance rates (~60–90%) being five- to tenfold higher than in dizygotic twins and siblings, and first-degree relatives showing approximately tenfold increased risk compared to the general population. Children with ASD often experience gastrointestinal disturbances, and the severity of dysbiosis^[1].

ASD encompasses various diagnostic classifications, each requiring specific criteria within three domains: communication, social interaction, and behavior problems. While ASD is widely used, it is not recognized by earlier classification systems like DSM-IV and DSM-IV-TR (American Psychiatric Association, 1994, 2000) or ICD-9/10 (World Health Organization, 1993, 2007). The DSM-5 includes diagnoses for childhood autism, autistic disorder, pervasive developmental disorder—not otherwise specified (PDD-NOS), other pervasive developmental disorders, Asperger syndrome, and atypical autism^[3].

Epidemiology

WHO (2019) reported that globally, 1 in every 160 children has ASD. In developed countries, such as the US, an increase in prevalence, rising from 1 in 500 children a decade ago to 1 in 68 in 2014 and 1 in 54 in 2016, has occurred^[4]. In India, the prevalence ranges from 0.15% to 1.01%^[5]. The prevalence of ASD in many low- to middle-income countries remains unknown^[1].

Genetics

Over the past decade, the focus has shifted from a broad understanding of genetic risk to examining specific genetic variations linked to ASD. A 2016 meta-analysis estimated that hereditary factors account for 74% to 93% of ASD risk^[6], though environmental influences are also significant. Sibling studies show that ASD affects 7% to 20% of younger siblings after an older sibling's ASD diagnosis, with higher prevalence in families with two older siblings with ASD^[7]. The risk of ASD is 3 to 4 times higher in boys compared to girls^[8]. Initial genetic insights came from rare syndromes like fragile X syndrome^[9] and tuberous sclerosis^[10], where ASD occurs in some cases. Additionally, research shows elevated levels of cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) in various tissues, including blood, brain, and cerebrospinal fluid, in autism^[11].

Oxidative stress and various disruptions in biochemical and inflammatory factors have been noted in the development of autism^[11]. Some researchers suggest a connection between autism and abnormalities in mitochondrial homeostasis, providing genetic and biochemical evidence that supports the involvement of mitochondrial dysfunction in the pathogenesis^[12].

Risk factors

Advanced maternal age (≥ 40 years) and paternal age (≥ 50 years)^[14], short inter-pregnancy intervals (< 24 months)^[16], low birth weight (< 1500 g), small-for-gestational-age status^[17], large-for-gestational-age status ($> 95^{\text{th}}$ birth weight percentile), and prenatal exposure to valproic acid are associated with increased ASD risk^[18, 19].

Non-specific factors such as metabolic conditions, weight gain, hypertension, and specific factors like hospitalization due to infections or a family history of autoimmune disease are associated with a mildly increased risk of ASD and developmental delays^[20].

Children with these conditions should be monitored for ASD during infancy and early toddler years. No consistent associations have been found between cesarean delivery or assisted conception and ASD risk^[21]. Preconceptual folic acid supplements are associated with a decreased risk of ASD and developmental disabilities, indicating a significant gene-environment interaction^[22]. While some links between air pollutants and maternal stressors during pregnancy have been identified^[21]. Studies have found no link between ASD and vaccinations^[23].

Signs and symptoms of autism spectrum disorder as described in DSM-5 (299.0)

Individuals with ASD differ widely, but the disorder is characterized by key features in two main areas: social communication and restricted, repetitive sensory-motor behaviors, regardless of culture, race, ethnicity, or socioeconomic status^[24, 25].

Diagnosis

- To diagnose ASD, an individual must demonstrate difficulties in all three social communication subdomains and have exhibited two of the four types of restricted, repetitive sensory-motor behaviors.
- Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger syndrome, or pervasive developmental disorder not otherwise specified should

be diagnosed with autism spectrum disorder.

- Symptoms must be present in the early developmental period, although they might not become fully apparent until social demands exceed the individual's limited capacities or might be masked by learned strategies in later life.
- Symptoms must cause clinically significant impairment in social, occupational, or other areas of current functioning^[24].

Treatment

Various treatment options are available for ASD, including medical management, rehabilitation, educational strategies, and dietary changes. However, interventions targeting the core features of autism are limited, and their effectiveness is often suboptimal^[26].

Current interventions for autism's core symptoms include (a) psychosocial treatments to enhance social and communication skills and (b) pharmacological treatments to reduce rigid or repetitive behaviors, which may be linked to mental health issues^[27].

Medications are primarily used to manage symptoms such as anxiety, irritability, hyperactivity, aggression, inattention, self-harm, and sleep problems or insomnia. While psychotropic drugs are commonly prescribed, they can have significant side effects^[28]. Risperidone is frequently used to severe behavioral symptoms in children with autism. Although it can improve behavioral symptoms, it is associated with side effects like rhinorrhea, increased appetite, excessive weight gain, and excessive sleep^[29].

Many parents seek alternative therapies with fewer side effects due to the limitations of conventional treatments. The Unani system offers potential neuroprotective benefits for autism. This review explores the potential of certain Unani drugs to provide neuroprotective benefits for autism.

METHODS

The information for this review was collected from classical Unani literature as well as from electronic databases such as Google Scholar, Scopus, PubMed, ScienceDirect, and Web of Science. Keywords used in the search included "autism," "autism spectrum disorder," "neuroprotective," and "*Ihtirāq*."

Correlation of ASD with Unani

Unani Medicine, also known as Greco-Arab Medicine, has a rich tradition of alleviating pain and promoting health, based on the humoral theory introduced by *Buqrāt* (Hippocrates). In '*Al-Ṭabī'a al-Insāniyyā*', Hippocrates proposed that the body contains four principal humors: *Dam* (blood), *Balgham* (phlegm), *Ṣafrā* (yellow bile), and *Sawdā* (black bile). A balance of these humors is essential for health, while an imbalance causes disease^[30].

Sawdā, produced in the liver and stored in the spleen, is transported to the brain via blood vessels. According to *Ibn Hubal*, psychiatric disorders result from an excess of *Ṭabī'* and *Ghayr Ṭabī' Sawdā* in the body, which mixes with blood and *Ruḥ-i-Nafsāni* (psychic pneuma). This imbalance leads to *Kudūrat* (dimness), *Tāriki* (gloominess), *Burūdat* (coldness), and *Yubūsat* (dryness), disrupting the temperament of *Ruḥ-i-Nafsāni*. Consequently, the affected person may exhibit irrational behavior and cognitive impairments^[31].

Contemporary View on Oxidative Stress (OS), Its Relation to *Ihtirāq*, and Neurodegenerative disorders

In Unani Medicine, *Harārat Gharīziyya* (innate heat) is vital for organ function and is produced by *Ruḥ* (pneuma). This concept correlates with the basal metabolic rate in modern medicine, representing energy expenditure during metabolism [32].

The term *Ihtirāq* describes conditions that disrupt the balance of humors, leading to various illnesses [33]. This concept parallels the modern understanding of OS, a critical mechanism in tissue damage and chronic disease development.

Ibn Sīnā (Avicenna) explained in *Al-Canon* that excessive *Harārat Gharīziyya* in the liver, possibly linked to hypermetabolism, leads to *Ihtirāq*. This results in abnormal forms of humor termed *Sawdā Ghayr Tabīyyā* (abnormal black bile), such as *Sawdā Balghamiyya* (from phlegm), *Sawdā Safrāwiyya* (from yellow bile), *Sawdā Sawdāwiyya* (from normal black bile), and *Sawdā Damawīyya* (from blood) [33].

Harman's free radical theory (1950s) suggests that the lifespan of aerobic organisms is influenced by damage from free radicals to cellular macromolecules [34]. The formal concept of OS was introduced in 1985 in Biochemistry of Oxidative Stress [35]. OS refers to an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize these reactive intermediates. ROS, or free radicals, are unstable molecules that can damage proteins, lipids, and DNA [36]. This imbalance in modern medicine resembles the disruption of bodily humors, i.e., *Ihtirāq* in Unani medicine.

Etiopathogenesis of *Ihtirāq*

In Unani, *Hararat Gharība* refers to excess or unnatural heat, which significantly impacts the balance of normal humors by causing *Ihtirāq*. Sylvie *et al.* found that increased inflammation and OS are linked to higher rates of resting energy expenditure, indicating elevated heat production [37]. This aligns with the concept of *Harārat Gharība*, where oxidation, an exothermic process, generates excess heat that can damage cellular components.

OS is linked to several neurodegenerative disorders, including ASD [11], Parkinson's disease, Alzheimer's disease, multiple sclerosis, memory loss, and depression [38].

Uṣūl-i- 'Ilāj (Management of *Ihtirāq* in Unani System of Medicine)

In the Unani system of medicine, several treatments are used to reduce *Harārat Gharība* and *Ihtirāq* and to eliminate abnormal humors. These treatments include '*Ilāj bi'l Ghidhā*' (dietotherapy), '*Ilāj bi'l Dawā*' (pharmacotherapy), and '*Ilāj bi'l Tadbīr*' (Regimenal therapy) [39]. Therefore, Unani Medicine offers a broad range of holistic interventions that precede the use of specific antioxidants.

'*Ilāj bi'l Ghidhā* (Dietotherapy)

- **Dietary Recommendations:** Unani medicine effectively addresses certain disorders through specific dietary practices or by controlling the quality and quantity of food intake. *Mā' al-Sha'ir* (barley water) is considered an excellent traditional meal for *tartīb* (moistening of the body) and for reducing excess heat. It is noted for its *Mulaṭṭif* (attenuant) properties.

Regular consumption of *Mā' al-Sha'ir* aids in detoxifying the body, acting as a *Munḍij* (concoctive) to help expel thin, morbid matter. Similarly, citrus fruits, watermelon, and other juicy fruits have comparable benefits. *Ibn Nafīs* recommended consuming easily digestible foods before those that digest more slowly. If they are mixed, the food item that digests slowly will not let the easily digestible food pass onwards. Even after their quicker normal metabolism, *ṭabī'at* will keep on digesting it, along with slowly digested food, leading to the *Ihtirāq*. It is also advised to drink water before and during meals [39, 40].

- ***Taqṭīl-i-Ghidhā' ba I'tibār-i-Kayfiyat* (Qualitative reduction of dietary intake):** Hippocrates quoted: "Let food be thy medicine, and medicine be thy food." If *Ihtirāq* is caused by *sudda* (obstruction) in the liver, it impairs the liver's digestive function. In this case, a diet high in cellulose but low in nutrition, such as vegetables and fruits, should be recommended. Oily and greasy foods should be avoided. This approach helps the *Ṭabī'at* to eliminate *mādda'-i-fāsida* (morbid matter) [39, 40].

'*Ilāj bi'l Dawā*' (Pharmacotherapy)

In Unani, many plant-based drugs are used to treat neurological disorders due to their neuroprotective properties. These remedies help with OS, mitochondrial dysfunction, inflammation, and immune imbalances. Rich in bioactive compounds, they target various systems and may be useful in managing autism. Below are descriptions of some Unani drugs and their neuropharmacological profiles.

Amla (Emblīca officinalis Gaertn)

Amla fruit has haemostatic, astringent, anti-diarrhoeal, brain tonic, cardiac tonic, hair tonic, and tranquilizer properties. It is used therapeutically for cardiac weakness, palpitations, neurasthenia, cerebral weakness, impaired vision, and hair fall [41].

Neuro-pharmacological Profile:

- Cognitive and Memory Enhancing Effects [42, 43]
- Neuroprotective and Anti-oxidant Activity [44, 45]
- Immunomodulatory activity [46, 47]

Badām (Prunus amygdalus Dulcis)

Almond kernels are a brain tonic and are utilized for treating cerebral abnormalities such as memory loss, insomnia, and headaches [48].

Neuro-pharmacological Profile

- Memory Enhancing Activity [49, 50]
- Anxiolytic Activity [51]
- Neuroprotective Activity [52]
- Immunostimulant Activity [53]
- Antioxidant activity [54]

Brahmi (Centella asiatica Linn.)

Brahmi is a nerve tonic, stomachic, carminative, and a tonic for vital organs such as the liver, kidneys, and brain. It is widely used to improve cognitive function and memory [55].

Neuro-pharmacological Profile

- Cognitive and memory enhancing Activities [55, 56]

- Neuroprotective Activity ^[57]
- Antiepileptic activity ^[58]
- Antioxidant activity ^[59]
- Anti-inflammatory activity ^[56]

Jadwār (*Delphinium denudatum* Wall.)

Jadwar is a brain and nervine tonic, cardiogenic, general tonic, and tonic for the viscera, stomach, and teeth. It is also noted for its exhilarating, sedative, and anti-inflammatory properties. It is recommended for treating conditions such as paralysis, insanity, epilepsy, migraine, mania, hysteria, and convulsions ^[60].

Neuro-pharmacological Profile

- Neuroprotective Activity ^[61]
- Anticonvulsant Activity ^[62]
- Anxiolytic Activity ^[63]

Polyherbal Unani Formulation (*Khamira Ābresham Hakīm Arshad Wala*)

It consists of *Bombyx mori cocoon*, *Pyrus cydonia*, *Crocus sativus*, *Ambra grasea*, *Corallium rubrum*, *Santalum album*, and *Nardostachys jatamansi*, among others. It serves as a *muqawwī* (tonic) for the heart, brain, and liver and is commonly used to address conditions such as palpitations and the common cold. Scientific validation supports its cardioprotective and nephroprotective properties, highlighting its role in preventing cognitive impairment and neurodegeneration ^[64]. The recommended dose is between 3 to 6 g ^[65].

'Ilāj bi'l Tadbīr (Regimenal therapy)

• **Riyādat (Exercise)**

Physical activity, whether active or passive, boosts physical fitness and overall health by enhancing blood circulation and improving the exchange of air and nutrients. Moderate exercise strengthens the immune system and effectively aids in the elimination of waste materials from the body. It increases *Ḥarārat Gharīziyya* and enhances the *Quwwat Dāfi'a* (expulsive faculty). However, intense exercise should be avoided as it can increase oxidative stress and produce *Ḥarārat Gharība* ^[66]. This is supported by biomolecular research, which shows that inflammation biomarkers, such as C-reactive proteins, are lower in active individuals compared to those who are sedentary.

• **Al-Nawm wa'l Yaqza (sleep and wakefulness)**

Sleep is one of the *Asbāb Sitta Darūriyya* (six essential factors) in Unani. Awakening is believed to lead to dryness because continuous use of the senses or physical activity increases metabolism, which produces more heat and dryness. Conversely, sleep restores *Ruṭūbāt* (moisture) and allows the body to heal and maintain chemical balance. Chronic sleep deprivation impairs mental function, diminishes quality of life, and increases health risks. Adequate sleep is essential for maintaining physical and mental health and reducing *Ihtirāq* ^[67, 68].

• **Dalk (Massage)**

The Unani system of medicine places significant importance on *Dalk* for treating and preventing various ailments. Renowned Unani physicians widely recommend *Dalk* for both curative and preventive purposes. *Ibn Sīnā* described *Dalk* as a means to eliminate residual fluid (*Ruṭūbāt*) after purgation, dissolve gaseous waste (*Riyāḥ*), counteract cold

temperament, and divert morbid matter (*Imāla*). Using oil in *Dalk* helps retain moisture (*Tarṭīb*) and alleviates pain⁶⁶. Recent research has found that massage can reduce neuromuscular excitability, as evidenced by changes in Hoffman's reflex amplitude ^[69].

• **Ḥammām (Turkish bath)**

Ḥammām, one of the oldest Unani treatments, involves a series of rooms with varying temperatures, each tailored to the patient's needs. The shower in a *Ḥammām* helps retain moisture (*Tarṭīb*) and keep the body hydrated, while the water pressure acts as a gentle massage to relieve muscle knots. *Ḥammām* therapy enhances blood circulation, stimulates *Ḥarārat Gharīziyya*, helps expel morbid matter through the skin, reduces humor viscosity, boosts immunity, and improves metabolism. It is particularly effective for conditions such as obesity, paralysis, muscular wasting, cold congestion, stress, and depression ^[66].

Discussion

ASD is a lifelong neurological condition affecting social interaction, communication, and behavior. Conventional treatments like antipsychotics and antidepressants can have significant side effects. Unani Medicine provides a holistic approach through Regimenal therapy, diet therapy, and pharmacotherapy. Unani drugs such as *Emblica officinalis*, *Prunus amygdalus*, *Centella asiatica*, and *Delphinium denudatum* offer a promising alternative with fewer adverse effects. These herbs have neuroprotective properties that may reduce oxidative stress and inflammation and improve cognitive function. Integrating Unani medicine with traditional treatments could provide a holistic approach to managing ASD symptoms.

Conflict of Interest: None

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