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Research Article

EVIDENCE BASED APPROACH FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE IN UNANI MEDICINE

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia in older adults and an important public health problem. There is progressive brain cell death that happens over a course of time. Due to the progressive aging of the population, Alzheimer's disease (AD) is becoming a healthcare burden of epidemic proportions for which there is currently no cure. In Unani System of Medicine, there is no direct description of any such disease but Alzheimer's disease is always associated with *Nisyan* or *Fasad-e-takhayyul*. In this paper, an attempt has been made to collect evidence based approach for the management of AD through Unani System of Medicine.

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INTRODUCTION

Alzheimer's disease is an irreversible, progressive neurodegenerative disease that slowly destroys memory and thinking skills, and, eventually, the ability to carry out the simplest tasks. It is the common cause of dementia among older adults. There is progressive brain cell death that happens over a course of time. There occurs gradual memory loss, as well as loss of judgment, trouble in concentrating, loss of language skills, inability to do routine work, difficulty in communication, confusion, frustration, as well as personality and behavioral changes, and may also develop psychological symptoms such as depression, aggression and wandering. In advanced stages, people with Alzheimer disease may lose all memory and mental abilities. Dementia is not a specific disease. It's an overall term that describes a group of symptoms. Near about 50 million peoples are having Alzheimer's disease and other form of dementia worldwide.¹ According to World Alzheimer's Report 2015, global prevalence of dementia rose from 30 million (2010) to 46.8 million and global expenditure on dementia rose from US\$ 604 million (2010) to US\$ 818 million (2015). In India, the prevalence of dementia was 33.6 in every 1,000 people of which 54% were cases of AD.²

In Unani system of medicine, there is no direct description of any such disease but it can be understood under the heading of

Nisyan (forgetfulness/dementia) and *Humq* (dementia) and *Fasad al-Zehan*. As some ancient Unani physicians discussed the symptoms of dementia under the heading of *Nisyan*³, *Zarar al-Quwa al-Salas of Quwa nafsaniyya* (i.e. impairment of three mental faculties -*Quwwat-i Hafiza /Zakira*, *Quwwat-i Fikr*, *Quwwat-i Takhayyul*⁵, *Fasad-i Fikr* (disturbance in cogitation), *Fasad-i Zikr* (disturbance in memory) and *Fasad-i Takhayyul* (disturbance in imagination)^{6,7} and *Nisyan/Humq*.^{8,9} *Nisyan* (forgetfulness, Faramoshi) is defined as the deficit due to impairment /disturbance in the functions of *Quwwat-i Hafiza/Zakira* (faculty of memory) alone⁷ or with impairment of *Quwwat-e-fikr* (faculty of thought) and *Quwwat-e-Takhayyul* (faculty of imagination).^{3,7,8} The impairment in these powers lead to loss of memory, thinking and imagination processes⁴ and *Humq* (dementia) defined as a disease in which loss of brain functions (distraction of mind) occurs due to weakness or impairment in first two faculties of brain with or without involvement of faculty of imagination.^{5,6}

Asbab (Causes)

The causes of dementia are not well understood in modern science. However, the most common cause of dementia is that brain cell degenerates because of build-up of abnormal proteins in the brain which leads to decline in mental as well as physical abilities of a person.

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As per the Unani medical concept, the human body is composed of four *Akhlat* (humours) i.e. *Dam* (Phlegm), *Balgham* (Phlegm), *Safra* (bile) and *Sawda* (black bile) and every human has particular temperament. Balance in the *Akhlat* (humours) in terms of quality and quantity is necessary for the health of an individual. Any deviation of the body temperament and imbalance in any one of the four humors lead to disease.

- Decrease in *Jawhar-i Dimagh* (brain matter or tissue) especially in old age.
- *Su-i Mizaj Barid Sazij* (simple morbid cold temperament).
- Accumulation of viscid *Balgham* (phlegm) and moistness in the brain.^{4,10}
- Excess of dryness (*yabusat*)³
- Due to head injury.⁹
- Due to *Zof-i Dimagh* (weakness of memory)⁸

Alamaat (Clinical Features)^{7,8,10}

- Decline in thinking skills.
- Ability to perform routine activities, social abilities, mood alteration and loss of memory.^{8,9}
- Profound forgetfulness (does not recognize his friends and relatives, his name etc).³
- Inability to deliver proper word or sentence.
- Irrelevant movements and hallucination.
- Inability in planning and performing complex tasks.^{5,6,8}

Due to predominance of Barudat (coldness)

- Patient feels comfortable with the heat producing measures.
- Light headiness
- Profound decrease in sensory and motor functions and other mental functions also.^{4,7}

Due to predominance of Balgham (phlegm)

- Heaviness in head (particularly in occipital region)
- laziness, excessive sleep and nasal discharge.^{3,4,7}
- Patient remains busy in doing irrelevant tasks/chores similar to children.⁸

Due to predominance of Burudat (coldness) and Yabusat (dryness)

- Forgetfulness.
- Lack of sleep.
- Dry nostrils and skin, difficulty in talking.
- Choking is also present.⁷
- Apprehension and anxiety with dementia.^{3,6,8}

Adviya Mufreda (Single drugs) used in Unani System of Medicine

1. *Asgand (Withania Somnifera* Linn.)¹¹: It is *Muqawwi hafiza* (memory enhancer) and useful in *Nisyan* (dementia).
2. *Kundur (Boswellia serrata* Roxb.)^{3,4} Oral administration of *Kundur* enhances memory and sharpens intelligence.⁴
3. *Lawz /Badam (Prunus amygdalus* Batsch)⁴ It is beneficial for *Jawhar-i Dimagh* (protects degenerative changes).

4. *Jundbedastar (Castoreum)*
5. *Akhrot (Juglans regia)*
6. *Waj (Acorus calamus* Linn.)^{3,11}
7. *Brahmi (Bacopa monnieri* Linn.): It removes morbid phlegm, enhances memory, strengthens brain and nerves, increases intelligence.¹⁴
8. *Halela Siyah (Terminalia chebula* Ritz.): It delays ageing, enhances memory and intelligence and strengthens senses, and is useful in *Nisyan* (forgetfulness).^{4,11}
9. *Zanjabeel (Zingiber officinale* Roscoe)⁴: It improves memory.
10. *Saad (Cyperus rotundus* Linn)⁴: It improves memory and increase intellects.

Compound Formulations

- *Itrifal Ustukhudus* - 5-10 gm.⁸
- *Majoon Falasfa* - 5-10 gm^{8,12}
- *Majoon Hafiz al-Aql*- 9 gm^{8,12}
- *Majoon Labub*- 4.5 gm^{8,12}
- *Majoon Waj* - 4.5 gm along with *Arq Badiyan*^{8,12}
- *Murabba Halela*- 1 piece daily^{8,12}
- *Murabba Waj* - 1piece daily⁸
- *Dawa al-Misk*⁸
- *Mufarreh Abresham* -4.5 gm daily⁸
- *Mufarreh Halaylaji*- 4.5- 9gm⁸

Evidence based research on Single drugs / Compound formulations

Riyazat-e-Khafeefa

Efficacy of *Riyazat-e-Khafeefa* (20 to 30 minutes of brisk walking (Speed 4 Km/ hrs) in the management of *Nisyan* was evaluated in 20 patients randomly assigned into two groups. Group I, advised brisk walking daily for 30 minutes and Group II received Placebo. At the end of six months memory improvement in Group I compared to Group II was assessed. The results showed that *Riyazat-e-Khafeefa* or brisk walking is useful in *Nisyan*.¹³

Brahmi (Bacopa monnieri)

- In a study, administration of extract of *Brahmi (Bacopa monnieri)* was seen to protect the cholinergic neurons and reduce anticholinesterase activity comparable to donepezil, rivastigmine, and galantamine. It also reduces hippocampal β -amyloid deposition and stress-induced hippocampal damage. Results showed *Brahmi* as a promising agent in AD and other forms of cognitive impairment.¹⁴
- Extract of *Brahmi (Bacopa monnieri)* (EBm) administration resulted in significant chelation of iron in an incubated substrate which demonstrates another mechanism for anti-Alzheimer's Disease activity of EBm.¹⁵
- In a research study, choline acetyltransferase (ChAT) expression in hippocampus of olfactory bulbectomized (OBX) mice was compared with sham-operated control mice. OBX reduced cholinergic activity and hence also ChAT in hippocampus. Subsequent administration of EBm and tacrine to the substrate, however, reversed this effect showing amelioration OBX-induced cognition

dysfunction. The above experiment demonstrated that daily administration of EBm protected the cholinergic neurons in the medial septal nucleus that projects into hippocampus.¹⁶

- A study on rat model of AD demonstrated the inhibition of degeneration of cholinergic neurons on administration of alcoholic EBm which suggests that *Brahmi* could be a potential drug for treatment of AD.¹⁷
- A research conducted on elderly people in the year 2012 demonstrated that *Bacopa monnieri* suppresses AChE activity resulting in enhanced cholinergic function, which in turn enhances attention and memory processing and increases working memory.¹⁸
- In another study, the research was done on children where a 12 week *Brahmi* treatment revealed significant benefits with improvement in sentence repetition, logical memory, and paired associate learning tasks.¹⁹

Asgand (*Withania somnifera*)

- In a study, computational tools were used to determine the bioactive compounds of (*Withania somnifera*) against AD. The ligands (anaferine, anahygrine, cuscohygrine, and isaopelletierine) of WS were found to be neurologically active as agonists at the neuronal nicotinic acetylcholine receptors (nAChR).²⁰
- In another study, *Wistar* albino rats were given 200mg/kg dose of protein extracts of Asgand (*Withania somnifera*) orally along with scopolamine (i.p) for 14 days. Rats were subjected to elevate plus maze and passive avoidance testing on 14th day to evaluate learning. Same models were repeated on 15th day to evaluate retention (memory). The results were compared with the negative control group treated with scopolamine only and positive control group treated with scopolamine and piracetam. Significant learning and memory enhancement was observed with the *protein extract* of *Withania somnifera* as compared to negative and positive control groups with p value <0.05.²¹
- In another study, experiments were performed on four groups of young adult female rats: Low fat diet (LFD) rats fed on regular low fat chow, High fat diet (HFD) rats on feed containing 30% fat by weight, low fat diet extract (LFDE) rats given regular chow and dry leaf powder of Ashwagandha 1 mg/g of body weight (ASH) and high fat diet extract (HFDE) rats fed on diet containing high fat and dry leaf powder of ASH. All the rats were kept on their respective diet regimen for 12 weeks. ASH treated rats showed significant improvement in their working memory and locomotor coordination during behavioral studies as compared to HFD rats.²²

Sumbul-ut-teeb (*Nardostachys jatamansi*)

- In a study, *Nardostachys jatamansi* exhibited memory retention and learning enhancing abilities in aged and young mice and reversed scopolamine and diazepam induced amnesia. In another study conducted by Joshi and Parle, 2006; *Nardostachys jatamansi* reversed aging induced amnesia.²³

- In another study, efficacy of *Nardostachys jatamansi* was reported in the prevention of stress induced memory deficit.²⁴

Dhaniya (*Coriandrum sativum*)

In a study conducted, *Coriandrum sativum* was given for 45 days for its efficacy on cognitive function in male *Wistar* rats. The study was conducted in comparison with aging, scopolamine and diazepam induced amnesia. It was concluded that *Coriandrum sativum* exhibited memory enhancing effects due to its antioxidant, anti-inflammatory and cholesterol lowering activities.²⁵

Brahmi (*Centella asiatica*)

- A study was conducted which reported that treatment with *Centella asiatica* (Linn) fresh leaf extract enhanced learning ability and memory retention power in *Wistar* rats. Adult rats of 2.5 months old were selected for this study. Three different doses (2, 4, and 6 mg/kg) of extracts were administered for 2, 4, and 6 weeks. Spatial learning (T-maze) and passive avoidance tests were performed after the treatment period. Results were compared with those of age matched control rats. Improvement in spatial learning was significant at the dose of 6 mL of extract. The use of *Centella asiatica* extract enhanced memory retention that was evident from passive avoidance test. This data showed that *Centella asiatica* enhances learning ability and memory retention power in adult rats.²⁶
- In another study conducted, the efficacy of *Centella asiatica* in AD was reported. *Aqueous* extract of *Centella asiatica* (100, 200 and 300 mg/kg) was administered for 21 days in streptozotocin (STZ)-induced cognitive impairment and oxidative stress in rats. STZ at 3 mg/kg was intracerebroventricularly injected into male *Wistar* rats bilaterally on days 1 and 3. Cognitive behavior was assessed after 13, 14 and 21 days of treatment. Rats were sacrificed for assessment of oxidative stress after 21 days of treatment. Cognitive behaviors of rats treated with *Centella asiatica* extract improved significantly. The maximum response was observed after administration of extract at the doses of 200 and 300 mg/kg.²⁷

Malkangni (*Celastrus paniculatus*)

- In a study conducted, it was found that Malkangni (*Celastrus paniculatus*) increases cholinergic activity which contributes its ability in improving memory performance.²⁸
- In another study conducted, *aqueous extract* of Malkangni (*Celastrus paniculatus*) has antioxidant and cognition enhancing properties.²⁹

Gugul (*Commiphora whighitti*)

In a study, memory enhancing and anti-dementia activity of Gugul (*Commiphora whighitti*) has been reported that is due to reduction in acetylcholinesterase contents in the hippocampus.³⁰

Asl us soos (Glycyrrhiza glabra)

- In a study conducted, memory enhancing activity of *Asl us soos (Glycyrrhiza glabra)* was reported in scopolamine induced dementia.³¹
- In another study conducted, it reported the memory enhancing activity of *Glycyrrhiza glabra* in mice. Three dose levels (75, 150, 300 mg/kg, p.o.) of *Glycyrrhiza glabra* extracts were administered to mice in 7 successive days. *Glycyrrhiza glabra* at 150 mg/kg was found effective in memory enhancement.³²

Amla (Emblica officinalis)

- In a study conducted, *Amla* exhibited significant improvement in memory retention of young and aged rats in a dose-dependent manner. It reversed the diazepam and scopolamine induced amnesia. As a memory enhancer and reversal of memory deficits, *Emblica officinalis* plays an important role in the treatment of memory deficits and AD.³³
- A study was conducted to investigate the memory enhancing effect of piracetam when used together with *Emblica officinalis* and *Curcuma longa* against aluminium-induced cognitive dysfunction and oxidative damage in rats. Aluminium chloride at 100 mg/kg was given orally to rats for 6 weeks. *Emblica officinalis* (100 mg/kg, p.o.), Curcumin (100 mg/kg, p.o.) and piracetam (200 mg/kg, i.p.) were concomitantly administered to rats daily for 6 weeks. Oxidative stress was significantly reduced and memory was significantly improved in rats treated with *Emblica officinalis* (100 mg/kg, p.o.), Curcumin (100 mg/kg, p.o.) and piracetam (200 mg/kg, i.p.) than the rats treated only with piracetam (200 mg/kg, i.p.).³⁴

Zanjbeel (Zingiber officinale)

- According to a study conducted, it improves memory impairment induced by scopolamine via inhibition of acetylcholinesterase activity.³⁵ As a booster of antioxidant and a reducer of free radical, *Zingiber officinale* plays an important role in the treatment of AD and memory deficits.³⁶
- In another study, male rats (250-300 g) were divided into treatment and control groups. The treatment group was further divided into three subgroups. Plant mixed in food at a ratio of 6.25% was administered in the first group. Plant extract at 50 mg/kg and 100 mg/kg (intraperitoneal) was administered to the second and third subgroups, respectively. Significant improving effects on recall, retention and acquisition were observed in male rats after intraperitoneal and oral administration of *Zingiber officinale*.³⁷
- Considering this the influence
- of Unani Polyherbal Formulation (UPF) was investigated for its
- nootropic activity. To investigate nootropic activity of the UPF
- various experimental paradigms of learning and memory were used
- including transfer latency (TL) on elevated plus-maze, spatial

- memory evaluation using radial arm maze, passive avoidance
- response (PAS) and object recognition test. Mice were divided in
- four groups viz control i.e vehicle treated, UPF 200 mg/kg, UPF
- 400 mg/kg and piracetam 150 mg/kg as standard. The investigation
- reported that UPF 200 and 400 mg/kg significantly reduced the
- TL on 2nd and 9th day and significantly increased the step down
- latency in the PAS at acquisition and retention test.

Unani Polyherbal Formulation (UPF)

In a study conducted, the influence of Unani Polyherbal Formulation (UPF) was investigated for its nootropic activity. Its main ingredients were: *Emblica officinalis* 100 g, *Delphinium denudatum* Wall 10 g, *Phoenix dactylifera* 10 g, *Prunus amygdalus* Batsch 10 g, *Benincasa hispida* 10g, *Trapa bispinosa* 10g, *Centella asiatica* 5g, *Paeonia officinalis* 2g, *Evolvulus alsinoides* 2g, *Pistacia lentiscus* 2g, *Sphaeranthus indicus* 2g and rose water. Various experimental paradigms of learning and memory were used including transfer latency (TL) on elevated plus-maze, spatial memory evaluation using radial arm maze, passive avoidance response (PAS) and object recognition test. Mice were divided in four groups viz control i.e vehicle treated, UPF 200 mg/kg, UPF 400 mg/kg and piracetam 150 mg/kg as standard. The study concluded that UPF showed significant effect on spatial learning and memory behavior as well as aversion induced learning and memory behavior. The attenuation of scopolamine induced memory disruption suggested possible use of drug against neurodegenerative disorder like Alzheimer's disease.³⁸

Zard Chob (Curcuma longa)

- In Alzheimer's disease, it has been shown that curcumin has the ability to bind A β peptides, prevent aggregation of new amyloid deposits and promote disaggregation of existing amyloid deposits.³⁹
- Scientific studies also reported that curcumin and its analogues demethoxycurcumin and bis-demethoxycurcumin can protect cells from A β -induced oxidative stress.⁴⁰
- Curcumin has the ability to inhibit A β oligomerization and fibril formation, enhance A β uptake by macrophages and inhibits the peroxidase activity of A beta-heme complex.⁴¹

Gilo (Tinospora cordifolia)

- It was concluded that *Gilo (Tinospora cordifolia)* possesses a memory improving effect in animals with memory deficits.⁴²
- The mechanism by which *Tinospora cordifolia* improves memory is the synthesis of acetylcholine and immunostimulation.⁴³
- Administration of *Tinospora cordifolia* increases the cognitive function in patients with AD.³⁰

Kundur (*Boswellia serrata*)

- A preclinical study reported that in rat models during gestation period when an aqueous extract of *B. serrata* given orally it exhibited that there is a significant increase in the power of learning at the post-learning stage, short-term memory, and long-term memory in their births⁴⁴.
- It is reported that when hypothyroidism was by *methimazole* in adult male Wistar rats, it leads to a significant decline in learning and memory but when kundur used for their treat it was found that enhancing memory and learning functions⁴⁵.
- In a study conducted, it was revealed that the treatment of Alzheimer's disease induced rats with *aqueous* infusions of *B. serrata* at the dose of 45 and 90 mg/kg/day for 12 successive weeks significantly ameliorates the neurodegenerative characteristics in rats.⁴⁶

CONCLUSION

Alzheimer's disease is the most frequently observed form of dementia, and it typically develops in elderly patients. In modern medicine, there is no proper treatment for this disease but in Unani System of Medicine, a number of Drugs eg. Brahmi, Asl us Soos, Asgand etc. have shown activities which can help to improve the cognitive impairment. Advance comprehensive studies are needed to make clear the exact mechanism of these drugs so that it can be beneficial for the human kind.

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