Review Article

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# An overview on multi-ingredient memory enhancers and Anti-Alzheimer's formulations from Traditional Persian Pharmacy

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## Abstract

Dementia and Alzheimer's, the common cause of this syndrome, have been given special considerations to be managed by natural medicaments. Parallel to conventional medications for dementia and Alzheimer, there are various remedies in pharmaceutical manuscripts of Persian medicine. This review provides various compound formulations to manage and control the sign, symptoms and complications of memory loss, Alzheimer's and allied disorders. These remedies have been cited in a series of traditional pharmaceutical manuscripts of Persian medicine, namely *Qarābādin* or prescription. With a view to the positive pharmacological or biological activities of the constituents of filtered formulations, many of those can be reformulated, and either experimentally or clinically evaluated in order to be introduced as new natural remedies in this field.

*Keywords:* Alzheimer, Formulation, Dementia, Persia, Traditional Medicine.

## 1. Introduction

There is an increasing demand to manage and control of various diseases with natural medicines (1). Among various neurological disorders, dementia and Alzheimer's, the common cause of this syndrome, have also been given special considerations for respective drug discovery (2). In regard of the complexity of this disorder, many research on the effectiveness of numerous candidate medicaments has failed to represent a promising outcome (3).

Although different neuronal factors are included in the pathogenesis of Alzheimer's disease, inflammatory reactions, immunological aspects and oxidative stress are of underlying mechanisms of this disorder (4, 5). In addition, Cholinesterase and N-methyl-D-aspartate (NMDA) receptor are considered as main or considerable reasons for the incidence of Alzheimer (6).

In association with conventional treatment lines for dementia and Alzheimer, there are various complementary and alternative medicaments from famous systems of traditional medicines (2). Traditional Persian Medicine (TPM) is one of those complementary systems of medicine with numerous pharmacological and pharmaceutical aspects (7).

Based on clinical information in TPM textbooks, Alzheimer's disease may be defined under

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the term, *Nesyān* or loss in memory (8). Under the chapter, "*Nesyān*", these are numerous mono and multi-ingredient medicines in various medical and pharmaceutical textbooks of TPM (2). Previously, some studies have focused on the terminology of memory loss, dementia, Alzheimer and respective mono-ingredient or simple medicines from standpoints of TPM scholars (2, 8, 9). However, a large section of those medications is based on the application of various related compound preparations as pharmaceutical dosage forms, known as an art in pharmaceutical sciences (10).

Accordingly, current study aimed to filter and introduce some of most prevalent multi-ingredient preparations have been traditionally applied for the management of *Nesyān* in TPM.

## 2. Material and methods

Six of most important *Qarābādin* textbooks of TPM as well as second and fifth volumes of the book, Canon of Medicine (in Persian) have been studied in this essay. These books are known as encyclopedias included a list of multi-ingredient preparations containing mineral, animal and herbal materials with pharmaceutical and medical applications (11). Searching keywords were "*Nesyān*" (Loss in memory), "*Hefz*" and "*Hāfezeh*" (memory) as well as "Farāmushkāri" (forgetfulness). Each of those preparations have been reported as a specific dosage form based on the administration route (12).

Table 1 briefly represented the information on *Qarābādin* textbooks which have been considered and studied. In this review, a list of those filtered preparations has been selected based on the number of ingredients (≤6). Moreover, formulations which have only been reported in one *Qarābādin* were excluded unless there were promising data on the ingredients in current medicine. Furthermore, formulations which had some ingredients mentioned in Urdu language and also those focusing on unsafe minerals such as lead and mercury or specific parts of animal were excluded.

## 3. Results and discussion

Amnesia which is generally defined as a deficit in memory is a well-known disorder. It may be resulted from various complications and conditions such as brain diseases or damages as well as consumption of certain medicaments (19).

Early Persian physicians used "*Nesyān*" in case of forgetfulness and discussed the ethological points. But the definition was not just limited to what is accepted as forgetfulness. They categorized the term in to *Fesād-e-zekr* (deterioration in memory), *Fesād-e-fekr* (deterioration in thought) and *Fesād-e-khial* (deterioration in imagination). These conditions were reported to be occurred in different cases namely deficit, loss and confusion of concerned function. In conditions of *Fesād-e-zekr*, patients may have no complications in mental functions or even in respective anatomical sec-

Table 1. Employed textbooks and respective information.

| Book (in Persian) | Author/ Date | Information | Citation |
|---|---|---|---|
| *Qarābādin-e-kabir* | Aghili Shirazi/ 1772 AD | An encyclopedia with sections on pharmaceutical practice and dosage forms alphabetically categorized based on a main component | (13) |
| *Qarābādin-e-Salehi* | Ghaeni Heravi/ 1765 AD | A pharmacopeia with over 200 types of dosage forms and related clinical and pharmaceutical descriptions | (14) |
| *Qarābādin-e-Ghāderi* | Ahmad-shah Arzani/ 1714 AD | A pharmaceutical textbook introducing various dosage forms based on diseases differentiated from head to toe | (15) |
| *Qarābādin-e-azam* | Hakim Azam Khān/ 1853 AD | Dosage forms are written alphabetically in addition to the author's and other scholars' experiences | (16) |
| *Tuhfat-ul-Momineen* | Daylamī Tonkaboni/ 1670 AD | A pharmacopeia of 763 simple herbal, animal and mineral drugs with a large chapter compound remedies | (17) |
| *Canon of medicine* | Avicenna/ 1025 AD | Second and last of a collection of five volumes which including various prescriptions and procedures | (18) |

tions. In return, patients may forget what have been heard or seen. On the other hand, *Fesād-e-fekr* was mentioned as the debility or loss of patterns related to thoughts, feelings and activities as well as cognition. In this case, quality of life may be affected and institutionalization or care giving might be needed. *Fesād-e-fekr* may also cause impairment of daily activities and loss of goal. Patient may do wrong or inappropriate things. The term, *Fesād-e-khiāl* was remarked as a deficit or loss in the ability of environment imagination. In this case, the patient mentions that he or she cannot remember the sleep dreams. In higher levels of this complication, hallucination and delirium may also be added to this condition. Hence, the patient may visualize unreal things and think the way something could be but isn't. Additionally, he/she cannot remember the geometry of objects. In this case confusion of imagination is occurred (20, 21).

According to these descriptions, Alzheimer's disease has a close similarity to what is known "*Nesyān*" in TPM and is related to those three conditions which have been mentioned.

By searching through these resources, nearly 130 formulation have been extracted. In detail, 56 of those remedies in line with the criteria (study method) were extracted from *Qarābādin-e-kabir*. Also, 24, 17, 16, 10 and 4 multi-ingredient formulations have been derived from *Qarābādin-e-Ghāderi*, *Qarābādin-e-Salehi*, *Qarābādin-e-azam*, *Tuhfat-ul-Momineen*, and *Canon of medicine*, respectively. Table 2 is related to these remedies and addresses the names, ingredients and considerations or points of preparations of a selection of filtered formulations. It is notable that these formulations are cited along with their specific or related dosage forms in traditional pharmacy (11). Most of the remedies, as cited, have been administered orally in type of solid or liquid dosage forms. Interestingly, nasal route of administration was also noted for a part of those formulations. This facts reveals that early Persian physicians have noticed that a short way to ameliorate or control the central nervous system diseases is nasal delivery (22).

Various biomedical pathways such as defective beta-amyloid metabolism, disordered cholinergic neurotransmission and inflammatory and oxidative processes are involved in the pathophysiology of Alzheimer's (2, 23). Some scientist have remarked that presence of β-amyloid peptide brain plaques is the main mechanism for Alzheimer (23). However, inflammatory reactions and neuro-inflammation of brain would lead to release of inflammatory cytokines and free radical attack which can deeply affect the condition (4, 24). In addition, oxidative stress is another item that would contribute to the progression and initiation of dementia and Alzheimer (5). It is also well accepted that enhancing the level of acetylcholine in brain with acetyl cholinesterase inhibitory activity-targeted medicaments is highly effective in the alleviation of Alzheimer. Apart from cholinergic hypothesis, butyryl cholinesterase, with minor role in the regulation of brain acetylcholine is also remarked effective in patients with Alzheimer's disease (25, 26).

To manage Alzheimer, medications with various target of actions or multi-target approach should be considered. Application of multi-ingredient formulations from traditional systems of medicine can have such multi-mechanisms of action (2, 27).

Although there is no evidences on the activity or effectiveness of these multi-ingredient formulation in management of Alzheimer, however, many of those ingredients could possess one or more activities as mentioned. Most of these medicaments have shown potent antioxidant activities and also anti-inflammatory effect. In addition, exerting acetyl or butyryl choline esterase activities have been reported from some of the ingredients. *Zingiber officinale* Roscoe which is present is many of *Qarābādin* formulations have exerted cholinesterase inhibition, anti-amyloidogenic, antioxidant and anti-inflammatory effects (28-30). These properties have also been reported for *Allium sativum* L. in previous studies (31-34). *Acorus calamus* L. have shown effectiveness via cholinesterase inhibition, anti-oxidation and anti-inflammation processes (35-37). These three properties have been also reported for *Piper nigrum* L., *Terminalia chebula* Retz. and *Peganum harmala* L. (2). Accordingly, aggregation of these constituents in a compound formulation can possess positive effects on management of memory loss

Table 2. Selected compound formulations for management of "*Nesyān*".

| No | Name (dosage form) | Ingredients (Proportion) | Ref. |
|---|---|---|---|
| 1 | *Safoof* for memory (oral powder) | *Piper nigrum* L. (1), *Bunium persicum* (Boiss.) B.Fedtsch. (1), Sugar (3) | (18) |
| 2 | *Safoof* for memory (oral powder) | *Piper nigrum* L. (1), *Boswellia* spp. (3) | (18) |
| 3 | *Majoon* (Confection) | *Bunium persicum* (Boiss.) B.Fedtsch. (1), *Piper longum* L. (1), *Boswellia* spp. (1), Honey (6) | (15) |
| 4 | *Saoot* (Nasal drop) | *Dysphania botrys* (L.) Mosyakin & Clemants (1), *Myristica fragrans* Houtt. (1) (Fruit), *Syzygium aromaticum* (L.) Merr. & L.M.Perry (1), *Origanum majorana* L. (1), *Myristica fragrans* Houtt. (4) (Fruit outer peel), and *O. majorana* fresh juice | (15) |
| 5 | *Sharbat-e-reyhāni* (Syrup)/ Prepared after 6 month (Oral) | Grape juice (300000), Sugar (1800), *Cinnamomum verum* J.Presl (4), *Myristica fragrans* Houtt. (4) (Fruit), *Syzygium aromaticum* (L.) Merr. & L.M.Perry (4), *Myristica fragrans* Houtt. (4) (Fruit outer peel) | (15) |
| 6 | *Majoon-e-Labān* (Oral) | *Boswellia* spp. (10), *Acorus calamus* L. (10), *Cyperus rotundus* L. (10), *Piper nigrum* L. (5), *Zingiber officinale* Roscoe (5), Honey (80) | (15) |
| 7 | Syrup of Esfand (Oral) | *Peganum harmala* L.(1) in grape juice (30) | (17) |
| 8 | *Majoon-e-soom* | *Allium sativum* L. (1) boiled in milk (1.5), mixed with honey (1.5) | (17) |
| 9 | *Shamoom* (Inhale) | *Myristica fragrans* Houtt. (1) (Fruit), *Syzygium aromaticum* (L.) Merr. & L.M.Perry (1), *Myristica fragrans* Houtt. (4) (Fruit outer peel), *Origanum majorana* L. (1), *Artemisia* spp. (1), mixed with apple juice | (13) |
| 10 | *Majoon-e-Kondor* (Frankincense confection)-1 | *Cyperus rotundus* L. (2), *Piper nigrum* L. (2), *Crocus sativus* L. (2), *Commiphora myrrha* (Nees) Engl. (2), *Pistacia vera* L. (5), *Zante currant* (5), Honey (36) | (13) |
| 11 | *Majoon-e-Kondor* (Frankincense confection)-2 | *Boswellia* spp. (10), *Acorus calamus* L. (10), *Cyperus rotundus* L. (10), *Piper nigrum* L. (5), *Alpinia officinarum* Hance (3), *Cinnamomum verum* J.Presl (3), Honey (123) | (14) |
| 12 | *Safoof-e-nesyān* (Oral powder) | *Piper longum* L. (1), *Boswellia* spp. (7), *Pistacia lentiscus* L. (4), *Cinnamomum verum* J.Presl (1), *Echium amoenum* Fisch. & C.A.Mey. (3), *Melissa officinalis* L. Presl (1), *Physalis alkekengi* L. (1), Sugar | (15) |
| 13 | *Safoof-e-nesyān* (Oral powder) | *Boswellia* spp. (1), *Cyperus rotundus* L. (1), *Piper nigrum* L. (1), *Crocus sativus* L. (1), *Commiphora myrrha* (Nees) Engl. (1) | (16) |
| 14 | *Majoon-e-Hafezeh* (confection) | *Senna alexandrina* Mill. (1), *Cyperus rotundus* L. (1), *Piper nigrum* L. (1), *Crocus sativus* L. (1), *Boswellia* spp. (1), *Alloxylon* spp. (1), Honey (18) | (16) |
| 15 | *Safoof-e-Hefz* (Oral powder) | *Boswellia* spp. (15), *Cyperus rotundus* L. (7), *Cinnamomum verum* J.Presl (7), *Zingiber officinale* Roscoe (15), *Acorus calamus* L. (15), *Syzygium aromaticum* (L.) Merr. & L.M.Perry (7), Sugar candy (198) | (16) |
| 16 | *Matbookh-e-aftimoon* (Decocted oral liquid) | *Cuscuta epithymum* (L.) L. (1), *Nepeta menthoides* Boiss. & Buhse (1), *Fumaria parviflora* Lam. (1), *Terminalia chebula* Retz. (1), *Operculina turpethum* (L.) Silva Manso (1), *Polypodium vulgare* L. (1) | (13) |
| 17 | *Jawarish-e-Shoneez* (Electuary) | *Nigella sativa* L. (1), *Trachyspermum ammi* (L.) Sprague (2), *Terminalia chebula* Retz. (1), *Zingiber officinale* Roscoe (2) | (16) |

and Alzheimer's disease via different underlying mechanisms.

## 4. Conclusion

This study provides various compound formulations to manage and control the signs, symptoms and complications of memory loss, Alzheimer's and allied disorders. These medicines can be reformulated, and either experimentally or clinically evaluated in order to be introduced as new natural remedies in this field

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## Conflict of Interest

None declared.

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