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Review Article

Treatment of dry eye disease in traditional Persian medicine: A narrative review

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Abstract

Background and aims: Dry eye disease (DED) is a globally prevalent disorder due to the loss of homeostasis of the tear film that causes a range of different signs and symptoms. This problem affects visual function and patients' daily activities and damages physical and psychological health and finally the quality of life while it has no definite cure until now. Thus, developing new medicines and formulations is needed. Meanwhile, traditional Persian medicine as an ancient comprehensive school among the world's traditional medicine is a good source of active ingredients and formulations.

Methods: Prescribed herbal medicines and related formulations for DED in traditional Persian medicine references including Exir-e-Azam, Tebb-e-Akbari, Moalejat-e-Aghili, and Makhzan-al-Advieh were investigated and analyzed in comparison with recent therapeutic studies.

Results: Our findings show that traditional Persian medicine scientists relied on mucilage-containing materials like psyllium and quince seeds and unsaturated and polyunsaturated plant oils such as sweet almond oil, pumpkin seed oil, and olive oil as principal components for treating DED.

Conclusion: DED treatment in Persian traditional medicine was based on using mucilages and plant oils mainly as ophthalmic drops to keep moisture and lubricate eyelid movement. Moreover, advised medicines were generally in accordance with modern medicine findings and found to have antioxidant, anti-inflammatory, and immunomodulatory activities that can beneficially modulate pathological mechanisms of dry eye disease.

Keywords: Dry eye disease, Herbal medicine, Mucilage, Persian medicine, Phytotherapy, Plant oil

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Introduction

Dry eye disease (DED) is one of the most common global ocular problems that affect millions of people around the world with a prevalence rate of 5%–50% based on ethnicity, age, and sex which is much more than other globally prevalent diseases like diabetes (9.3% in 2019 and estimated to be 10.2% by 2030) (1,2). DED's prevalence increases with the age and women are affected more considerably. Also, Asian populations are more affected than Europeans and North Americans, which indicates the role of racial and cultural factors in the etiology of DED (1,3). DED patients report a myriad of symptoms that include dryness, irritation, redness, foreign body sensation, itching or burning, photophobia, stringy mucous discharge, eye strain, eye fatigue, heavy eyelids, and pain in addition to blurred vision and poor sleep quality (4,5). As a result of these symptoms, visual function and performance are compromised, leading to difficulties in carrying out daily activities. In addition to physical health, the patient's psychological well-being is also gradually impaired. Limitations in the level of independence and the impact of environmental factors finally lead to low quality of life (5). Meanwhile, the increasing use of new technologies that involve viewing digital screens causes more suffering for the patients and highlights the importance of DED (6).

Based on the definition by Tear Film and Ocular Surface Society International Dry Eye Workshop (TFOS DEWS II) in 2017, DED is "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (7). The loss of homeostasis of the tear film is due to reduced tear production (hypo-secretive DED), excessive tear evaporation (evaporative DED), or both of them (mixed DED). However, increased tear osmolarity causes damage to epithelial cells of conjunctiva, cornea, and goblet cells that secrete tear mucins. Thus, inflammation involves all the ocular surfaces, leading to a vicious cycle that exacerbates the situation causing injury to the nerves that stimulate the lacrimal gland that produces tear film (8). Considering the etiology and severity of DED, treatment approaches are classified into four steps. The first step comprises patient education, food regime adjustment, removing causative environmental factors, and avoiding medicines that lead to a reduction in tear production.

The second step relies on the use of preservative-free artificial tears, lacrimal plugs, moisture, and temperature-preserving devices, intense pulse light therapy, and topical medicines including corticosteroids, cyclosporine, secretagogues, immunomodulators, antibiotics, and lifitegrast. In the third step, autologous/allogenic serum eye drops, oral secretagogues, and therapeutic contact lenses are used. Chronic corticosteroid therapy, amniotic membrane graft, or surgical intervention are utilized in complicated cases as the fourth step (4).

In spite of all the advances in minimizing the causative factors of DED and applying various therapeutic approaches, there is still no definite and complete cure for DED (4). This situation, in addition to the limitations of modern medicines, attracts researchers to develop new drugs. In this regard, traditional medicines provide a rich source to discover new medicines and lead compounds. This study aims to review herbal medicines used for the treatment of symptoms of dry eyes in traditional Persian medicine.

Materials and Methods

First, a literature search using the terminologies for DED in traditional Persian Medicine (Jafaf-ol-ain and Khoshonat-ol-gharniah) was carried out in the reference books including Exir-e-Azam, Tebb-e-Akbari, Moalejat-e-Aghili, and Makhzan-al-Advieh. Herbal medicines used in various forms were noted. Related prescriptions were extracted and their individual ingredients were matched to botanical references for their scientific names. In the next step, English articles published in PubMed, Scopus, and Google Scholar about herbal components of extracted medicinal formulations were searched. Then, the collected articles' content was investigated and relevant data were used for this review.

Results and Discussion

Sweet almond oil

Sweet almond is one of the Rosaceae family plants with the scientific name *Prunus dulcis*, whose nut is known in traditional Persian medicine as "Lowz" or "Badam" (9). The medicinal use of almond nuts dates back to ancient times. In traditional Persian medicine, almond has been used for the treatment of nervous system problems, and respiratory and urinary tract disorders (10). Also, recent pharmacological investigations have reported various biological effects of almond nuts that include anticancer, antianxiety, sedative, antimicrobial, laxative, antioxidant, hepatoprotective, anti-inflammatory, prebiotic, cognitive enhancer, cardio-metabolic protection, and hypnotic (10).

Almond nuts contain several compounds like fatty acids (like oleic acid, linoleic acid, palmitic acid, stearic acids, and arachidic acid), proteins and amino acids (proteins like globulin and albumin, essential amino acids like leucine, phenylalanine, and tyrosine, nonessential amino acids like glutamic acid, arginine, and aspartic acid), minerals (like calcium, copper, iron, magnesium, manganese, potassium, phosphorus, selenium, sodium, and zinc), vitamins (thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate, and vitamin E, principally α-tocopherol), phenolic compounds (like phenolic acids, flavonoids, stilbenes, lignans, hydrolyzable and condensed tannins, and phytoestrogens) and carbohydrates (starch and dietary fibers) (10).

Among these compounds, fat-soluble components make up a bulk of almond oil. Almond oil principally consists of triglycerides of monounsaturated fatty acids (mainly oleic acid [C18:1n-9] 43.30-81.57% and palmitoleic acid [C16:1n-6] 0.18-2.52%), polyunsaturated fatty acids (mainly linoleic acid [C18:2n-6] 6.21-37.13%), and saturated fatty acids (mainly palmitic acid [C16:0] 4.30-15.78%, stearic acid [C18:0] 0.24-10.40%, and trace amounts of arachidic acid [C20:0]), respectively (11). However, in addition to triglycerides that make up most part of almond oil, other lipophilic compounds enter nuts oils and hence tocopherols and tocotrienols (especially α-tocopherol), phytosterols (like β-sitosterol, Δ5-avenasterol, campesterol, Δ5, 24-stigmastadienol, Δ7-avenasterol, stigmasterol, A7-stigmasterol, and Δ7-campesterol), and squalene are also present in the oil (11).

In traditional Persian medicine, sweet almond oil has been advised for the treatment of eye dry by dropping oil in the eye (12,13). Considering the composition of almond oil mentioned previously, triglyceride can lubricate the eye and ameliorate dryness and sandy sense. Also, omega-3 and omega-6 fatty acids can decrease inflammation that appears in DED. Vitamin E is another component of almond oil that helps in the reduction of inflammation and suppression of the pathology of DED (11,14,15).

Pumpkin seed oil

Pumpkin with the scientific name *Cucurbita pepo* (Cucurbitaceae) (Kadoo, Yaghtin, and Gharaa in traditional Persian medicine) is a plant whose different parts are used widely around the world from ancient times as food, vegetable, or medicine (16). In different regions, various parts of this plant have been used traditionally for the common cold, bladder and prostate problems, fever, fatigue, thirst-quenching, nausea, gastritis, enteritis, pains, and burns (16). In addition, pumpkin seeds that are known as Tokhme-Kadoo in traditional Persian medicine have been used traditionally as a diuretic, anthelmintic, and taeniacide (17). In traditional Persian medicine, pumpkin seed oil has been prescribed for the treatment of dry eye by dropping directly (12).

Pumpkin seeds are oil-rich seeds that contain a dark greenish red color oil with about 38% of the dry weight yield and are primarily polyunsaturated vegetable oil (16-18). The main ingredients of this oil are polyunsaturated fatty acids (linoleic acid [C18:2n-6] 47.5% and linolenic acid [C18:3n-3] 0.7%), unsaturated fatty acids (oleic acid [C18:1n-9] 25.5%), and saturated fatty acids (palmitic acid [C16:0] 17.6% and stearic acid [C18:0] 7.6%) (19). Squalene, tocopherols (mainly δ-tocopherol), phytosterols

(mainly Δ7-sterols like desmosterol, campesterol, stigmasterol, β-sitosterol, spinasterol), and carotenoids (mainly lutein and zeaxanthin) are the other components of pumpkin seed oil (17). The combination of unsaturated fatty acids, in addition to phytosterols and tocopherols, makes pumpkin seed oil an effective anti-inflammatory traditional remedy that can suppress the inflammation of the eye for the treatment of DED.

Violet flower oil

Banafsaj or Banafsheh is a famous plant that has been used in traditional Persian medicine for the treatment of the common cold, dyspnea, cough, fever, headache, palpitation, insomnia, dysuria, skin diseases, and constipation in Iranian traditional medicine. This plant corresponds with sweet violet (*Viola odorata*, Violaceae) and its biological effects like analgesic, anti-inflammatory, diuretic, antioxidant, antihypertensive, and antibacterial activities have been reported in recent years (20).

In addition to the above-mentioned traditional uses, administrating violet oil in eyes has been prescribed for dry eyes in traditional Persian medicine (12,13,21). Violet oil is traditionally produced by macerating sweet violet petals in olive oil and then filtering olive oil which is then used for medicinal purposes. This method of violet oil preparation corresponds with the old method of essential oil extraction known as enfleurage. In this method, volatile compounds (monoterpenes and sesquiterpenes) of sweet violet flowers are dissolved into olive oil as a fixed oil. Thus, what is applied as violet oil in traditional Persian medicine consists of essential oil of sweet violet flowers and olive fruit extracted fixed oil.

Sweet violet flower essential oil contains about 60 different compounds with anti-inflammatory activity. Among the sweet violet flower essential oil components, linalool (7.33%) is the main anti-inflammatory compound that is responsible for most of the anti-inflammatory activity of violet oil (22,23).

Olive oil is one of the oldest vegetable oils that is mostly extracted from the fruit mesocarp of *Olea europaea* (Oleaceae). From the phytochemical aspect, olive oil is composed of triglycerides of monounsaturated fatty acids (mainly oleic acid [C18:1n-9] 72.77% and palmitoleic acid [C16:1n-7] 1.15%), polyunsaturated fatty acids (linoleic acid [C18:2n-6] 9.47% and linolenic acid [C18:3n-3] 0.60%), and saturated fatty acids (palmitic acid (C16:0) 12.09 and stearic acid (C18:0) 3.01%), respectively. Moreover, squalene, tocopherols (especially α-tocopherol), phytosterols, carotenoids, and a few phenolic compounds make a small component of olive oil (24).

The anti-inflammatory and antioxidant activities of sweet violet oil make it a suitable anti-inflammatory and lubricating agent used for the treatment of dry eye in traditional Persian medicine.

Lettuce seed oil

Lettuce (*Lactuca sativa*, Asteraceae; Kahou and Khas in traditional Persian medicine) is a famous ancient leafy plant around the world which nowadays is mostly used as salad or food (25). In spite of the present prominent culinary use of this plant, it has been historically used in traditional Persian medicine in various health conditions including the dry eye (12). For this purpose, the lettuce seed oil is used as an ophthalmic drop.

Lettuce seed oil contains triglyceride of linoleic acid [C18:2n-6] 49.5%, oleic acid [C18:1n-9] 36.4%, and arachidic acid [C20:0] 35.06% that categorizes it in the polyunsaturated vegetable oils. In addition to fatty acids triglycerides, other anti-inflammatory compounds including tocopherols (mainly α-tocopherol) and phytosterols (mainly β-sitosterol, Δ7-stigmasterol, and campesterol) are found in lettuce seed oil (26). This functional identity demonstrates the anti-inflammatory activity of lettuce seed oil and justifies its use for the treatment of dry eye as a lubricating and anti-inflammatory remedy.

Psyllium mucilage

Psyllium, *Plantago ovata* (Plantaginaceae) is a widely distributed plant that is known as Esfarzeh in the Persian language and Isbaghoul in traditional Persian medicine. In different regions of the world, this plant has been used in traditional medicine for the treatment of pain, wounds, irritable bowel disease, rheumatic disorders, skin irritations, hemorrhoids, constipation, diarrhea, and infectious problems (27,28). In traditional Persian medicine, the mucilage produced in the coat of psyllium seeds is prescribed for ameliorating dry eye (12). For mucilage extraction from psyllium seeds, the seeds are macerated in water for a while and the aqueous extract is subjected to filtration. The filtrate that contains psyllium mucilage is utilized for dry eye by directly dropping it in the eye.

Mucilages are herbal water-soluble fibers that are chemical polymers of carbohydrates. These polysaccharides are clear and colorless and because of the high number of hydroxyls in their structure, they can make gels and show high water-holding capacity. Psyllium mucilage can absorb water 80 times as much as its weight (28,29). Thus, psyllium mucilage can help preserve the water in the eye and ameliorate evaporative DED. Also, psyllium seed husk polysaccharides have antioxidant, immunomodulatory, and anti-inflammatory activities that can additionally help DED patients (30).

Coriander and Love Lies Bleeding

This Persian traditional medicine consists of an aqueous extract of two famous plants, coriander (*Coriandrum sativum*, Apiaceae) and Love Lies Bleeding (*Amaranthus caudatus*, Amaranthaceae). The prepared extract is prescribed for DED patients as an ophthalmic drop (13).

Love Lies Bleeding (Bostan Afrooz and Zinat-o-Riahin in traditional Persian medicine, Taj Khoroos in the Persian language) contains various phytochemicals like

phenolic acids, carotenoids, flavonoids, unsaturated fatty acids, betalains and triterpenes that have antioxidant and anti-inflammatory activities (31).

Another ingredient of this medicinal formulation, Coriander (Geshniz and Kozboreh in traditional Persian medicine) is famous for its traditional culinary and medicinal uses as one of the earliest used plant species. In different regions of the world, it has been consumed for gastrointestinal disorders (like flatulence, dysentery, diarrhea, and vomiting), respiratory diseases, and urinary complaints (32). In addition to DED, coriander has been prescribed for the treatment of some other ophthalmic diseases like blepharitis and conjunctivitis (33). For the treatment of DED, aerial parts of coriander have been prescribed that contain a variety of secondary metabolites including phenolic acid, coumarins, flavonoids, carotenoids, tocopherols, and phytosterols that have significant free radical scavenging and anti-inflammatory activities (32).

This combination of phytochemicals in this traditional medicinal remedy can reduce inflammations in dry eyes and also help patients' overall well-being.

Barley poultice

Barley (Jo and Shaieer in Persian and traditional Persian medicine) is a member of the cereals family (*Hordeum vulgare*, Poaceae) that has been used by humans from ancient times as a source of energy-giving food. In traditional Persian medicine, a poultice of barley flour and goat milk is applied to the eyelid for the treatment of DED (13).

In addition to the usual carbohydrates (starch and dietary fibers), proteins, lipids, vitamins, and minerals that are found in barley grains, several other natural products have been isolated from barley grains. These compounds include flavonoids, tocopherols, lignans, phytosterols, and folates that contribute to biological activities like antioxidant, antibacterial, hypoglycemic, anti-obesity and anti-dyslipidemia, cholesterol-lowering, anticancer, anti-inflammatory, immunomodulatory, and antihypertensive ones (34).

In addition, goat's milk has a long history of use as a functional food or medicine. However, it has also been used along with cow's milk and some characteristics differentiate them, making goat's milk preferable. These include high protein content, better fat digestibility, buffering capacity, and alkalinity in comparison to cow's milk and may be the reason for being used as the treatment of DED (35).

Quince seed mucilage, tragacanth and violet flower oil

One of the compound formulations that has been prescribed for DED in traditional Persian medicine is the mixture of quince seed mucilage, tragacanth, and violet oil (12,13).

Mucilage is produced in the outer layer of quince seeds (*Cydonia oblonga,* Rosaceae) known as Beh and Safarjal in the Persian language and traditional Persian medicine. It is extracted by immersing seeds in water and using filtrate. Mucilage is composed of water-soluble polysaccharides that have a high capacity for water absorption and maintaining water. Quince seed mucilage properties include antioxidant, anti-inflammatory, anti-allergic, and antimicrobial activities that are beneficial for DED patients (36).

Tragacanth gum (Katira in Persian) is an old economic herb product that has been used for centuries for various medicinal and cosmetic purposes. The source plant for the production of Tragacanth in traditional Persian medicine matches *Astragalus gossypinus* (Fabaceae). However, nowadays tragacanth is obtained from several *Astragalus* species including *Astragalus tragacantha, Astragalus gummifer, Astragalus microcephalus, Astragalus brachycalyx, Astragalus myriacanthus, Astragalus gossypinus*, and *Astragalus kurdicus* (37). Tragacanth is a gum exudate, mostly a mixture of polysaccharides that are secreted by the plant after injuries to protect it from dehydration and infectious agents. This gum is soluble in water and has been applied for preparing ophthalmic formulations after thoroughly mixing in water and filtration. In addition to the polyhydroxy function of tragacanth soluble polysaccharides which results in their high water-holding capacity, other biological activities have also been reported from herbal gums. These activities include immunomodulatory, antioxidant, anticoagulant, cholesterol reducing, antiviral, anti-inflammatory, keratinocytes DNA repair, and antitumor that can be beneficial for DED patients (38).

The combination of quince seed mucilage, tragacanth gum, and violet flower essential oil (prepared in olive fixed oil) makes this formulation a water-conservative, lubricating, anti-inflammatory, and immunomodulatory medicine that helps in the treatment of DED by multiple mechanisms of action.

Gathered data about above mentioned traditional herbal medicines is summarized in Table 1.

Conclusion

Traditional Persian medicine is a rich source of herbal, animal, and mineral-based products that are prescribed alone or after mixing and obtaining a compound medicinal formulation which is known as Qarabadin. In this review, it was found that traditional Persian medicine mostly recognizes lack of moisture (Tari) as the main cause of DED and so the appropriate treatment is directed to retain moisture or ameliorate the sensation of dryness by lubrication. For this reason, for the treatment of DED, Persian traditional medicine principally focuses on the local use of mucilage-containing plants such as psyllium and quince seeds and herbal oils like sweet almond oil and pumpkin oil. In addition, the combination of mucilage and oils has also been used. Modern studies indicate that antioxidant and anti-inflammatory activities are also important for the treatment of DED and so the traditionally

Table 1. The list of traditional Persian herbal medicines for the treatment of dry eye disease, their ingredients, sources, phytochemicals, and beneficial effects for patients

Herbal medicine	Route of administration	Ingredients and Source	Phytochemicals	Beneficial effects	Reference
Sweet almond oil	Ophthalmic drop	Sweet almond nut oil (*Prunus dulcis*)	Monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, tocopherols, tocotrienols, phytosterols, squalene	Lubrication, anti-inflammation	(12,13)
Pumpkin Seed oil	Ophthalmic drop	Pumpkin Seed Oil (*Cucurbita pepo*)	Polyunsaturated fatty acids, unsaturated fatty acids, saturated fatty acids, Squalene, tocopherols, phytosterols, carotenoids	Lubrication, anti-inflammation	(12)
Violet flower oil	Ophthalmic drop	Sweet violet flowers essential oil (*Viola odorata*)	Monoterpenes, sesquiterpenes	Lubrication, anti-inflammation, antioxidant	(12,13,21)
		Olive oil (*Olea europaea*)	Monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, squalene, tocopherols, phytosterols, carotenoids, phenolic compounds		
Lettuce seed oil	Ophthalmic drop	Lettuce seed oil (*Lactuca sativa*)	Polyunsaturated fatty acids, saturated fatty acids, tocopherols, phytosterols	Lubrication, anti-inflammation	(12)
Psyllium mucilage	Ophthalmic drop	Psyllium seed Mucilage (*Plantago ovata*)	Mucilage (Polysaccharides)	Water conservation, antioxidant, immunomodulation, anti-inflammation	(12)
Coriander & Love Lies Bleeding	Ophthalmic drop	Coriander aerial parts aqueous extract (*Coriandrum sativum*)	Phenolic acid, coumarins, flavonoids, carotenoids	Antioxidant, anti-inflammation	(13)
		Love Lies Bleeding aerial parts aqueous extract (*Amaranthus caudatus*)	Phenolic acids, flavonoids, betalains, triterpenes		
Barley poultice	Eyelid poultice	Barley flour (*Hordeum vulgare*)	Carbohydrates, proteins, lipids, vitamins, minerals, flavonoids, tocopherols, lignans, phytosterols, folates	Antioxidant, antibacterial, hypoglycemic, anti-inflammation, immunomodulation	(13)
		Goat milk (*Capra hircus*)	Proteins, fats		
Quince seed mucilage, tragacanth and violet flower oil	Ophthalmic drop	Quince seed mucilage	Mucilage (polysaccharides)	Lubrication, water conservation, antioxidant, anti-inflammation, anti-allergic, antimicrobial, immunomodulation, antiviral	(12,13)
		Tragacanth gum	Gum (polysaccharides)		
		Sweet violet flowers essential oil (*Viola odorata*)	Monoterpenes, sesquiterpenes		
		Olive oil (*Olea europaea*)	Monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, squalene, tocopherols, phytosterols, carotenoids, phenolic compounds		

used remedies in traditional Persian medicine provide a new area of research for better treatment of DED and possible discovery of new medicines.

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Conflict of Interest Disclosures

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