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Herbal-based drugs for dry eye; treatment and adverse reaction

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Dry eye syndrome is one of the most common types of eye diseases. Due to the significant prevalence of the disease, there is an important need for treatment of dry eye in a simple but efficient way. Artificial tears are the most common agents used for treating dry eye but are not very useful. In recent years, the use of herbal remedies has attracted much attention, because the process of producing most herbal remedies is simple, inexpensive and has fewer side effects. In many clinical studies, the potential interactions between medicines and herbs have been demonstrated. According to reports, some herbal products have the potential to be used for the treatment of dry eye while the use of certain products can lead to this syndrome. In this review, we have listed some of the herbal drugs and components which can prevent or treat the dry eye or cause it.

Keywords: Dry eye, Herbal agents, Traditional medicine, Treatment

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The International dry eye Workshop, defined dry eye syndrome (DES) as a multifactorial disease of the tears and ocular surface that induced tear film instability and visual disturbance. This disease is associated with symptoms such as burning, itching, pain, foreign body sensation, blurred vision, and photophobia that can lead to ocular complications such as corneal perforation, epithelial defects, corneal thinning, impaired vision and infection[1-3]. Estimated number of patients with DES is around 100 million worldwide. In addition, it is reported that the global prevalence of dry eye ranges from 14% to 33%. Studies show that about 15% of adults in the USA are affected by this disease. In a study conducted in Taiwan with 2038 participants aged 65 years and over, 33.7% were diagnosed with dry eyes[2,4]. In addition, some epidemiological studies from Japan, Turkey and China estimate that conjunctivochalasis (CCh), as a disease that leads to dry eye, affects between 44 and 98% of people above 60 years. A survey in Iran by Hashemi *et al.*[5], showed that the prevalence of CCh in the adult people (45–69 years) is 6.1%. Dry eye treatment options are limited to artificial tears and tear protection techniques. In most cases of mild or temporary illness that occurs in response to environmental conditions or other illnesses, pain relief therapies are sufficient. However, in more severe cases, dry eye disorder with corneal ulcers can occur[6,7]. There are some treatment options for dry eye including tear supplements such as tear stimulants, lubricants, oral supplements, anti-inflammatory drugs, and split retention techniques, for instance, moisture chamber spectacles/shields, punctual occlusion using punctum plugs or cautery, contact lenses, and tarsorrhaphy[8]. In general, dry eye can be induced by unsuitable lifestyle. Prolonged exposure to glare or air conditioning and also reduced blinking can result in an unstable tear film. In some patients, in addition to the use of topical eye drops, more than one treatment is needed to treat dry eye. On the other hand, only a small proportion of people with dry eye regularly use artificial tears. So the use of alternative or combination methods to treat dry eye may be preferred[9]. Generally, eye drops are preferable because they are cost-effective and patient-friendly; however, an eye drops vial usually contains a preservative agent allowing for repeated use. According to the studies, preservative agents are

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toxic to eyes; for example, benzalkonium chloride (BAC) which is often used as a preservative in ophthalmic drugs, has negative affect on tear film, cornea and conjunctiva. Due to these limitations, one of the notable therapies for dry eye is the use of herbal medicines, which has less therapeutic restrictions. For many years, herbal drugs have been used for many approaches such as infection treatments, wound healing and molecular stimulation in laboratory researches[4,10]. In this review, we discuss herbal drug, which can help to treat the dry eye or cause it.

Herbal medicines

Herbal medicines are clinically significant, because they are safer than many treatments that can cause unwanted side effects or interfere with prescription drugs. Depending on the climate and the type of vegetation in different countries, various types of herbs for treatment of ophthalmic disorders with dry eye symptoms have been reported. Some of these plants are listed in Table 1[11-13].

It should be noted that herbal based-therapies have long been used in the treatment of various diseases such as dry eye due to low cost and less side effects compared to other therapies. However, little is known about the effectiveness or side effects of herbal drugs. Some main effects of herbal medicines used for the treatment of dry eye disease are summarized in Table 2[14].

Herbal-based drugs used in the treatment of dry eye

Lycium barbarum (Goji berries)

Lycium barbarum (Goji berries) is a tree native to Asia and southeastern Europe, whose medicinal properties are well known. The fruit of this plant, commonly called goji berries (*Gou qi zi* in Chinese), has long been used for medicinal and nutritional purposes throughout Asia. For example, goji berries are processed into tinctures due to their antioxidant effects[29]. In addition, it has been demonstrated that goji berries have a variety of medical properties including antioxidant, anti-inflammatory, antitumor, renal protective and hepatoprotective activities, immune enhancement, as well as reducing the risks of hypoglycemia, hypolipidemia, and metabolic syndromes. In addition, studies have demonstrated that goji berries can reduce the side effects of radiotherapy and chemotherapy; and improve the general health of cancer patients[30,31].

Its effects on the treatment of dry eye have also been confirmed. For example, Chien *et al*.[6], examined the beneficial effect of the goji berry on dry eye disease in rats, and they found that after one week of goji berry extract administration, Schirmer's test score, tear breakup time (TBUT) and the severity of the keratoconjunctival staining were significantly increased. There were no mortality and abnormal histopathology changes in the kidney or liver tissues of rats treated by goji berry extract for 21 consecutive days. According to the results, they concluded that the goji berry is safe and has beneficial effects in relieving dry eye.

Polygonum cuspidatum

Polygonum cuspidatum is an herbaceous perennial plant of the genus *Polygonum* in the family *Polygonaceae*, found in North America and Asia. Its dried root is officially listed on the Chinese Pharmacopoeia under the name “Hu Zhang” which is frequently used as a cholagogic drug and hepatoprotective and in traditional chinese medicine (TCM)[32]. This plant is used as a public herbal medicine for the treatment of amenorrhea, cough, arthralgia, jaundice, hepatitis, leucorrhoea, hyperlipidemia scalding and bruises, carbuncles, and snakebites. Studies have demonstrated that the critical bioactive constituents of *P. cuspidatum* are anthraquinones such as emodin and its glycosides, polydatin, resveratrol and flavonoids including catechin and quercetin[33,34]. In general, the leaves and roots of *P. cuspidatum* contain amino acids, vitamins and flavonoids that have different therapeutic effects such as anti-inflammatory, anti-oxidative, antibacterial, anti-virus, neuroprotective, cardioprotective and wound-healing effects. For example, ethanol extracts of *P. cuspidatum* lead to hepatitis B virus (HBV) inhibition in HBV-producing cell lines through anti-inflammatory activity[35]. Considering the therapeutic potentials of *P. cuspidatum,* studies have been conducted on the treatment of dry eye using this plant. For example, Park *et al*.[33], studied the effect of *P. cuspidatum* aqueous extract to treat dry eye models *in vitro* and *in vivo*. Their results showed that treatment by *P. cuspidatum* restored anti-oxidative proteins such as heme oxygenase-1 (HO-1), superoxide dismutase-1 (SOD-1) and glutathione peroxidase (GPx) in hyperosmolar stress-induced human corneal epithelial cells (HCECs). In addition, administration of

Table 1 — List of herbal medicines used to treat ophthalmic disorders with dry eye symptoms[11-13].

Herbal varieties	Condition	Plant growing areas*
Schinus molle (California peppertree)**	Conjunctivitis Ophthalmia	Originated in Europe, but has been taken to many other places like Australia
Acacia catechu (Cutch tree)	Conjunctivitis	This plant is found in parts of South Asia and Southeast Asia, including Thailand, Indonesia, India, and Myanmar
Centaurea cyanus (Cornflower)	Conjunctivitis Ophthalmia	Plant is native to Europe
Euphrasia officinalis (Eyebright)	Conjunctivitis	This plant is found in parts of West Europe, including Britain, to East Asia.
Hibiscus sabdariffa (Roselle)	Conjunctivitis	Native to West Africa to Sudan
Ilex aquifolium (Holly)	Conjunctivitis	Native to North Africa, South and West Europe, and West Asia
Abrus precatorius (Liquorice)	Conjunctivitis	Native to many parts of the world
Convallaria majalis (Lily of the valley)	Conjunctivitis	Native to Northern Europe and Asia
Calendula officinalis (Pot marigold)	Conjunctivitis	Native to Southern Europe
Curcuma domestica (Turmeric)	Conjunctivitis	This plant is grown in tropical South and Southeast Asia
Arisaema atrorubens (Jack in the pulpit)	Inflammation	Native to Eastern North America
Asarum europaeum (Asarabacca)	Ophthalmia	Native to Central to Southern Europe
Stellaria media (Chickweed)	Ophthalmia	Native to Europe, but naturalized in many parts of North America
Corydalis cava	Ophthalmia	Native to Central Europe and Southeast Europe
Datura stramonium (Thorn Apple)	Ophthalmia	Native to central America, but it has been introduced in many world regions
Rhus toxicodendron (Eastern poison oak)	Ophthalmia	This plant grow throughout the United States and Canada
Phyllanthus amarus (Gale-o-wind)	Ophthalmic disorders	This plant is a widespread tropical plant commonly found in coastal areas especially Indian Ocean
Solanum nigrum (Black nightshade)	Ophthalmic disorders	Native to Eurasia and introduced in the Australasia, South Africa, Americas
Leonurus japonicas (Chinese motherwort)	Ophthalmic disorders	Native to Asia, including China, Korea, Japan, and to Cambodia
Syzygium aromaticum (Clove)	Ophthalmic disorders	Native to Indonesia
Senecio bicolor (Cineraria)	Ophthalmic disorders	Native to the Mediterranean region
Armoracia rusticana (Horseradish)	Ophthalmic disorders	Native to West Asia and Southeastern Europe
Glycyrrhiza glabra (Liquorice)	Ophthalmic disorders	Native to Europe and West Asia

* https://www.pfaf.org/
** Common name (From pfaf)

P. cuspidatum significantly inhibited expression of inflammatory cytokines such as tumor necrosis factor-α, interleukin-6 and activation of NF-κB p65 in hyperosmolar stress-induced HCECs. Generally, *P. cuspidatum* protected against apoptosis, oxidation and hyperosmolar stress-induced inflammation by inhibiting expression of MMP9, COX-2, BAX; activation of caspase 3, NF-κB, and PARP; and increased expression of anti-oxidative proteins and MUC4. Accordingly, they concluded that this plant

Table 2 — Main effects of some herbal medicines used for the treatment of the dry eye[14].

Plants	Main effects	References
Buddleja officinalis (Mi Meng Hua)**	Displays androgen-like activity to maintain the initial volume of tear secretion and tear film stability	15
Aristotelia chilensis (Macqui)	Increases tear fluid volume	16
Hippophae rhamnoides (Sea Buckthorn)	Preserves inflammatory cytokines and tear secretion in the lacrimal gland	17
Prunus armeniaca (Apricot)	Promotes the flow of tear fluid and mucin	18
Rhynchosia volubilis	Prevents the expression of Bax and cytochrome c while improving that of Bcl-2 and Inhibits squamous metaplasia and apoptosis in the cornea.	19
Lycium barbarum (Goji)	By anti-inflammatory and antioxidant activates, enhances the tear volume and repairs the damaged ocular surface cells.	20
Phytochemicals		
Curcumin -Origin from *Curcuma longa* (Cockspur Thorn)	Protects against hyperosmotic-induced IL-1b elevation in the human corneal epithelial cell via the MAPK pathways and produces an anti-inflammatory effect	21
Antioxidant glasses (*Schizonepeta tenuifolia*; *Rehmannia glutinosa*; *Cassia tora*)	Exerts preventive effect on inflammation and membrane damage in dry eye by improving all clinical parameters, TNF-α, IFN-γ, IL-1β and IL-6levels, percentage of CD4+CXCR3+ T cells, number of 4-HNE-positive cells, goblet cell density and extracellular reactive oxygen species production	22
Lacrisek (phytoestrogen compound)	Decreases tear osmolarity and significantly increases tear production	23
Ferulic acid and kaempferol	Increase the expression of Ferulic acid and kaempferol, lower IL-1B, IL-6, IL-8 and TNFα exerts an antioxidant effect	24
Plant-based compounds (Chinese medicinal plants)		
Qiwei Baizhu powder, Zhibai Dihuang decoction, Liuwei Dihuang decoction, and kidney-Qi pills)	Reduces levels of IL-1, IL-8 and TNFα and improves eye dryness	25
Sheng Jin Run ZaoYang Xue granules (Bei Sha Shen, Dihuang, Maidong, Shihu, Heshouwu, Gouqi, Juhua, Guizhencao, Ziwan and Zhigancao)	Treats dry eye, which is one of the symptoms of Sjögren's syndrome	26
Triphala Ghrita Netratarpan *(Phyllanthus emblica, Terminalia chebula*, *Terminalia bellirica* in ghee base)	Reduces the signs of computer vision syndrome	27
Ji-Sheng-Shen-Qi-Wan, Well Zhen Zi, Dan Shen, Gou Qi Zi, Well Zhen Zi, Gu Jing, Hang Bai Ju, and Huai Niu Xi	Effects on estrogen receptors and hormonal regulation	28
Chi-Ju-Di-Huang-Wan (Chi-Ju-Di-Huang-Wan' is the formula 'Liu Wei Di Huang Wan' adds Fructus Lycii and Hos Chrysanthemi)	Reduces abnormalities in the corneal epithelium so it can be used as an artificial tear	15

** Common name (From pfaf)

might have the potential to preserve eye health and treatment of some eye disease such as the dry eye[33].

Chi-Ju-Di-Huang-Wan

'Chi-Ju-Di-Huang-Wan' is a commonly used Chinese herbal medicine for the treatment of essential hypertension as a monotherapy or in combination with other antihypertensive agents. It is also recommended to treat severe dizziness, dull headache, sore bones, deafness, tinnitus, night sweats, fever and vision problems such as blurred vision, eye pain, and dry eye[36, 37]. Generally, Chi-Ju-Di-Huang-Wan is a famous ancient Chinese herbal formula for support eye health. This formula is appropriate for the dryness of the eye, excessive moisture with wind and pain around the eye or the syndrome associated with

blurred vision. In this formula, Liu Wei Di Huang Wan is composed of six different component including Shan Yao, Fu Ling, Shu Di Huang, Shan Zhu Yu, Mu Dan Pi, and Ze Xie. Liu Wei Di Huang Wan has beneficial effects for protection of rats from depressive-like behaviors[38]. According to the studies, this formula is an effective drug to treat of dry eye because it repairs epithelial abnormalities. Furthermore, this agent also affects the stability of tear film[39]. Accordingly, in a study by Chang *et al*.,[37] the therapeutic effects of the Chi-Ju- Di-Huang-Wan was investigated to treat dry eye *in vivo*. In their study, 80 patients with dry eye were divided into two groups. In the experimental group, patients were treated with Chi-Ju-Di-Huan-Wan and topical eye drops. Control group was treated with topical eye drops and placebo. All patients were examined for tear film by Rose Bengal, break up time, fluorescein stain and Schirmer's tests. According to the results, there was a considerable difference in the Rose Bengal test at week 2 and tear break up time at week 4 while no significant difference was there between the two groups according to the Schirmer's test. Their study showed that Chi-Ju-Di-Huang-Wan can be used as a useful drug to treat dry eye by the effect on the stabilization of the tear film and decreasing the abnormality of corneal epithelium[37].

Chamomile

Chamomile as an ancient medicinal herbs and is a member of *Asteraceae*/*Compositae* family and known by two common varieties *viz*. including Roman Chamomile (*Chamaemelum nobile*) and German Chamomile (*Chamomilla recutita*). Having terpenoids and flavonoids, chamomile is considered as a medicinal herb. Chamomile is commonly used to treat several human disorders such as hay fever, muscle spasms, ulcers, gastrointestinal disorders, inflammation, insomnia, rheumatic pain, wounds, and hemorrhoids[40]. In addition, eye washing with chamomile tea is a folk therapy used by the general public for the treatment of infections and disorders of the eyes such as conjunctivitis, blocked tear ducts and other ocular reactions. Chamomile is presented on the GRAS (generally recognized as safe) FDA list. However, allergic reactions[41] were reported in some patients.

People who are sensitive to ragweed and chrysanthemums or other members of the *Compositae* family are more susceptible to develop contact allergies to chamomile, especially if they are taking other allergen agents. In general, evidence of cross-reaction of chamomile with other drugs has not been well established and needs further studies. It is noteworthy that there is ample evidence that chamomile can cause severe conjunctivitis if applied topically around the eyes. Accordingly, in a study by Subiza *et al*.,[42] they described patients who rinsed their eyes with chamomile tea for the treatment of runny and irritated eyes. All cases had acute conjunctivitis and angioedema occurred in two patients. These patients had a history of seasonal allergic rhinitis. One possibility for conjunctivitis in these patients may be due to sensitivity to allergens present in *Matricaria chamomilla* pollen. Therefore, they conclude that eye washing by chamomile tea can induce allergic conjunctivitis[4,11].

Datura

Datura belongs to the family *Solanaceae* . This genus has nine species of poisonous vespertine flowering plants. Of the nine species, some are more well-known such as *Datura metel* for the use in traditional Chinese medicine, *Datura innoxia* for the use in pre-Colombian America, and *Datura stramonium* for its long history of use in sacred rituals. Datura has been used around the world for thousands of years in medicine. In ancient India, datura was used in the treatment of fevers, inflammations and mental disorders[43,44]. However, due to the variety of alkaloids, datura is a powerful hallucinogen and deliriant. According to d studies, datura leaves are the most toxic part of the plant and contain a large amount of toxic alkaloids such as daturine. These alkaloids are responsible for both pharmacological and hallucinogenic effects at higher levels, and careless use often leads to hospitalization and mortality. Accordingly, this plant has been grouped under Schedule E-1 of Drugs and Cosmetics Act-1940[45]. Generally, the therapeutic properties of the plant are due to the presence of different active components such as saponins, tannins, steroids, alkaloids, polyphenols and glycosides[46].

According to some reports, the dried leaves of this flower are used for the treatment of eye inflammation and disorders such as viral conjunctivitis. This disease is an acute conjunctival infection usually caused by adenovirus. Its symptoms are watery discharge, irritation, and photophobia, however, during infection; inflammation can alter the tear film

secretion that caused dry eye. For the treatment, datura root and leave are crushed in water and the liquid is strained. This datura water is used in instilling in eyes with viral conjunctivitis[46].

Herbal-based drugs which cause dry eye

Echinacea and kava are the main herbal products associated with conjunctivitis and dry eye syndrome which are discussed in more detail below.

Echinacea purpurea

Echinacea purpurea (L.) Moench is a member of one of the Asteraceae (Compositae) family. Extracts of this plant have been used traditionally in North America to treat various types of wounds and infections[47]. In general, the plant's roots and leaves or the whole plant are used for the treatment of cough, fever, burns, common cold, urinary tract infections, and influenza. Many studies have demonstrated that extracts of the plant have potent antimicrobial and antiviral activities. In addition, studies confirmed its multiple immune-modulatory activities and stimulation of some immune functions such as suppression of the proinflammatory responses of epithelial cells to bacteria and viruses or phagocytic activity of macrophages, which appear as changes in the secretion of various cytokines and chemokines[47]. However, the products of this plant are one of the most important herbal agents that cause dry eye. Accordingly, seven reports of eye irritation and conjunctivitis were reported after topical *Echinacea* use. However, based on cording to the reports, the ocular symptoms got resolved within a day after stopping this agent[4,11].

Kava

Kava, also often called kava kava, comes from the *Piper methysticum* plant which is a perennial shrub, native to the Pacific Ocean societies. Liquid extracts of kava, that are traditionally prepared from masticated roots, have been used for thousands of years. Kava is considered in traditional medicine to have a sedative activity that soothes the nerves, induces sleep, as well as calms the mind and body[48]. Its bioactive components are called kavalactones, which constitute about 15% of the dry weight of the root of the plant. Studies showed that kavalactones might have the following effects on the body including anxiety reduction, protect neurons from damage, reduce pain sensations and reduce the risk of cancer[49-52]. It should be noted that according to the National Institutes of Health (NIH), kava has a mild anxiety-reducing effect, but it may also cause severe liver damage. Although kava is legal in the US, but the FDA suggests that people should use it with caution. Based on reports, kava is associated with some ocular adverse effects such as conjunctivitis and dry eye. This effects are dose dependent (using in long-term with high doses)[53]. Accordingly, a spontaneous reporting system for adverse drug reactions (ADR) in Germany and Switzerland (1989-2001) reported a variety of symptoms in association with kava. Of the 36 cases that were studied, 27 cases had allergic conjactivitis[54].

Conclusion

Dry eye disease is a common eye problem that can reduce vision function and quality of life. Administration of herbal drug may improve the dry eye symptoms. Furthermore, the beneficial effects of herbal drugs such as antioxidant, anti-inflammatory and anti-infection activities may promote the healing process. Herbal remedies for the prevention and treatment of dry eye are currently under considerable evaluation. Compared with eye drops and artificial tears, herbal remedies can be a useful dietary supplement to relieve the symptoms of dry eye. However, it should be noted that uncontrolled use of some herbal drugs might have adverse effects. Therefore, the side effects of these drugs should also be carefully considered.

Conflicts of interest

The authors have stated that there are no conflicts of interest regarding the current paper.

Author Contributions

M R and K J wrote the manuscript, H A revised the manuscript, A B wrote and revised the manuscript.

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