Review Article

Ophthalmology Section

Effect and Mechanisms of Medicinal Plants on Dry Eye Disease: A Systematic Review

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ABSTRACT

Introduction: Dry Eye Disease (DED) is one of the most common problems and reasons for referring to ophthalmology clinics, which has been exacerbated by the increased use of computers and mobile phones.

Aim: The purpose of the present systemic review was to review the effects and mechanism of medicinal plants in DED treatment.

Materials and Methods: The key words "Dry eye" or "Keratoconjunctivitis sicca" or "keratitis sicca" in combination with "medicinal plant", "herb", and "phyto" were used to conduct the review. Clinical and experimental published articles in English language between 2000-2018 were retrieved from databases including the Institute for Scientific Information (ISI), PubMed and Scopus.

Results: Totally, 199 articles were retrieved from the electronic database and finally 17 articles were included in the final analysis. Various plants such as *Buddleja officinalis, Aristotelia chilensis, Prunus armeniaca, Hippophae rhamnoides, Lycium barbarum*, and *Rhynchosia volubilis* Lour are effective in treating DED through different mechanisms.

Herbal derivatives such as curcumin, antioxidant glasses, phytoestrogen, ferulic acid, and kaempferol can be used as food supplement independently and in some cases along with chemical drugs. Chinese herbal formulations and compounds such as 'Chi-Ju-Di-Huang-Wan', 'TriphalaGhritaNetratarpan', and 'ShengJinRunZaoYangXue' granules can play a role in inducing anti-oxidant and anti-inflammatory properties in the treatment of the disease.

Conclusion: Generally, medicinal plants reduce tear film stability by decreasing osmolarity and increasing tear production. Several mechanisms, including the reduction of Reactive Oxygen Species (ROS) (antioxidant activity), the prevention of cell apoptosis, the modulation of inflammatory factors, and the regulation of androgens, can affect lacrimal glands and membrane cells, thereby helping to treat DED.

Keywords: Keratitis sicca, Keratoconjunctivitis sicca, Medicinal herb

INTRODUCTION

Dry eye disease or keratoconjunctivitis sicca is a multifactorial disease that is developed due to inflammation of the ocular surface and lacrimal glands, meibomian gland dysfunction, and neuropathic pain disorder [1]. Various environmental factors such as air dryness, smoke, allergens, systemic diseases, and age (in premenopausal women) contribute to DED [2-5]. The disease has increased in recent years with the advent of monitors and prolonged use of computers and is one of the most important causes of referral to ophthalmology clinics characterised by symptoms such as scratches and foreign bodies in the eye [6-8].

Due to the high prevalence of DED, it is necessary for physicians to have important information about care, often debilitating symptoms, and preventable and curable nature of the disease [5].

DED treatment is based on a tear substitute. New treatments focus on certain drugs such as secretagogues, lubricants, topical androgens, antibiotics, immunosuppressive drugs, and new anti-inflammatory drugs [9,10]. Meanwhile, herbal treatments have been used in the treatment of various diseases due to being less costly and causing fewer side effects [11-19]. Although, the use of herbal medicines has been used in many countries for the treatment of eye diseases since long time [20-23], however, little information is available on the validity of the efficacy or probable side effects of these drugs. Also, regarding the high prevalence of the disease, and considering that there is still no study in this regard, the authors aimed to investigate the effect and mechanism of medicinal plants in treating DED in the present systemic review.

MATERIALS AND METHODS

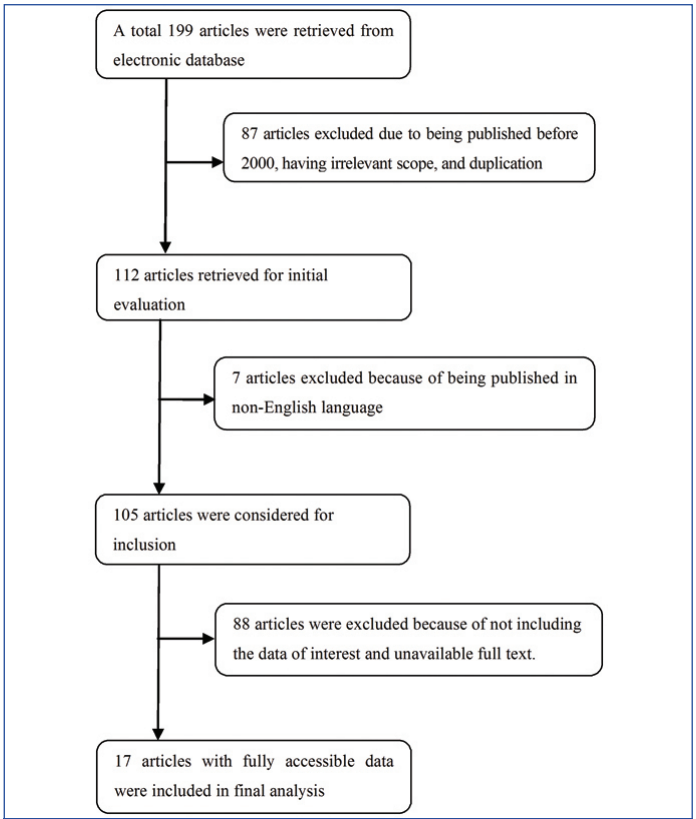
The key words 'Dry eye' or 'Keratoconjunctivitis sicca' or 'keratitis sicca' in combination with medicinal plant, herb, and phyto were used to conduct the review. Relevant articles (from 2000 till date) were retrieved by using keywords from databases including ISI, PubMed, and Scopus with EndNote software. Then, the plants and the plant-based products that were effective on DED were selected and entered to the study according to inclusion criteria. A standard form, which included items such as year of publication, aim and the title of the study, intervention, outcome, variables, journal name, period, and number, was designed. The articles contents that were in accordance with the purpose of the study were recorded in the form and entered to the study with agreement of researchers. The articles whose full texts were not accessible, the articles published in non-English languages, and those that did not address the subject of this review were excluded after the author's agreement was achieved. [Table/Fig-1] is the flowchart that illustrates how the articles were selected for final analysis.

RESULTS

The 17 studies that were included in the review and were effective on treatment on DED are tabulated in [Table/Fig-2] [24-40].

DISCUSSION

Dry eye disease is a multifactorial disease. Hence, the treatment must be based on underlying cause of the disease. Medicinal plants and their derivatives can impact DED in several ways. Medicinal plants improve tear film stability by decreasing osmolality and inflammation increasing tear production. Tear hyperosmolarity has been reported to begin dry eye inflammation through the



[Table/Fig-1]: Flowchart of the process of selecting and analysing the articles.

activation of epithelial and stromal cells on the ocular surface, which increase the presence of pro-inflammatory cytokines [41]. Inflammation can cause dysfunction in the lacrimal glands cells responsible for tear secretion or retention and leads to ocular surface disease. Plant compounds can be used to regulate levels of gonadal hormones by exhibiting androgen-like activities. As a result, it can inhibit topical inflammation in the lacrimal glands and reduce cell apoptosis [41,42]. In addition, plants and their compounds can contribute to the treatment process by inhibiting the expression of pro-inflammatory cytokines (IL-1 beta, IL-6, and TNFα) and reducing nitric oxide production [30,43,44]. Artificial tears are the most common treatment for eye diseases therapy; they provide temporary symptomatic relief; however, are unable inhabitation of inflammatory cytokines activity [34]. Also, reduction of ROS (antioxidant activity) and the prevention of cell apoptosis can reduce the symptom of DED. A 8-Hydroxy-2 deoxyguanosine (8-OHdG), 4-Hydroxynonenal (HNE) and Malondialdehyde (MDD) are major biomarkers that cause oxidative damage in ocular surface [41,45]. In DED patients, the levels of these in the tear and conjunctiva increase and cause disruption in the normal functioning of the eye and finally leads to oxidative damage, possibly inflammation and apoptosis [41]. Anti-apoptotic activity and increased expression of some genes in the lacrimal gland epithelial cells represent one of the mechanisms in treating DED [46]. Medicinal plants indicate androgen-like activity and can affect lacrimal glands and membrane cells, thereby contributing to DED treatment. Androgens may increase meibomian gland function and lacrimal gland function [47].

Medicinal plants				
References	**Plants**	**Study Design**	**Type of administration**	**Main effects or mechanisms**
Peng QH et al., [24]	*Buddleja officinalis*	Experimental (in vivo)	Extract	Displaying androgen-like activity to keep basic tears secretory volume and tear film stability
Hitoe Set al., [25]	*Aristotelia chilensis*	Clinical pilot trial	standardised extract (MaquiBright)	Increasing tear fluid volume
Kim CS et al., [26]	*Prunus armeniaca*	Experimental (in vivo)	Kernel extract	Promoting the secretion of tear fluid and mucin
Kimura Y et al., [27]	*Hippophae rhamnoides*	Experimental (in vivo)	Pulp oil	Preserving tear secretion and inflammatory cytokines in the lacrimal gland
Chien KJ et al., [28]	*Lycium barbarum*	Experimental (in vivo)	Extract	Enhancing the tear volume and repairing the damaged ocular surface cells by exhibiting antioxidant and anti-inflammatory activity.
Kang SW et al., [29]	*Rhynchosia volubilis Lour.*	Experimental (in vivo)	Ethanol extract	Inhibiting squamous metaplasia and apoptosis in the cornea and inhibiting the expression of cytochrome c and Bax, while improving that of Bcl-2.
Phytochemicals				
References	**Phytocompound and plant deravities**	**Origin**	**Study Design**	**Main effects or mechanisms**
Chen M et al., [30]	Curcumin	Turmeric (Curcuma longa)	Experimental (in vivo)	Protecting against hyperosmoticity-induced IL-1b elevation in human corneal epithelial cell via the MAPK pathways and producing anti-inflammatory effect
Scuderi G et al., [31]	Lacrisek (phytoestrogen compound)	a-lipoic acid (100 mg), eicosapentaenoic acid (240 mg), and extract of fenugreek (200 mg), which contains diosgenin (1.3%), steroidal saponins (50%), and alkaloids	Randomised clinical trial	Decreasing tear osmolarity and significantly increasing tear production
Choi W et al., Choi W et al., and Huang JY et al., [32-34]	Antioxidant glasses	*Extract of Schizonepetatenuifolia var. japonica Kitagawa, Angelica dahurica Bentham ET hooker, RehmanniaglutinosaLiboschitz var. purpurea Makino,* and *Cassia tora L extracts/Cassiae semen* and *Ophiopogonisjaponicus*	Randomised Clinical trial/Experimental (in vivo)	Exerting preventive effect on membrane damage, and inflammation in DED byimprovingall clinical parameters, IL-1β, IL-6, TNF-α, and IFN-γ levels, percentage of CD4+CXCR3+ T cells, goblet cell density, number of 4-HNE-positive cells, and extracellular reactive oxygen species (ROS) production
Chen HC et al., [35]	Ferulic acid and kaempferol	-	Experimental (in vitro)	Ferulic acid and kaempferollower IL-1B, IL-6, IL-8, and TNFα expression and produce antioxidant effect

Plant-based compounds				
References	**Plant-based compounds**	**Compounds**	**Study Design**	**Main effects or mechanisms**
Peng QH et al., [36]	Chi-Ju-Di-Huang-Wan	Chi-Ju-Di-Huang-Wan' is the formula 'Liu Wei Di Huang Wan' adds Fructus Lycii and Hos Chrysanthemi	Experimental (in vivo)	Reduce abnormalities in the corneal epithelium and be used as an artificial tear
Chen YL et al., [37].	Chinese herbal treatment	Ji-Sheng-Shen-Qi-Wan, Well Zhen Zi, Dan shen, Gou Qi Zi, Well Zhen Zi, Gu Jing, Hang Bai Ju, and HuaiNiu Xi	Case-report	Effects on estrogen receptors and hormonal regulation
Sawant DP et al., [38].	Triphala Ghrita Netratarpan	Phyllanthus emblica, Terminalia chebula, Terminalia bellirica in ghee base	Clinical trial	Reduced the symptoms of the computer vision syndrome
Hu W et al., [39].	Sheng Jin Run ZaoYang Xue granules	Beishashen, Dihuang, Maidong, Shihu, Heshouwu, Gouqi, Juhua, Guizhencao, Ziwan and Zhigancao	Clinical trial	Treat DED, which is one of the symptoms of Sjögren's syndrome
Wu SQ et al., [40]	Chinese medicinal plants	Qiwei Baizhu powder, Zhibai Dihuang decoction, Liuwei Dihuang decoction, and kidney-Qi pills	Clinical trial	Reduce levels of interleukin (IL)-1, IL-8, and TNFα and to improve eye dryness

[Table/Fig-2]: Medicinal plants, phytochemicals and plant-based compounds effective in dry eye disease [25-41].

Clearly, it should be noted that some herbs did not have any positive effect on DED treatment (in humans or animals) [48,49]. Anticholinergic alkaloids are one of the strongest causes of the disease [50]. The most important plant compounds that lead to the development of DED include niacin, echinacea, and kava, and it should be noted that herbal drugs per se can cause eye complications for consumers, which is due to the natural origin of these products, are usually ignored by the consumers and even by the doctors who prescribe the herbal drugs [51,52].

For example, pouring black tea (*Camellia sinensis*) directly into the cornea with the corneal epithelial defect should be prevented, as it leads to anterior stromal discolouration in individuals [53]. On the other hand, determining the effective dose of medicinal plants is another factor affecting their efficacy. Determining the effective dose in DED treatment means the determination of dose for the highest efficacy and also in the toxic dose [28,35].

In some studies, this issue has been neglected and different quantities of plant extract or derivatives at different intervals have not been studied, which was one of the major problems with these studies [54,55].

CONCLUSION

Medicinal plants improve tear film stability by decreasing osmolality and increasing tear production. Several mechanisms, including the reduction of ROS (antioxidant activity), the prevention of cell apoptosis, the modulation of inflammatory factors, and the regulation of androgens, can affect lacrimal glands and membrane cells, thereby contributing to DED treatment.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Research and Technology Deputy of Shahrekord University of Medical Sciences for supporting the present study.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 13, 2018**
Date of Peer Review: **May 23, 2018**
Date of Acceptance: **Jun 15, 2018**
Date of Publishing: **Sep 01, 2018**