



Review Article

Retrospective evaluation of the curative effect of traditional Chinese medicine on dry eye disease

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ABSTRACT

Dry eye disease (DED) is a multifactorial illness with an increasingly high global prevalence and multiple risk factors that widely influences patients' daily lives. It is essential to identify treatments with few or no side effects for patients with DED. We have reviewed studies published from 2001 to 2020 that investigated traditional Chinese medicine (TCM) and integrated Chinese and Western medicine for DED treatment. Current Chinese medicines used in DED therapy were categorized into four types, namely anti-oxidants, anti-inflammatory agents, hormone-like agents, and cell-repairing agents. Compound herbs, including Chi-Ju-Di-Huang-Wan and Qiming granule, can effectively alleviate dry eye symptoms. Moreover, patients with DED who were treated with Western medicine combined with TCM experienced significantly magnified therapeutic effects and reasonable costs of treatment. In conclusion, TCM can be a promising approach for treating DED, and combined treatment with TCM and Western drugs may represent a new strategy for improving the curative effect.

KEYWORDS: *Dry eye disease, Integrated Chinese and Western medicine treatment, Traditional Chinese medicine*

INTRODUCTION

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and it is accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles according to the 2017 TFOS DEWS II global dry eye definition [1]. The pathophysiology of DED is associated with a multifactorial process that causes tear deficiency, excessive tear evaporation, and ocular surface cell damage, contributing to tear film imbalance and dry eye symptoms. The rising osmolarity of tears activates stress signaling pathways in ocular epithelial cells and immune cells, which produce innate inflammatory mediators (e.g., interleukin [IL]-1 β , tumor necrosis factor [TNF]- α , and IL-6) that might further attract CD4⁺ T cells. A series of inflammatory reactions leads to injury of the cornea, conjunctiva, and lacrimal epithelial cells [2]. The prevalence of DED ranges from approximately 5%–50% among countries, with its incidence being highest in South East Asia and lowest in the USA and Europe [1,3]. According to the statistical data from the Taiwan National Health Insurance Research Database covering the period 2000–2013, the prevalence rates of DED

in males and females were 6.81 and 16.16%, respectively. In addition, the incidence is highest in women aged 50–74 and men older than 75 [4]. In addition to age and gender, several DED risk factors have widely been investigated, such as the contact lens, arthritis, smoking, and drinking [5]. Based on data from the National Health Insurance of Taiwan covering 2004–2013, air pollution, such as carbon monoxide and nitrogen pollution, and rising temperatures were positively associated with the risk of DED [6]. A population-based study in Taiwan revealed that patients with DED had a higher risk of Sjögren's syndrome [7]. In addition, presbyopia is related to the development of DED. The probability of a patient with presbyopia will develop DED after 5 years is 8.8%, which is 2-fold higher than in patients without presbyopia [4]. Osteoporosis is also a risk factor for the development of DED, and the subsequently worsening of vision in such patients could increase the probability of fall and bone fracture [8]. In addition, research has found


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that elderly women with DED and recurrent oral aphthae, especially those aged 50–69, might have an increased risk of oral cavity cancer [9].

The effects of DED on patients' daily lives have received increasing attention. Therefore, the discovery of drugs with few or no side effects would have considerably high value for the treatment of DED. This review article examined articles published between 2001 and 2020 that reported Chinese medicine and the combined use of Chinese and Western medicines in patients with DED, including both single and compound herbs. The prospect of integrated Chinese and Western medicine was also discussed.

CURRENT WESTERN MEDICINE TREATMENT

Currently available DED treatments include artificial tears, aqueous secretagogues (e.g., diquafosol sodium), food additives (e.g., polyunsaturated fatty acids), anti-inflammatory drugs (e.g., rebamipide, cyclosporine), anti-oxidants, punctal plugs, and lifestyle intervention [10]. Patients with DED have higher rates of comorbidities, especially hypertension, diabetes mellitus, thyroid disease, cardiovascular diseases, cataract, and glaucoma, than those without DED. Consequently, medication use, including both ophthalmic agents and drugs to treat comorbidities (e.g., decongestants/vasoconstrictors, anxiolytics, beta-blockers), is higher in patients with DED than in those without DED. There is a need for new approaches or multidisciplinary teams to treat patients with DED according to their comorbidities and treatment history [11]. Potential strategies such as acupuncture, the short interfering RNA SYL1001, and nanomedicine therapy are other options for patients with DED who are unsatisfied with current treatments [12].

CURRENT RESEARCH ON TRADITIONAL CHINESE MEDICINE IN THE TREATMENT OF DRY EYE DISEASE

In this review, the traditional Chinese medicines (TCMs) used clinically in the treatment of DED are categorized into two types. The first type is single herbs including Cassiae semen, *Ophiopogonis japonicus*, Lycii Fructus, *Achyranthis radix*, *Buddleja officinalis*, *Bidens pilosa* L., *Schisandrae chinensis* fructus, *Liriope platyphylla*, and the active ingredients of Chinese herbs (curcumin, ferulic acid [FA], and kaempferol [KM]). The second type comprises compound formulations including Chi-Ju-Di-Huang-Wan, Zhibai Dihuang, Liuwei Dihuang, and Qiming granule. All of these treatments have proven efficacy based on clinical research or experience.

Single-herb Chinese medicines

Anti-oxidants

Cassiae semen, containing the vital compound emodin, plays an influential anti-oxidative role in the linoleic acid peroxidation system [13]. Because Cassiae semen and *O. japonicus* have been identified as anti-oxidants, oral anti-oxidant supplements containing these Chinese herbal additives might increase tear production, thereby ameliorating

general dry eye symptoms by reducing oxidative stress damage [14].

Another Chinese herb, Lycii Fructus (Gou qi zi), contains the anti-oxidants zeaxanthin and lutein [15]. Moreover, it had been reported to contain *Lycium barbarum* polysaccharide, which exerts anti-excitotoxic, anti-inflammatory, and anti-apoptotic effects. Through the mechanisms of anti-oxidation, neuroprotection, blood-retinal barrier protection, and immunomodulation, *Lycium barbarum* polysaccharide has a potent ameliorative effect on retinal disease in animal models of diseases and conditions such as glaucoma, ischemia/reperfusion injury, age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa [16,17]. Another report stated that Lycii Fructus can improve DED symptoms dose-dependently in rats by increasing the tear volume and protecting ocular surface cells, and no toxic effects were observed in the liver or kidneys [18].

Curcumin has multiple effects, acting as a natural anti-oxidant to scavenge reactive nitrogen species and reactive oxygen species or serving as an anti-inflammatory agent that promotes angiogenesis in the treatment of corneal diseases such as DED, conjunctivitis, pterygium, anterior uveitis, glaucoma, cataract, and diabetic retinopathy [19].

Anti-inflammatory agents

Achyranthis radix contains numerous anti-inflammatory molecules, such as saponins and phytoecdysones. It can improve irregularity of the corneal surface and simultaneously inhibit corneal epithelial cell death and increase goblet cell density, as noted in a rat model of DED induced by urban particulate matter [20].

One study reported that topically applied esculetin, which was extracted from the Chinese herb-drug "Qinpi," inactivated the ERK1/2 pathway, which was correlated with chronic ocular surface inflammation and which enhanced the anti-inflammatory function of cyclosporine A, thereby improving DED symptoms in a rabbit dry eye model [21].

Another study found that the herbal extracts FA and KM can downregulate the expression of pro-inflammatory cytokines (IL-1B, IL-6, IL-8, and TNF- α) in human corneal epithelial cells [22]. FA is a component of *Angelicae sinensis* Radix with anti-oxidant effects [23]. Moreover, KM is present in *Ginkgo biloba* and propolis, and it has been reported to have anti-inflammatory, anti-oxidant, and anti-tumor activity [24]. Research illustrated that dropping a buffer solution containing 100 μ M FA and 1 μ M KM into the eyes of rabbits can increase tear secretion and repair corneal epithelial cells without irritant effects [22].

Hormone-like agents

The androgen receptor is widely expressed in ocular tissues such as lacrimal gland epithelial cells and the cornea [25]. Sexual hormone imbalance leads to the dysregulation of ocular structures, increasing the risk of DED, especially in women [26]. Androgen therapy might be a therapeutic option, but their side effects are undesirable. *B. officinalis* contain effective flavonoids, namely polyphenolic heterocyclic

compounds similar to androgens. Based on their structural similarities, certain flavonoids are agonists of membrane androgen receptors and exert androgen-like effects [27,28]. The therapeutic effects of *B. officinalis* have been described in a series of studies. *In vitro* research illustrated that the expression of the STAT1 phosphoprotein can be upregulated through the biological effects of androgens after rat lacrimal gland epithelial cells were treated with *B. officinalis*-containing plasma [29]. A study of castrated rats revealed that eye drops containing *B. officinalis* extract can increase the Schirmer I test value, prolong the tear film break-up time value, and upregulate androgen receptor expression in the lacrimal gland compared with the findings in nontreated castrated rats [30]. Another study in castrated rabbits reported that the intragastric administration of *B. officinalis* extract intensified TGF- β 1 expression and reduced IL-1 β and TNF- α expression in the lacrimal gland, thereby diminishing local inflammation and damage in lacrimal epithelial cells caused by androgen deficiency [31].

The incidence of DED is high in postmenopausal and perimenopausal women [26]. Further, DED symptoms were reported in postmenopausal women who were tested using the questionnaires for the Ocular Surface Disease Index and affected their quality of life [32]. The effect of hormone therapy is controversial [33]. A study in rats illustrated that the Chinese herb *B. pilosa* L., which contains androgen-like compound flavonoids, can relieve dry eye symptoms associated with androgen deficiency [34]. The study administered an anti-androgenic agent, finasteride, to a female animal model and observed significantly reduced expressions of the sex hormone receptors in the cornea and lacrimal gland [35]. Oral administration of *B. pilosa* L. extract in rats with DED induced by finasteride promoted tear secretion, increased tear film stability, and reduced inflammation in the lacrimal gland by inhibiting inflammatory cytokine levels (IL-1 β , FasL, and TNF- α) [34]. Although the above-mentioned studies can prove that the herbs have a therapeutic effect on androgen deficiency dry eye, further pharmacological testing to treat the DED situation in the menopausal state is warranted.

Cell-repairing agents

Xiaosheng prescription, comprising Rehmanniae Radix, *A. sinensis* Radix, Codonopsis Radix, *S. chinensis* Fructus, Ophiopogonis Radix, Bupleuri Radix, Menthae Haplocalycis Herba, and Paeoniae Radix Alba, are used to treat DED in patients with liver stagnation and yin deficiency in the Eye Hospital of the China Academy of Chinese Medicine Sciences. Human corneal epithelial cells treated with Xiaosheng prescription have a higher survival rate and lower lactate dehydrogenase release and apoptosis rates in hypertonic solution than model cells. Furthermore, mice with xerophthalmia mouse induced by scopolamine hydrobromide exhibit increased tear secretion after the oral administration of Xiaosheng prescription extract solution. Schisandrin and schisantherin A might be vital ingredients that effectively protect human corneal epithelial cells against hypertonic injury [36].

L. platyphylla has displayed wound-healing and anti-inflammatory effects in the clinic. One study revealed

that *L. platyphylla* can protect against ocular damage induced by particulate matter exposure. Topical *L. platyphylla* extract applied in rats with DED induced by urban particulate matter increased tear volume, decreased corneal epithelial cell injury and apoptosis, restored the corneal mucin-4 layer, and maintained the conjunctival goblet cell density [37].

Chinese medicine compound herbs

Chi-Ju-Di-Huang-Wan, including the formulation of Liu Wei Di Huang Wan plus Fructus Lycii and Hos Chrysanthemi, is the most frequently used TCM for DED. One study of patients diagnosed with DED revealed that Chi-Ju-Di-Huang-Wan can stabilize the tear film and decrease the degeneration of corneal epithelial cells [38].

The combination of the Chinese herbal formulas Chi-Ju-Di-Huang-Wan and Si Wu Tang can increase tear secretion by inhibiting the upregulation of tear vascular endothelium growth factor, and no adverse effects were noted in patients with DED after 3 months of oral treatment [39].

Qiming granule, a broadly used compound in China composed of Radix Astragali, Radix Puerariae Lobatae, Radix Rehmanniae, Fructus Lycii, Semen Cassiae, Fructus Leonuri, Pollen Typhae, and Hirudo, has been reported to have remarkable efficacy in the treatment of DED and other eye diseases. A meta-analysis revealed that Qiming granule can significantly extend the tear film break-up time, enhance tear secretion, and repair corneal damage in patients with DED [40].

INTEGRATED CHINESE AND WESTERN MEDICINE IN DRY EYE DISEASE TREATMENT

Currently available DED treatments manage tear insufficiency, eyelid abnormalities, and ocular inflammation, and the options include surgical approaches, dietary modification, local environmental considerations, complementary medicines, and staged management algorithms. However, there is a need for more convincing evidence of the efficacy of these treatments and alternative therapies [41]. Based on the unsatisfactory effects of DED treatments, a study of patients treated with artificial tears plus acupuncture recorded significantly improves of dry eye symptoms and decreased conjunctival redness after 1 month compared with the findings for artificial tears alone. However, no difference was noted after 4 weeks between the effects of artificial tears plus herbal medicine (Qi Ju Gan Lu Yin) and artificial tears alone. Moreover, the levels of cytokines in tears such as TNF- α and IL-4 are reduced after treatment with artificial tears and acupuncture. In addition, tear IL-12 concentrations can be reduced by combined treatment with artificial tears and herbal medicine. Consequently, combined treatment with artificial tears and acupuncture can effectively improve dry eye symptoms. More research is needed to determine the optimal treatment time and identify the most potent combinations of artificial tears and herbal medicine [42].

Patients with insulin-dependent and noninsulin-dependent diabetes mellitus are susceptible to DED because of poor diabetic control and peripheral neuropathy, which cause ocular

surface changes and tear insufficiency [43,44]. A clinical study found that corneal sensitivity, superficial punctate keratopathy, and tear quantity could be significantly improved by administration of the Chinese herb Goshajinkigan (also called Ji-Sheng-Shen-Qi-Wan) in patients with insulin-dependent diabetes mellitus who received insulin for >5 years [45]. Another study found that combined treatment with Chinese and Western medicine in patients with diabetes-induced xerophthalmia reduced the expression of inflammatory factors (IL-1, IL-8, and TNF- α), enhanced tear production, and decreased corneal injuries [46].

In Singapore, the prevalence of complementary and alternative medicine use is approximately 76% over a 12-month period, and TCM was the most commonly used (88%) complementary medicine [47]. A questionnaire-based study revealed that 87% of TCM practitioners slightly or strongly believed that TCM is an adequate therapy for treating DED. The TCM cost per episode for acupuncture and herbal treatment once to twice a week is approximately S\$20–50 compared with S\$60–100 per physician consultation for Western medicine with additional drug costs [48].

Consequently, integrated Chinese and Western medicine treatment has great potential and utility. Additional research is needed to verify the efficacy of combination treatment.

CONCLUSION

TCM still has great applicability in the treatment of DED. TCM, which has fewer side effects, consists of herbal medicine, acupuncture, and moxibustion according to patients' different constitutions. In addition, integrated Chinese and Western medicine treatment can further augment the therapeutic effect. Consequently, TCM represents a new treatment option for DED. As anti-oxidants, anti-inflammatory agents, hormone-like compounds, or cell-repairing compounds, herbal medicines represent affordable, safe, and effective therapies for DED. In future, integrated Chinese and Western medicine treatment can represent a more effective treatment option for DED.

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Conflicts of interest

There are no conflicts of interest.

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