

Advances in the Treatment of Uveitis with Traditional Chinese Medicine

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Abstract: Uveitis is a prevalent ocular condition that can lead to blindness, commonly affecting young adults and often linked to systemic autoimmune disorders. Contemporary medical treatment primarily involves the use of glucocorticoids, non-steroidal anti-inflammatory drugs, and immunosuppressants. Nevertheless, these treatments are associated with challenges such as high recurrence rates, adverse side effects from prolonged use, and diminished therapeutic effectiveness. In contrast, Traditional Chinese Medicine (TCM) presents distinct advantages in the management of uveitis, including significant alleviation of clinical symptoms, reduction in disease duration, decreased recurrence rates, minimized side effects, and beneficial immunoregulatory effects. TCM has demonstrated satisfactory therapeutic outcomes in uveitis treatment through multiple mechanisms. This article provides a comprehensive review of recent animal studies and clinical research concerning the application of Traditional Chinese Medicine in uveitis treatment, offering valuable insights for its clinical implementation.

1. Introduction

Uveitis encompasses a group of inflammatory conditions affecting the uvea, retina, retinal blood vessels, and vitreous humor [1]. It primarily impacts young and middle-aged adults, and is characterized by recurrent episodes and a chronic course. According to the literature, the annual incidence of uveitis ranges from approximately 20 to 50 million cases, with a global prevalence estimated at 100 to 150 million cases [2]. In China, approximately 3 million individuals are affected by uveitis, and the disease accounts for 5% to 10% of blindness cases [3]. The pathogenesis of uveitis remains incompletely understood, although it is associated with factors such as autoimmune disorders, inflammatory responses, infections, and physical or chemical trauma [4]. Without timely intervention and treatment, uveitis can lead to complications, including cataracts, glaucoma, and an increased risk of blindness [5].

Uveitis is widely recognized as an intraocular inflammatory condition with multiple etiological factors, frequently associated with systemic autoimmune diseases. Clinically, treatment often

involves the administration of glucocorticoids, either alone or in conjunction with immunosuppressive agents [6]. Nevertheless, prolonged use of these pharmacological treatments is associated with ocular and systemic toxicities, diminished therapeutic efficacy, increased risk of dependency, and a high rate of recurrence [7]. Traditional Chinese Medicine (TCM) offers several advantages, including broad availability, multi-target and multi-pathway therapeutic mechanisms, and minimal adverse effects, positioning it as a viable treatment option for uveitis [8]. TCM demonstrates unique benefits in managing uveitis, such as effectively alleviating symptoms, shortening the disease course, reducing recurrence rates, and minimizing side effects [9]. This review aims to synthesize the current research advancements in the application of TCM for uveitis treatment, drawing on both clinical and animal experimental studies.

2. TCM Overview of Uveitis

In TCM, there is no direct equivalent term for uveitis. However, based on its clinical manifestations, uveitis is categorized under "Tongshen Jinxiao" (contracted pupil) and "Tongshen Ganque" (atrophic pupil) within TCM terminology. Contemporary TCM practitioners exhibit varied interpretations and perspectives on this condition, taking into account factors such as individual constitution, environmental influences, and lifestyle habits. According to Professor Peng Qinghua [10], uveitis is typically characterized by "root deficiency with branch excess," where the deficiency of healthy qi is considered the root cause, and the binding of wind, dampness, and blood stasis are regarded as the branch manifestations. Bi Hongsheng [11] propose that the common etiologies of uveitis involve exogenous pathogenic factors associated with the six excesses (wind, cold, summer-heat, dampness, dryness, fire), with wind, dampness, and fire being the most prevalent, often presenting in combination. Wei Qiping [12] posits that in the initial stages of uveitis, Excess Syndrome is prevalent, necessitating a treatment approach that emphasizes eliminating pathogenic factors, complemented by wind-dispelling medicines. In contrast, during the intermediate and advanced stages, the primary therapeutic approaches should focus on strengthening healthy qi to eradicate pathogens and safeguarding the spleen and stomach. Bi Xuqi et al. [13] approaches the treatment of uveitis through five dimensions: "pathogenic heat, pathogenic toxin, pathogenic dampness, blood stasis, and asthenia." They assert that "pathogenic heat and pathogenic toxin" constitute the fundamental etiological factors, whereas "pathogenic dampness and blood stasis" contribute to the onset and progression of the disease.

3. Treatment of Uveitis with TCM

3.1 Clinical Trials of TCM Compound Prescriptions for Uveitis

In the clinical management of uveitis, persistent challenges remain concerning the stability of treatment efficacy, control of side effects, and recurrence rates. TCM compound formulations, based on the principle of syndrome differentiation and treatment, offer distinct advantages in addressing uveitis. Numerous clinical trials have substantiated the therapeutic efficacy of TCM compounds. Ma et al. [14] conducted a randomized study involving 30 patients diagnosed with acute anterior uveitis (AAU) characterized by the liver-gallbladder fire blazing type. The participants were allocated into two groups: the observation group, which received Qinggan Mingmu Decoction, a TCM formulation, and the control group, which was administered conventional Western medical treatment. Upon completion of the treatment regimen, the observation group demonstrated a significantly higher total effective rate compared to the control group. This outcome suggests that TCM compound prescriptions can substantially enhance clinical efficacy in the treatment of AAU. Additionally, Zhang et al. [15] administered a combination of Shuanglian Mingmu Infusion and Western medicine to 24

patients with AAU of the liver-gallbladder fire blazing type over a four-week period. The treatment resulted in significant improvements in clinical symptoms, visual acuity, anterior chamber inflammatory cell scores, and keratic precipitates relative to baseline measurements. These findings indicate that Shuanglian Mingmu Infusion may exert therapeutic effects on AAU by modulating the secretion of inflammatory cells within the anterior chamber. Li et al. [16] administered oral Yiyang Jiulian Powder in conjunction with standard treatment to 60 patients with AAU of the wind-dampness with heat type for a duration of one month. Following the intervention, patients exhibited marked improvements in clinical symptoms, visual acuity, and anterior segment inflammatory indicators. Yang et al. [17] treated 78 elderly patients with chronic uveitis using Yangyin Liangxue Decoction combined with glucocorticoids. The combined therapy achieved a notable clinical effective rate, and Yangyin Liangxue Decoction was found to reduce pro-inflammatory T lymphocytes, enhance immune function, and lower the recurrence rate of chronic uveitis. Collectively, TCM-based treatments for uveitis can effectively improve patients' clinical symptoms and restore visual acuity. Compared with Western medicine monotherapy, TCM interventions demonstrate distinct advantages in reducing side effects and lowering recurrence rates, thus exhibiting definite efficacy in the clinical management of uveitis.

3.2 Treatment of Uveitis with TCM Extracts

The extraction of highly potent and structurally consistent active compounds from natural TCM has emerged as a significant area of research in the treatment of uveitis. Matrine, derived from the dried roots of *Sophora flavescens* Ait., exhibits antibacterial, anti-inflammatory, and antitumor properties. It is capable of inhibiting the inflammatory response induced by lipopolysaccharide (LPS) [18]. Empirical studies have demonstrated that matrine decreases the levels of interleukin-6 (IL-6), IL-1, and tumor necrosis factor- α (TNF- α) in the serum and aqueous humor of LPS-induced uveitis in rabbits. Furthermore, it suppresses the expression of toll-like receptor 4 (TLR4), myeloid differentiation factor 88, and nuclear factor-kappa B p65 (NF- κ Bp65) in retinal tissues, thereby alleviating ciliary congestion and retinal edema in these animals [19]. Berberine, an isoquinoline alkaloid with anti-inflammatory properties, is extracted from *Coptis chinensis* Franch. It inhibits the differentiation of T helper 17 (Th17) and T helper 1 (Th1) cells, reduces the secretion of inflammatory mediators, and modulates the balance between regulatory T cells (Treg) and Th17 cells in patients with Behçet's disease [20]. Total glucosides of paeony (TGP), extracted from *Paeonia lactiflora* Pall., exhibit anti-inflammatory, analgesic, and anti-stress properties, in addition to enhancing immune regulation. TGP has been shown to normalize abnormal peripheral blood T cell subsets and improve cellular immune function in patients with uveitis, indicating its potential role in modulating immune function in these individuals [21]. Furthermore, TGP inhibits the infiltration of inflammatory cells into the anterior chamber and vitreous body in lipopolysaccharide (LPS)-induced uveitis in rats, and it reduces swelling of the iris and ciliary body as well as retinal edema and thickening [22]. Tripterygium glycosides (TG), derived from *Tripterygium wilfordii* Hook. f., are extensively utilized as anti-inflammatory agents and immunosuppressants [23]. TG has been demonstrated to downregulate the expression of TLR4 and NF- κ Bp65, thereby inhibiting the endotoxin-induced inflammatory response in macrophages and suppressing the release of tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), interferon-gamma (IFN- γ), intercellular adhesion molecule 1, and monocyte chemoattractant protein 1 [24]. Curcumin is a polyphenolic compound extracted from the rhizomes of *Curcuma longa* L. Its therapeutic effect on uveitis is associated with its antioxidant and anti-inflammatory properties [25]. By inhibiting the expression of NF- κ B and the release of IL-1, IL-6, IL-8, and TNF- α , curcumin protects iris ciliary body cells and retinal pigment epithelial cells from LPS-induced inflammatory responses.

3.3 Treatment of Uveitis with TCM Compound Prescriptions

Compared with single-target chemical drugs, TCM compound prescriptions for uveitis exhibit characteristics such as multi-component, multi-pathway, and multi-target synergistic effects, with fewer adverse reactions and favorable therapeutic efficacy. Yin et al. found that Longdan Xiegan Decoction could effectively reduce the mRNA and protein expression levels of Notch1, DLL4, IL-10, and IL-17 in the spleen, lymph nodes, and ocular tissues of experimental autoimmune uveitis (EAU) rats, improve the balance of the Th17/Treg ratio, thereby alleviating the inflammatory response and protecting the ocular tissue structure [26]. Zhu et al. demonstrated through their research that Qufeng Huoxue Pills could decrease the concentrations of IL-2 and Foxp3 in the serum of EAU rats, achieving an anti-inflammatory effect [27]. Additionally, Gao et al. discovered that this prescription might exert its anti-inflammatory effect by inhibiting the expression of apoptosis-related factors Bax and Caspase-3 in uveitis and promoting the expression of Bcl-2 [28]. Yuan et al. found that Qingre Mingmu Granules exhibited a favorable anti-inflammatory effect on EAU rats, with efficacy superior to that of Tripterygium Tablets. The underlying mechanism might be related to inhibiting the secretion of IL-2, IL-17, IFN- γ , and other inflammatory factors, promoting the secretion of IL-10, and regulating cellular immunity [29]. Jin et al. found that Jiawei Danzhi Xiaoyao Powder could effectively improve the visual acuity of patients with acute uveitis of the liver-gallbladder fire blazing type in the short term and downregulate the secretion of inflammatory factors including IL-1, IFN- γ , IL-6, IL-17, and TNF- α [30]. Zhou et al. discovered that modified Simiao Yong'an Decoction had a definite therapeutic effect on anterior uveitis, which was beneficial for improving clinical symptoms, enhancing visual acuity, and reducing recurrence. Its mechanism was considered to be related to the regulation of the body's inflammatory response [31].

3.4 External Therapy for Uveitis

3.4.1 TCM Fuming Therapy for Eyes

Eye fumigation and washing is one of the external treatment methods in traditional Chinese medicine. Lin Zhihui investigated the efficacy of TCM fuming therapy, incorporating ingredients such as chrysanthemum, forsythia, folium isatidis, schizonepeta tenuifolia, and dandelion, in conjunction with standard TCM treatment for patients with uveitis. The findings demonstrated that the integration of TCM fuming therapy with syndrome differentiation and treatment in TCM could lead to a reduction in hormone dosage, a decrease in recurrence rates, and favorable clinical outcomes [32]. Zou et al. utilized the Juhuang Fuming Formula, a TCM preparation, for fuming therapy in patients with uveitis characterized by liver-gallbladder fire blazing syndrome. Their results indicated that TCM fuming therapy significantly mitigated ocular inflammatory responses and enhanced visual acuity [33]. Liu et al. combined TCM fuming therapy, using ingredients such as chrysanthemum, honeysuckle, dandelion, and folium isatidis, with conventional Western medicine for the treatment of anterior uveitis. Post-treatment, patients exhibited notable relief in clinical symptoms and a shortened disease course [34]. The results suggested that this external therapy effectively ameliorated clinical symptoms and visual acuity in affected eyes, reduced inflammatory reactions, and improved patients' quality of life.

3.4.2 Catgut Embedding Therapy and Acupuncture Therapy

Catgut embedding therapy at acupoints and acupuncture therapy also play important roles in the treatment of uveitis, exhibiting significant curative effects by regulating immune function and alleviating inflammatory responses. Zhao et al. selected the Pishu (BL20) and Shenshu (BL23)

acupoints for catgut embedding in experimental autoimmune uveitis (EAU) rats. The results showed that catgut embedding therapy reduced anterior segment inflammation in EAU rats, enhanced IL-4 levels, inhibited IFN- γ expression, and corrected the Th1/Th2 cellular immune imbalance [35]. Zheng et al. found that catgut embedding therapy effectively alleviated anterior segment inflammation and pathological changes in EAU rats, reduced the sharp increase in aqueous humor protein content caused by anterior segment inflammation, inhibited CD4⁺ T lymphocytes and the CD4⁺ T/CD8⁺ T lymphocyte ratio, and promoted the activation and expression of CD8⁺ T lymphocytes [36]. Jiang et al. treated patients with refractory uveitis using TCM acupoint catgut embedding therapy, selecting Mingmen (GV4), Shenshu (BL23), Quchi (LI11), Gaohuang (BL43) as the main acupoints. The results indicated that catgut embedding therapy improved clinical efficacy, enhanced immune function, improved visual acuity, and reduced the recurrence rate [37]. The results showed that acupuncture therapy alleviated patients' conditions, reduced recurrence, and decreased hormone dosage and side effects. These studies confirm that catgut embedding therapy at acupoints and acupuncture therapy can provide safe and effective treatment approaches for uveitis by regulating immune imbalance, inhibiting inflammatory cell activity, and reducing hormone dependence, thereby enriching the clinical methods of TCM in treating this disease.

3.4.3 TCM Iontophoresis

Under the influence of a direct current electric field, TCM iontophoresis facilitates the direct penetration of drugs to the targeted treatment site. This method maintains a high local drug concentration and extends the drug retention time, thereby enhancing the cure rate. In a study by Han Xue et al., TCM iontophoresis combined with hormonal therapy was employed to treat uveitis, demonstrating a significant therapeutic effect while mitigating the adverse reactions and complications associated with hormone use. Zhang et al. applied TCM direct current iontophoresis to patients with uveitis, resulting in improved visual acuity, a shortened disease course, and significant alleviation of clinical symptoms [38]. Shang utilized direct current iontophoresis with a modified Yiyang Jiulian Powder, a TCM formula, for the treatment of uveitis. This approach yielded notable therapeutic outcomes, reduced hormone dosage and side effects, improved clinical symptoms, and significantly increased the cure rate [39]. Furthermore, Han et al. employed TCM iontophoresis to address anterior uveitis of the liver meridian wind-heat type, effectively alleviating symptoms and delaying recurrence [40].

4. Conclusion

Uveitis is characterized by complex pathogenesis, prolonged course, and high recurrence rate. Its pathogenic mechanism has not been fully elucidated, making it one of the clinically intractable blinding ophthalmic diseases. TCM exhibits unique efficacy in treating refractory diseases, featuring multiple components and multi-target actions. Both single herbs and compound prescriptions can effectively alleviate the symptoms of uveitis. The multi-target effects of TCM involve various signaling pathways and factors, achieving comprehensive therapeutic effects through overall regulation to inhibit intraocular inflammation and restore uveal function. In addition, TCM external therapies can also significantly relieve symptoms in uveitis patients. Therefore, this review explores TCM treatment of uveitis through animal experiments and clinical studies, aiming to provide a reference for the clinical application of TCM in the management of uveitis.

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