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Potential Role of Astragaloside IV in the Treatment of Fungal Keratitis

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Abstract

Fungal keratitis (FK) is a worldwide visual impairment disease. The pathogenesis of fungal keratitis involves fungi, corneal cells, inflammatory cell infiltration, collagen degradation, inflammatory cytokines and their interactions. Accumulated evidence indicated that Astragaloside IV (AS-IV) possesses a broad range of pharmacological properties, such as efficacy in anti-inflammation, alleviating fibrosis, and immunomodulatory effects. This paper summarizes new findings regarding AS-IV in immune and inflammatory diseases and analyzes the perspective application of Astragaloside IV in fungal keratitis.

Keywords

Astragaloside IV, Inflammatory, Immune, Collagen Degradation, Fungal Keratitis

1. Introduction

The cornea acts as a barrier to protect the eyes from external attacks including microbial pathogens. Fungal Keratitis may cause corneal immune inflammation, usually leading to corneal melting and scarring, and severe visual impairment. Antifungal therapy is not effective for some fungal strains, which can cause fungal endophthalmitis and blindness [1] [2] [3] [4]. In addition, apart from fungicide, there is no drug to inhibit the degradation of corneal collagen and inflammation in the treatment of fungal keratitis.

At least three different pathways are involved in the development of fungal keratitis: 1) The recognition of infectious agents by the Toll-like receptor (TLR) system initiates the primary innate immune response and later the adaptive immune response [5] [6]; 2) Degradation of collagen fibers by Matrix Metallo proteins (MMPs) synthesized and secreted by corneal cells (including corneal

epithelial cells and corneal stromal fibroblasts) and infiltrating inflammatory cells [7]; 3) Toxic effects of fungal toxins on corneal cells and direct degradation of collagen fibers. New drugs are needed to treat fungi infections which can regulate the function of corneal cells and suppress immune inflammation [8] [9].

Astragalus membranaceus (Fisch) Bge (Huang-Qi) is a well-known herbal medicine with tonic property and has been widely used to treat cancer and other immune disorders in China and Southeast Asia for thousands of years [10]. Astragaloside IV (AS-IV) is considered to be the major bioactive ingredients of Astragalus species. AS-IV initiates the innate and adaptive immune systems by modulating multiple aspects involved in inflammatory process to generate its anti-inflammatory and immunomodulatory effects. As an anti-inflammatory and immunomodulatory agent, the potential role of AS-IV in FK therapy needs to be investigated.

2. Method of Literature Search

Papers and abstracts of relevant studies for this review were obtained from the MEDLINE database. The following search words (inclusive MESH headings) were used: fungal keratitis and TLR, Astragaloside and TLR, fungal keratitis and MMP, Astragaloside and MMP, fungal keratitis and cytokine, Astragaloside and cytokine, fungal keratitis and IL, Astragaloside and IL, fungal keratitis and TNF, Astragaloside and TNF. The search covered publications from 1985 to 2021, and articles published in English.

3. Astragaloside IV and TLR Signaling Pathway

Toll-like receptor (TLR) is a type of transmembrane receptor that acts as the "eye" of primary innate immunity, monitoring and recognizing various pathogen-related molecules, and acting as a bridge between primary innate immunity and adaptive immune response, plays an important role in the identification and defense of pathogens and their products. The expression of TLR2 and TLR4 is significantly increased in fungal infected corneas [11] [12]. Blocking TLR can reduce the corneal inflammation [13]. Aspergillus can up-regulate the expression of TLR2 and TLR4, and increase the production of IL-1 and IL-6 [14]. Anti-TLR2 or anti-TLR4 antibody can inhibit the production of IL-10 by corneal epithelial cells induced by aspergillus [15]. Therefore, TLR and its signal pathway can be used as a target to study the development of fungicide and to research fungal corneal infection in the immune inflammation mechanism.

AS-IV can downregulate TLR4/NF-kappaB signaling pathway and inhibits myocardial cell apoptosis and protected myocardial cells [16] [17] [18]. On memory impairment induced by transient cerebral ischemia and reperfusion in mice, AS-IV significantly reduces the expression of TLR4 and its downstream adaptor proteins and subsequently inhibits NF-kappaB phosphorylation [19]. In Lung Tissue, AS-IV significantly attenuates the level of TLR4 and inhibits neutrophil infiltration and activation in lung tissue [20] [21], and similar results were

seen in the heart, aorta, kidney and liver [20]. In the unilateral ureteral obstruction (UUO) model mouse, AS-IV significantly reduces the Pro-inflammatory cytokines and lps-induced epithelial cells, and at the same time, TLR4 and NF-kappaB, CyrillicB signaling pathway are also inhibited *in vivo* and *in vitro* [22]. In recent studies, As-IV has a similar effect on the reproductive system. Administration with As-IV restrains the high expression of TLR-4 in a rat preeclampsia-like model [23] and in macrophages co-cultured with ovarian cancer cells [24]. In addition, AS-IV can also promote the proliferation of bone marrow mesenchymal stem cells (MSCs) and inhibit the increased expression of TLR4 induced by high glucose [25].

4. Astragaloside IV and Matrix Metalloproteinase

Research has shown that Matrix metalloproteinase (MMPS) are enzymes that play an important role in the development of corneal ulcers. Excessive degradation of collagen fibers in corneal stroma leads to corneal ulcer. Matrix metalloproteinase-1 (MMP-1) is mainly responsible for the degradation of type I collagen fibers. The degradation of type I collagen fibers by MMP-2 and-9 occurs after type I collagen fibers are lysed by MMP-1 and subsequent denaturation of three-dimensional collagen chains [26]. MMP-2 can degrade the basement membrane of epithelial cells and promote the development of corneal ulcer [27]. The expression of MMP-2 and MMP-9 were significantly increased in fungal infected corneas [28] [29]. Thus, inhibition of MMPS production and action during fungal corneal infection may inhibit the progression of corneal ulcers.

AS-IV could markedly reverse the UVA irradiation-induced increase of MMP-1 release in fibroblasts, which prevents collagen reduction and increases dermal thickness in photoaging skin [30] [31] [32] [33]. AS-IV inhibits platelet-derived growth factor (PDGF)-BB-stimulated vascular smooth muscle cells (VSMCs) proliferation and migration and inhibits the up-regulation of MMP-2 [34]. The up-regulations of MMP-9 which are related to cerebral vasogenic edema or cytotoxic edema can be inhibited significantly by AS-IV administration [35]. AS-IV can also suppress the expression of MMP-13 in osteoarthritispatients-derived chondrocytes [36]. Besides, AS-IV could regulate the expression of MMP-2, reduce the formation of collagen fibers, which plays an important role in hepatic fibrosis [37].

AS-IV has also been found to play a role in tumor research. AS-IV reduces MMP and inhibits PC12 cell apoptosis induced by oxidative injury [38]. The migration and invasion characteristics that are related to inflammatory response play important roles in the development of lung cancer. Xudong Cheng's study suggests that AS-IV can significantly decrease the levels of MMP-2, MMP-9 and suppress the migration and invasion ability of A549 cells [39]. Similar findings have been reported in breast cancer, glioma, vulvar squamous cell carcinoma (VSCC), ovarian cancer [24] [40] [41] [42].

In particular, in 2021 Ramesh Babu Kasetti published an AS-IV article on

ocular disease, and the study showed the antifibrotic effects of AS-IV are mediated via inhibition of NF-kappaB and modulation of MMPs [43]. This findings may encourage more ophthalmologists to join AS-IV studies related to ophthalmic diseases.

5. Astragaloside IV and Inflammatory Cytokines

Among inflammatory cytokines, interleukin (IL) plays an important role in the formation of corneal ulcer. The expression of IL in the corneas of fungal infection was significantly increased [44]. Our previous work has demonstrated that IL-1 stimulates the production of MMP-1, -2, -3 and-9 in corneal stromal fibroblasts and promotes the degradation of corneal collagen [45].

Under the stimulation of inflammatory cytokines, corneal epithelial cells and corneal stromal fibroblasts can produce various inflammatory cytokines, chemokines and adhesion factors, which can promote the aggregation of neutrophil and aggravate the inflammatory reaction of cornea [46] [47].

AS-IV inhibits the production of IL, TNF-α and NO in macrophages and Microglia [48] [49] [50] [51]. In LPS-induced acute kidney injury, AS-IV reduces the production of TNF-α and IL-6 in Plasma and activates the ERK Signal Pathway [52].

In addition, there are many experimental studies have confirmed AS-IV inhibits the production of inflammatory cytokines (including IL-1, IL-6, IL-8, IL-10 and TNF-α, etc) in the heart, lungs, brain, ovary, placenta, necrotizing enterocolitis, arthritis and so on [17] [19] [20] [21] [23] [24] [36] [53] [54] [55] [56].

6. Conclusion

Fungal keratitis is very stubborn. In addition to antifungal therapy, developing drugs which can inhibit the degradation of corneal collagen and immune inflammation is needed to prevent the development of ulcers. Toll-like receptor (TLR) plays a key role in innate immune responses in corneal infection. Corneal collagen fibrils serve as the basal component of the corneal stroma, the degradation of corneal collagen by MMPs activated by cytokines and chemokines may lead to the corneal ulcer. Therefore, inhibition of immune inflammation associated with TLR, MMPS and cytokine, and thus reducing the degradation of corneal collagen is considered a potential target for treatment of the corneal ulcer [57] [58]. This review shows that AS-IV can affect TLR signal path, MMPs and the expression of inflammatory cytokines in the heart, lungs, brain, liver, kidneys, ovaries, skin and other organs. AS-IV has definite immunomodulatory and anti-inflammatory effects, which have potential value in the treatment of fungal keratitis to inhibit the degradation of corneal collagen and suppress the immune inflammation.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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