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Review

Exploring Herbal Alternatives for Conjunctivitis Management: Opportunities and Challenges

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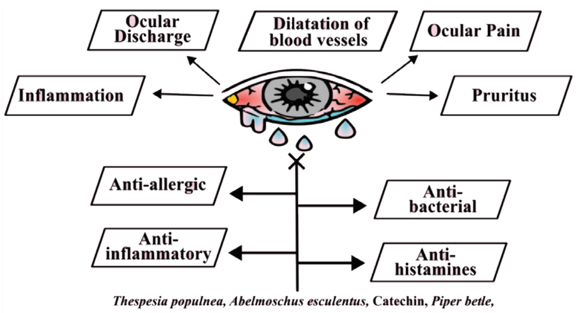
Abstract

The eyes, vital sensory organs, are particularly vulnerable to various ophthalmic conditions. Conjunctivitis, or "pink eye", is one such condition characterized by inflammation and redness of the conjunctival mucosa, caused by both infectious and non-infectious agents. Affecting approximately 6 million people annually in the United States alone, its highly contagious nature presents a public health concern. Current treatments, predominantly synthetic drugs, often result in undesirable side effects. In response, there is growing interest in exploring herbal remedies as safer alternatives. Medicinal plants, rich in bioactive compounds such as alkaloids, glycosides, and terpenoids, show potential in managing conjunctivitis. Specific herbs, including *Euphrasia officinalis* L. (eyebright), *Matricaria chamomilla* L. (chamomile), and *Aloe vera* (L.) Burm.f., have demonstrated promising results in in vitro and animal studies by mitigating mast cell degranulation and modulating key inflammatory pathways. This review aims to delve into the efficacy, safety, and mechanisms of action of these and other herbal treatments for conjunctivitis, offering a focused evaluation of their therapeutic potential.



Keywords: Conjunctivitis; Inflammation; Medicinal herbs; Anti-allergic; Efficacy; Prevention

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Introduction

Conjunctival hyperemia, also known as conjunctivitis, refers to the inflammation of the conjunctival tissues, a medical condition marked by various factors. These include allergic or immunological responses, bacterial, viral, fungal, or parasitic infections, mechanical irritation, or exposure to harmful substances, all contributing to the dilation of conjunctival blood vessels, resulting in redness, swelling, and increased temperature. Importantly, these infections can affect one or both eyes [1,2]. Moreover, it is crucial to emphasize that this condition is prevalent in tropical and subtropical regions. There is a common belief that direct contact with the ocular discharges of an infected individual can highly transmit the contagious nature of the condition [3]. Diagnosing this medical condition relies on observing various signs and symptoms, including the presence of watery (serous), mucus-like (mucoid), or mucus-pus (mucopurulent) ocular discharge, discomfort, pain, increased prominence of blood vessels in the eye, persistent sensation of foreign matter, itching, eyelid swelling, dryness, and eye puffiness [4,5]. Moreover, individuals with conjunctivitis commonly experience photophobia. Alongside ocular symptoms, sneezing and nasal congestion may also manifest. It is crucial to highlight that these symptoms arise from the heightened activation of various signaling pathways and modulators involved in the inflammatory process [6]. The conjunctiva consists of epithelial layers, namely stratified squamous epithelium and stratified columnar epithelium, along with stromal layers characterized by a thin, semi-transparent, and elastic composition [7,8]. These layers collectively serve as a gateway for allergens, pathogens, and foreign bodies. Additionally, the conjunctiva acts as a protective barrier for the posterior portion of the eyelids and the white area of the eyes. It can be divided into three main regions: the conjunctival fornices, which join the palpebral and bulbar conjunctiva, facilitating flexible movement; the palpebral conjunctiva, covering the interior of the eyelids; and the bulbar conjunctiva, lining the anterior scleral region. Moreover, the conjunctiva is rich in goblet cells and lymphatic tissues, both contributing to its strong vascularity [9,10].

Throughout history, herbal medicines have been globally employed as traditional remedies for numerous human ailments, spanning centuries. In instances of acute conjunctival hyperemia, the condition typically resolves spontaneously within a few days. However, in cases of chronic conjunctivitis or to hasten the recovery process, various agents are often utilized, such as antihistamines, mast cell stabilizers, corticosteroids, artificial tears, antibiotics, and antiviral medications [11]. However, it is crucial to take into account the potential adverse effects associated with the use of antihistaminic ophthalmic formulations, including dryness, redness, and ocular irritation [12]. Moreover, the antibiotic chloramphenicol, specifically, has been linked to a condition known as blood dyscrasias across all age groups, as well as the gray baby syndrome in infants and recent review reported that 30-40% of bacterial conjunctivitis cases now show resistance to first-line antibiotics [13–15]. Furthermore, prolonged corticosteroid use in allergic conjunctivitis has been linked to complications such as cataracts and glaucoma [16]. The factors mentioned above underscore the primary concern regarding the adverse effects of chemical substances on the ocular surface. Hence, it is vital to explore alternative options, such as the use of herbal drugs, to mitigate the potential burdens associated with chemical usage. Additionally, factors like the growing population, escalating treatment costs, adverse side effects, and the emergence of drug resistance due to synthetic drugs necessitate a greater emphasis on utilizing plants for disease control and treatment. The study objective seeks to provide an in-depth analysis of herbal remedies for the treatment of conjunctivitis, with a critical examination of studies conducted in in vitro, in vivo, and clinical trial settings to investigate their safety, effectiveness, and underlying mechanisms of action, as well as constraints and prospects for future research.

Types of Conjunctivitis

Bacterial conjunctivitis

The conjunctiva, a thin, transparent membrane covering the white part of the eye and the inner surface of the eyelids, is usually considered healthy when it hosts a small number of bacterial colonies typically less than 10. However, in cases of bacterial conjunctivitis, a highly contagious infection impacting the conjunctiva, there is a notable increase in the bacterial flora [17,18]. This bacterial proliferation is often accompanied by visible symptoms, including the presence of a yellow-white mucopurulent discharge and eyes that appear glued together [19]. Moreover, another hallmark symptom of bacterial conjunctivitis is the presence of a papillary reaction, signifying the enlargement and inflammation of the small projections on the surface of the conjunctiva [20]. Interestingly, despite the presence of bothersome symptoms, individuals with bacterial conjunctivitis typically do not experience itching. It is important to note that bacterial conjunctivitis usually manifests as a bilateral infection, affecting both eyes simultaneously [21,22]. Upon examining the discharge linked with bacterial conjunctivitis, it becomes apparent that it primarily consists of neutrophils, a type of white blood cell responsible for combating bacterial infections [23]. Lastly, it is worth mentioning that the organisms causing bacterial conjunctivitis can vary depending on the patient's age

[24]. In other words, the types of bacteria causing the infection may differ between children and adults (Figure 1).

In neonates, it is commonly observed that *Chlamydial trachomatis* is the causative agent for conjunctivitis, which typically occurs approximately one week after birth in babies born to mothers suffering from a cervical chlamydial infection. [25-27]. It is noteworthy that *Hemophilus influenzae* and *Staphylococcus pneumoniae* contribute to 29% and 20% of conjunctivitis cases among children, respectively [28,29]. *S. pneumoniae*, the second most prevalent cause of bacterial conjunctivitis in children, often triggers epidemic outbreaks among young adults. In recent occurrences, unencapsulated strains of *pneumococci* have caused outbreaks, affecting 92 individuals undergoing training at a military facility and 100 students enrolled at DatMouth University. [30]. Moreover, it has been noted that conjunctivitis caused by *H. influenzae* often coincides with upper respiratory infections and otitis media [31]. Conjunctivitis caused by *S. aureus* tends to recur frequently in adults, especially in the middle-aged population. In adults, the presence of *S. aureus* and *H. influenza* is often associated with the occurrence of conjunctival hyperemia. Additionally, conjunctiva infected with *S. aureus* tends to undergo recurring episodes and is also linked to the development of chronic blepharoconjunctivitis [32-34]. Moreover, it has been noted that around 20% of individuals consistently harbor *S. aureus* in their nasal passages, with an additional 60% experiencing intermittent carriage. In both cases, these bacteria have the potential to act as a reservoir for recurrent ocular infections [35]. Other microorganisms commonly implicated in conjunctivitis among adults include *S. pneumoniae*, coagulase-negative Staphylococci, as well as species of *Moraxella* and *Acinetobacter* [36]. Furthermore, among the 1041 subjects diagnosed with conjunctivitis, 17% exhibited polybacterial infections, primarily caused by the *Streptococcus mitis* group of bacteria. Additionally, viral coinfection was identified in some cases. The prevalence of polybacterial infections underscores the significance of employing broad-spectrum antibiotic agents in conjunctivitis treatment [37,38].

Viral conjunctivitis

According to classical definitions, viruses are categorized as obligate intracellular parasites. Observations indicate that approximately 80% of investigations into conjunctivitis cases are attributed to viral infections [39]. Viral conjunctivitis is chiefly caused by a variety of viruses, including adenovirus, enterovirus, coxsackie virus, chlamydia, herpes simplex virus (HSV), varicella-zoster virus (VZV), measles virus, and mumps virus [40-45]. Among these viruses, adenovirus is responsible for approximately 60% of all cases of conjunctival hyperemia. To illustrate this, a study analyzed 176 conjunctivitis samples, revealing that 74.2% of them tested positive for adenovirus. Following adenovirus, enterovirus 70 and enterovirus 71 were detected in 6.4% of the samples each; while coxsackie virus 16 and 24 were found in 1.6% of the samples, each representing two subjects [46]. Symptoms of viral conjunctivitis encompass erythema, engorged blood vessels, ocular discharge mainly consisting of

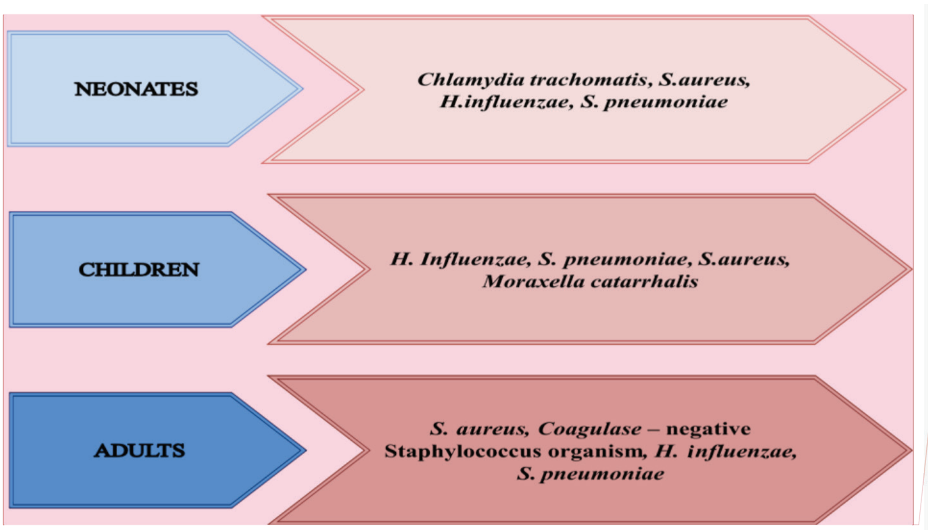

Figure 1. Predominant bacterial agents in Bacterial Conjunctivitis across age groups
In neonates, bacterial conjunctivitis is commonly caused by *Chlamydia trachomatis*, *S. aureus*, *H. influenzae*, and *S. pneumoniae*, contributing to conjunctival hyperemia. Among children, *H. influenzae*, *S. pneumoniae*, *S. aureus*, and *M. catarrhalis* are primary pathogens, while in adults; *S. aureus*, coagulase-negative *Staphylococcus*, *H. influenzae*, and *S. pneumoniae* are frequently implicated. This illustration emphasizes that while specific pathogens vary by age, *S. aureus*, *H. influenzae*, and *S. pneumoniae* are consistently prominent across all groups, underlying their central role in bacterial conjunctivitis development.

lymphocytes, pain, photophobia, and the formation of pseudomembrane. Identifying the causative agent in viral conjunctivitis cases can be challenging, emphasizing the vital role of laboratory diagnostics [47]. Adenovirus, a prominent causative agent of viral conjunctivitis, belongs to the Adenoviridae family, specifically the Mastadenovirus genus. These viruses are characterized by double-stranded, non-enveloped DNA. Adenoviral conjunctivitis is further classified based on serotypes. Serotypes 3, 4, and 7 are typically linked to pharyngoconjunctival fever (PCF); whereas serotypes 8, 11, 19, and 37 are associated with highly contagious epidemic keratoconjunctivitis (EKC). EKC often presents severe symptoms such as excessive discharge, heightened tear production, membrane formation, and multiple subepithelial corneal infiltrates. Chronic keratoconjunctivitis is predominantly caused by serotypes 2, 3, 4, and 53, which are less commonly implicated in adenoviral ocular diseases [48-50]. Moreover, viral conjunctivitis can also be caused by other viruses such as rubella, rubeola, Epstein-Barr, and Newcastle viruses [51].

Allergic conjunctivitis

Allergic conjunctivitis is defined as a type-1 hypersensitivity reaction, as classified by Coombs and Gell. This reaction is mediated by IgE, initiating an anaphylactic response. In the sensitization phase, IgE immunoglobulin interacts with allergens like dust, pollen, and animal dander, penetrating the conjunctiva. This interaction triggers the release of signaling modulators, which facilitate the recruitment of immune cells to the inflamed conjunctival mucosa [52-54]. As a result, plasma cells increase the production of IgE immunoglobulins, which triggers the degranulation of mast cells. This degranulation releases various substances such as histamine, tryptase, chymase, leukotrienes, chemokines, acid hydrolase, peroxidase, phospholipase, tumor necrosis factor (TNF)-α, and prostaglandins D2 [55-58].

These substances contribute to the early phase reactions, characterized by the involvement of basophils, Th-2 cells, and eosinophils. This infiltration leads to the generation of eosinophilic cationic protein (ECP), major basic protein (MBP), leukotrienes, platelet-activating factor (PAF), enzymes, lipid mediators, nitric oxide, and acid hydrolase. Additionally, mast cell degranulation also results in the infiltration of excessive tearing, itching, redness, and edema. These substances further accelerate the late phase reaction that occurs upon re-exposure to allergens [59,60]. The late phase reaction is marked by symptoms including photophobia, ocular pain, visual impairment, and discharge, all linked to the presence of eosinophils [61,62] (Figure 2). Allergic conjunctivitis presents in various clinical forms, including seasonal or intermittent allergic conjunctivitis (SAC), persistent or chronic allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), contact lens-induced conjunctivitis (CLC), and giant papillary conjunctivitis [63]. Vernal keratoconjunctivitis refers to a persistent form of seasonal allergic conjunctivitis, marked by an enduring inflammatory response affecting both the conjunctiva and the superficial cornea [64-66]. This persistent form of allergic conjunctivitis is also termed atopic keratoconjunctivitis, stemming

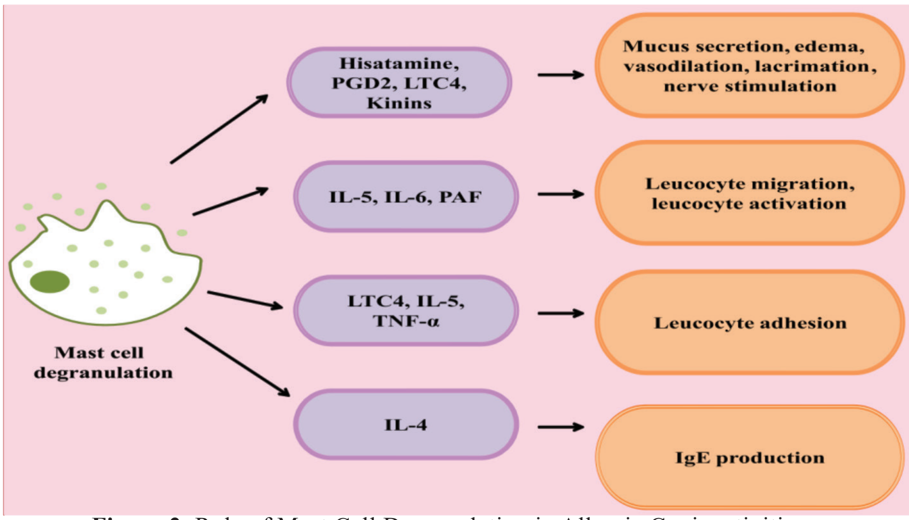

Figure 2. Role of Mast Cell Degranulation in Allergic Conjunctivitis.
This figure highlights the complex network of inflammatory mediators and immune responses that underlie allergic conjunctivitis. Upon activation, mast cells release inflammatory mediators like histamine, PGD2, and LTC4, causing mucus secretion, blood vessel dilation, excessive tearing, and nerve stimulation. Cytokines such as IL-5, IL-6, and PAF recruit white blood cells to the site; while LTC4, IL-5, and TNF-α enhance cell adhesion to the conjunctival tissue. Additionally, IL-4 promotes IgE production, which increases mast cell degranulation, amplifying the inflammatory response.

from the underlying condition referred to as "atopy." Atopy is a hereditary disorder characterized by an overproduction of antibodies by the immune system in response to allergens, leading to a year-round disease. Importantly, symptoms of this condition may exacerbate during the winter season [52,66]. Symptoms of ophthalmic allergy, commonly associated with upper respiratory allergies and allergic rhinitis, are notably influenced by interconnected epidemiological factors of allergic rhinitis and allergic conjunctivitis [67]. Consequently, individuals afflicted with any of these allergies will inevitably experience symptoms associated with the other conditions [68].

Herbal remedies for conjunctivitis

Traditional herbal treatment

Since ancient times, plants have served as a valuable repository of medicinal compounds. The use of plants in treating various human ailments is documented in Ayurveda and other Indian literature. India boasts a rich diversity of plant species, many of which are believed to possess therapeutic properties. While conventional medicine has its merits, challenges such as population growth, limited pharmaceutical resources, high treatment costs, adverse drug reactions, and multi-drug resistance associated with synthetic drugs have underscored the importance of focusing on herbal remedies for disease management. The affordability of herbal treatments has also garnered significant attention. India, known for its abundant medicinal plants, stands as one of the world's oldest civilizations. For centuries, indigenous herbs have been used in the treatment of conjunctivitis as traditional medicine and household remedies. Plants like *Acacia arabica* (Lam.) Wild, *Berberis asiatica* Griff., *Ocimum gratissimum* L., *Vitellaria paradoxa* C.F.Gaertn., *Butea monosperma* (Lam.) Kuntze, *Vitis vinifera* L., *Mentha arvensis* L., *Calendula officinalis* L., and various others are employed for this purpose [69-78]. However, scientific evidence provides a thorough understanding of the efficacy of medicinal plants. Both in vitro and in vivo studies elucidate the mechanisms through which these plants alleviate conjunctival hyperemia (Table 1). These mechanisms may encompass antihistamines, antibacterial, anti-inflammatory, or anti-allergic properties, as well as enhanced compatibility. Two Malvaceae species native to the Caribbean, namely *Thespesia populnea* (L.) Corr. and *Abelmoschus esculentus* (L.) Moench, have been employed in conjunctivitis treatment. The ethanolic extracts of the flowers and fruits from both species underwent testing using the agar plate disc diffusion method against Gram-positive *Bacillus cereus*, Gram-negative *Pseudomonas aeruginosa* bacteria, and the fungus *Candida albicans*. The findings revealed antibacterial activity in both samples, although the antifungal activity was inconclusive [79]. In Ghana, *Heliotropium indicum* L. is utilized as a traditional remedy for treating conjunctivitis. The topical application of the aqueous extract of the entire plant to guinea pigs sensitized with ovalbumin (OVA) led to a notable reduction in total serum IgE levels. This demonstrated anti-allergic activity via immunosuppressive effects [80]. By inhibiting nuclear factor-κB (NF-κB) activation, *Heliotropium indicum* could help decrease the expression of inflammatory genes and reduce symptoms of conjunctivitis [81]. Catechins are polyphenolic compounds belonging to the flavonoid group. In this study, guinea pigs with OVA-induced allergic conjunctivitis were treated with a combination of catechin and the H1-antihistamine drug cetirizine. The administration of this combination resulted in a notable decrease in histidine decarboxylase enzyme activity in the catechin-treated animals, while the cetirizine group did not exhibit any activity among enzymes and histamine content. In summary, catechin demonstrated anti-allergic activity by inhibiting the histidine decarboxylase enzyme, and the combination showed anti-allergic activity at a minimal dosage [82]. Taraxerone, a terpenoid compound derived from *Leucas lavandulifolia* Sm. of the Lamiaceae family, was examined for its immunomodulatory effects across various cell types, including peripheral blood mononuclear cells, neutrophils, macrophages, and Swiss albino mice, using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. At elevated concentrations, taraxerone inhibited the production of activated nitric oxide, interleukin (IL)-4, IL-6, and phagocytosis. These findings suggest that taraxerone holds potential as a potent therapeutic agent for allergic conjunctivitis treatment [83]. A computational assessment of *Glycyrrhiza glabra* L. was performed against the Gram-positive bacterium *Staphylococcus spp*., a frequent causative agent of conjunctivitis. Isocitrate dehydrogenase, a critical enzyme in the biochemical pathway, was targeted. Among the phytochemicals studied, rosmarinic acid displayed the strongest interaction and possesses the potential to hinder the life cycle of *Staphylococcus* [84].

Aloe vera, a prominent medicinal plant belonging to the Asphodelaceae family, features robust, pointed leaves emerging from a short stem near the ground. The methanolic extract of *Aloe vera* was employed to evaluate its effectiveness in treating keratoconjunctivitis in infected sheep using the disc diffusion and well diffusion techniques against *Moraxella ovis*, *S. aureus*, and *Proteus spp*. The examination of the extract revealed significantly higher antibacterial activity against the Gram-positive bacterium *S. aureus* compared to Gram-negative bacteria [95]. This may involve the downregulation of inflammatory markers

Table 1. Medicinal plants and its mode of action in conjunctivitis treatment

Plant/ Phytometabolites	Methodology In vitro/ Cell line or cell culture	In vivo/ Species	Dosage / ROA	Results	Ref.
Thespesia populnea (L.) Corr. *Abelmoschus esculentus* (L.) Moench	Agar plate disc diffusion/ Gram positive *Bacillus cereus* bacteria, gram negative *Pseudomonas aeruginosa bacteria* and fungus *Candida albicans*		30 µL of both extracts were placed in disc	Ethanol extracts from *T. populnea* fruits and flowers effectively inhibited the growth of both bacteria. Ethanol extracts from *A. esculentus* fruits and flowers showed slight inhibition of bacterial growth. However, tests with the fungus *Candida albicans* yielded inconclusive results.	[79]
Catechin		OVA – induced model/ Guinea pig	Catechin, 100 mg/kg; cetirizine, 10 mg/ kg and combination of both 50 mg/kg & 5 mg/kg; orally for 14 consecutive days and sensitization by ovalbumin; i.p. injection for period of 14 days	Catechin demonstrated potent anti-allergic activity by inhibiting the histidine decarboxylase enzyme.	[82]
Piper betle L.	Agar well diffusion method/ *Staphylococcus aureus*		*P. betle* extract concentrations (0.5%, 1%, 1.5%, 2%, 2.5%, and 3%); the negative control group was treated with standard 10% DMSO solution, the positive control group with ceftriaxone	Showed a significant difference in between 0.5% and 1%; 0.5% and 1.5%; 0.5% and 2%; 0.5% and 2.5%; 0.5% and 3%; 1% and 2%; 1% and 2.5%; 1% and 3%; 1.5% and 2.5%; 1.5% and 3%; 2% and 3% concentrations, extract showed significant difference on inhibiting the growth of *S. aureus* which had potential effect and used as an antibacterial agent.	[85]
Oleanolic acid (OA)	Eosinophil cell line EoL-1 and RBL-2H3 mast cells	Ragweed pollen (RWP)-specific allergic conjunctivitis (EAC) mouse model/ females BALB/c mice	Both cell lines were treated with 50 mg/ml of RWP or eotaxin in presence or absence of either 5 or 10 µM of OA for 24 h/ sensitization with 200 µl from a mixture of 50 µg RWP in 0.25 mL Inject Alum; i.p. for 10 consecutive days and on 10^{th} day 1.25 mg of RWP powder were instilled; OA with final conc. of 0.2 ml, w/v of DMSO; i.p. and ocular instillation.	OA treatment limited mast cell degranulation and eosinophil infiltration in conjunctival tissue, along with reducing allergen-specific Ig levels in EAC mice, suppressed RWP-specific T-cell proliferation reduced the synthesis of proinflammatory mediators, in EoL-1 eosinophils and RBL-2H3 mast cells exposed to allergic and/or critical inflammatory stimuli such as RWP, sPLA2-IIA, or eotaxin.	[86]
Pistia stratiotes L.		OVA – induced murine model/ ICR mice	Sensitization, 0.2 ml containing 100 µg OVA and 0.01 mg aluminum hydroxide in phosphate buffer saline of pH 7.4 for consecutive 15 days; On 15-18^{th} days 1.5 mg OVA in 10 µL phosphate buffered saline instilled into conjunctival sacs/ Pretreatment, Aqueous extract of PS in conc. 10, 50 or 100 mg/ kg; per os before 1 h of OVA administration; 5 mg/kg of CET; per oral as std. drug.	Pretreatment with PS (at doses of 50 and 100 mg/kg) before OIAC significantly decreased serum OVA-specific IgE levels, and dose-dependently reduced conjunctival redness, chemosis, tearing, and lid scratching whereas no significant difference was observed with CET pretreatment.	[87]

Heliotropium indicum L.		OVA – induced allergic conjunctivitis model/ Guinea pig	Sensitization, 0.2 mL solution containing 100 μg OVA and 0.01 mg aluminum hydroxide in PBS (pH 7.4) at an interval of 2 weeks. On day 8, conjunctivitis was induced by topical instillation of 1.5 mg OVA in 10 μL PBS into the conjunctival sac/ Pretreatment, HIE, 30, 100, and 300 mg/ kg; 10 mg/kg chlorpheniramine; 30 mg/kg Prednisolone and 10 mL/kg PBS; per os; twice daily for one week	At doses of 30 and 300 mg/kg, there was a significant reduction in allergic inflammation, whereas the 100 mg/kg dose did not show the same effect. Histopathological assessment revealed that treatment with 30 and 300 mg/kg resulted in reduction in mononuclear infiltrations.	[88]
Euphrasia officinalis L.	Human normal corneal cell line		A dose of 100 µL of cell suspension (1×10^5 cells/mL) was added to the appropriate medium and ethanol, ethyl acetate and heptane extracts of *E. officinalis* extract concentration	All extracts tested exhibited a reduction in pro-inflammatory cytokine expression (IL-1β, IL-6, and TNF-α), as well as a decrease in anti-inflammatory IL-10 expression, when added to the cell culture medium for 24 h in human corneal cells.	[89]
Quercetin		OVA – induced allergic conjunctivitis model/ C57BL/6 mice	Sensitization were carried out; pretreatment with quercetin, 1mg/kg, 2 mg/kg and 4 mg/kg; Bafetinib, 10 µM and Tolimidone, 10 µM; per os; for successive experimental days.	Quercetin might act through its ability to inhibit Lyn/PLCγ/IP3R–Ca^{2+}, Lyn/ERK1/2, and Lyn/NF-κB signalling; Lyn kinase inhibitor.	[90]
Phaeanthus ophthalmicus (Roxb. ex G.Don) J.Sinclair	Serial dilution method/ Methicillin-resistant *Staphylococcus aureus*, CRE *Klebsiella pneumoniae*, vancomycin resistant *Enterococcus* and MβL-*Pseudomonas aeruginosa*		100 µL test extract in the dilution series; positive drug celecoxib	It showed the inhibitory potential of the alkaloids on both COX isoforms, with better selectivity against COX-2 and 2 showed selectivity against the COX-2 isoform compared to 1	[91]
Vitellaria paradoxa C.F.Gaertn.	Agar well diffusion method/ *Staphylococcus aureus*	-	Ethanolic seed oil extract of *V. paradoxa*, 100, 50 and 25 mg/mL	Oil seed extract of *V. paradoxa* at 100 mg/mL exhibited the highest zone of inhibition at 37.4 mm for 24 h followed by 50 mg/ml and lowest using 25 mg/ml; exploration for its use as an ocular antibacterial agent	[92]
Nigella sativa L.		OVA –induced allergic conjunctivitis Balb/c mice	Senstization by OVA; TQ, 0.05%, 0.1%, 0.5%; ocular/ Dexamethasone; ocular; for consecutive experimental days	Administration of TQ suppressed the ocular symptoms, inflammatory cell infiltration in conjunctiva, abrogated the mRNA expression and serum level of interleukin including 1L-4, IL-5, IL-13 and TGF-β in mice immunized and exposed to OVA.	[93]

Myracrodruon urundeuva		OVA – induced allergic conjunctivitis model/ Guinea-pigs	Sensitization, 10 µg ovalbumin each, dissolved in 0.5 mL saline, 0.5 ml solution; i.p.; for 2 consecutive weeks, and on 24th day 5 mg ovalbumin diluted in 10 µL saline into the right eyes/ Chalcones, 0.5 mg; 0.05 mg of 0.1% fluorometholone acetate (std. drug); ocular instillation; thrice daily for successive seven days	Chalcones from *M. urundeuva* stem barks presented anti-inflammatory and antioxidant effects, and drastically inhibited the MPO activity, pointing them as candidates for the treatment of allergic conjunctivitis.	[94]
Aloe vera (L.) Burm.f.	Disc diffusion and well diffusion/ *Moraxella ovis, S. aureus* and *Proteus* spp.	Kerato-conjunctivitis infected sheep	One drop of AV extract added in disc diffusion and 20 µ of AV extract added in well diffusion method/ AV extract instilled in sheep for 5 consecutive days	A methanolic extract of *Aloe vera* showed significant in vitro antibacterial efficacy against *Staphylococcus aureus, M. ovis, Proteus* species The antimicrobial activity of *Aloe vera* extract showed greater antibacterial activity against Gram+ *S. aureus* as compared to Gram- bacteria *Moraxella ovis* and *Proteus*	[95]
Matricaria chamomilla L.	Liquid cultures of *Streptococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pneumonia*		Chamomile eye drops for 5, 10, 15, and 45 min	Reduction in *P. aeruginosa* CFUs when the bacteria were exposed to any of the three concentrations of the chamomile drops as early as 5 min, with maximal reduction upon exposure to the 30% concentration at 45 min. Reduction in *S. aureus* CFUs, was observed for all three concentrations as maximal in the 5 min of exposure, which was almost immediate at 10% concentration. *Streptococcus pneumoniae* reduction happened at 5 min and continued through the 45-min observation period for all three concentrations.	[96]

such as IL-1 and IL-6, promoting a more balanced immune response in the conjunctival tissue [97]. *Hydrastis canadensis*, commonly known as "Goldenseal," is utilized as an antiseptic and has demonstrated efficacy as a remedy for catarrhal and purulent conjunctivitis [98]. *Graptopetalum paraguayense*, a Chinese folk medicinal plant belonging to the Crassulaceae family, was used in the study. Fresh juice extracted directly by pressing out *Graptoveria* leaf was applied twice daily without dilution to the irritated eyes of eight volunteers selected with both bacterial and allergic conjunctivitis. Improvement in conjunctival mucosa was observed within 2-3 days, attributed to the synergistic activity of bioactive phytometabolites in the *Graptoveria* plant [99]. The investigations outlined in references [79,85,89,91,92,96] face potential drawbacks due to a lack of animal studies demonstrating the impact of samples on complex organ systems. Similarly, the dissertation on [82,87,88,90,93,94] suffer from insufficient in vitro experiments, limiting understanding of tissue sensitivity. The paper discussing [99] encounters challenges in elucidating the precise mechanism of action, which may necessitate further examination. *In silico* studies mentioned in [84,91] primarily demonstrate binding affinity, yet the choice of ligand, whether an agonist, antagonist, or inverse agonist, could lead to complex hypotheses [100-102]. Clinical studies remain essential constraints for understanding the utilization of herbal drugs in humans and the potential adverse effects they may induce.

Herbal formulations

An ideal drug carrier system should exhibit optimal drug loading and release properties, ensuring an extended shelf life and demonstrating higher therapeutic efficacy with minimal side effects. These systems play a crucial role in overcoming multi-drug resistance and penetrating cellular barriers, thereby enhancing drug efficacy. Additionally, they can modulate drug pharmacokinetics and biodistribution, ultimately reducing side effects. Novel drug delivery systems are crucial for improving the bioavailability of herbal drugs. They provide several benefits over traditional formulations, such as enhanced solubility, increased bioavailability,

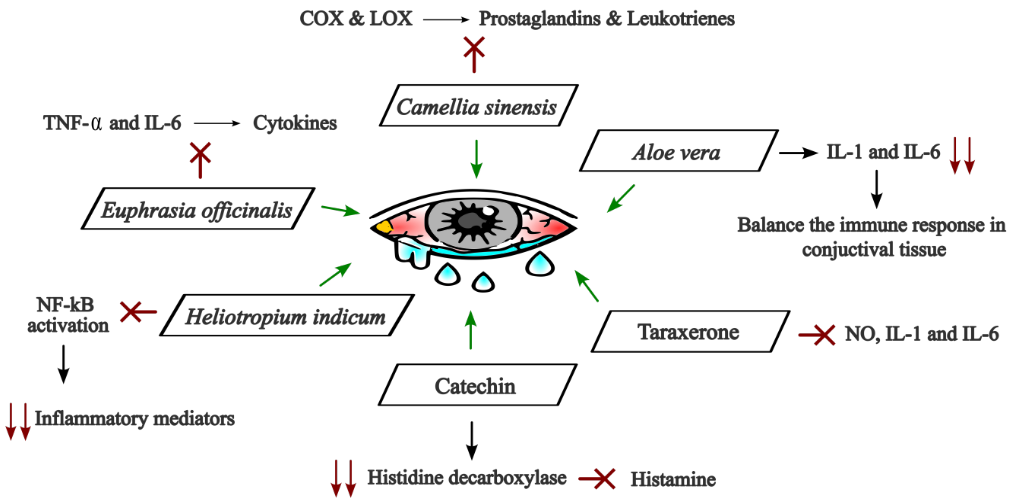

Figure 3. Cellular Mechanisms of Herbal Remedies in Conjunctivitis Treatment
This diagram illustrates the cellular-level actions of herbal compounds in managing conjunctivitis by inhibit mast cell degranulation, reduce cytokine production, and prevent white blood cell adhesion to conjunctival tissue. These actions collectively help alleviate inflammation, reduce symptoms like redness and swelling, and support ocular health by modulating the inflammatory response associated with conjunctivitis.

and greater pharmacological activity [103]. They also improve tissue distribution, provide sustained delivery, and protect drugs from degradation. The analysis of various herbal formulations and their efficacy in anti-conjunctival activity was conducted.

Recently an investigation centered on evaluating the effectiveness of a gel formulation containing *Sesbania grandiflora* (L.) Poir. flower extract against infectious conjunctivitis. The antimicrobial efficacy of the formulation was assessed using strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. The agar well diffusion method was employed under optimal conditions to determine the antimicrobial activity. The results indicated that the formulation exhibited varying degrees of activity against different strains. Specifically, it showed the minimum activity against *C. albicans*, resulting in a zone of inhibition with a diameter of 13.21 ± 3, while demonstrating the maximum zone of inhibition with a diameter of 19.54 ± 1 against *P. aeruginosa*. This suggested the presence of both antibacterial and mild antifungal activities in the formulation [104].

Camellia sinensis (L.) Kuntze, a member of the Theaceae family, stands out as a notable nutraceutical plant. Green tea, sourced from the unfermented leaves of *C. sinensis*, contains a higher concentration of catechins compared to black tea, which undergoes fermentation [105]. The potential of aqueous extracts of *C. sinensis* was investigated for the green synthesis of silver nanoparticles used in treating allergic conjunctivitis *in vivo*. Allergic conjunctivitis was induced in Dunkin-Hartley Guinea pigs by intraperitoneal injection of ovalbumin and aluminium hydroxide in a phosphate-buffered saline solution at two-week intervals. On the eighth day, conjunctivitis was fully induced by instilling ovalbumin into the eyes of selected animals. The effects of various concentrations of AgNPs derived from *C. sinensis* (10, 20, 40, and 80 µg/kg) were compared with standard drugs chloramphenicol (10 mg/kg) and prednisolone (30 mg/kg), as well as a control group treated with phosphate-buffered saline (10 mL/kg). Quantification of serum OVA-specific total IgE, IgE, and IgG revealed a significant reduction and mild mononuclear infiltration compared to the control group. The concentrations of 40 and 80 µg/kg of AgNPs resulted in reduced severity of allergic conjunctivitis. In chronic cases, corneal involvement, managed with steroids, may lead to severe ocular complications, which can be mitigated by employing a novel drug delivery system [106]. The possible mechanism could be due to the presence of polyphenols in *C. sinensis,* particularly epigallocatechin gallate (EGCG), have been shown to inhibit the activity of enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), which are involved in the inflammatory response. By blocking these enzymes, *C. sinensis* can potentially reduce the synthesis of inflammatory mediators such as prostaglandins and leukotrienes [107]. A novel approach entails the use of nanosplanlastic nanovesicles for drug delivery, offering promise in treating chronic allergic conjunctivitis. By synthesizing green tea extracts into nanosplanlastic nanovesicles, the contact time with conjunctival and corneal surfaces is prolonged, presenting potential as a therapeutic option for this condition [108].

Justicia procumbens T.Anderson ex Nees, a member of the Acanthaceae family, is commonly known as the Oriental Water Willow and Shrimp Plant. Historically, this plant has been primarily used for managing fever, cough, jaundice, edema, asthma, sore throats, and snake bites [109]. Experimental findings have shown that the ethanol extract of *J. procumbens* is safe for consumption up to a dosage of 100 mg. Acute irritancy studies involving albino rabbits were conducted to assess the anti-conjunctival activity of this extract. Allergic conjunctivitis was induced by applying turpentine liniment to selected animals. Eye ointment formulations containing doses of 20 mg (0.4% w/w) and 10 mg (0.2% w/w) were topically administered to the rabbits' eyes. The efficacy of this ointment was then compared to that of standard betamethasone (0.5% w/w), revealing significant anti-inflammatory properties in rabbits afflicted with conjunctivitis [110]. Belonging to the Acanthaceae family, *Blepharis maderaspatensis* (L.) Heyne ex Roth showcases a wide array of pharmacological activities, encompassing cancer prevention, sedative properties, anti-arthritic effects, antimicrobial and antifungal attributes, along with anti-ulcer and cytotoxic effects. [111]. In this study, eye drops were prepared and evaluated at various concentrations against bacterial smears associated with acute conjunctivitis. Bacterial strains commonly found in acute conjunctivitis, including aerobic gram-positive *S. aureus* and *S. pneumoniae*, as well as gram-negative *E. coli* and *Neisseria gonorrhoeae*, were subjected to evaluation using the disc diffusion method. The prepared formulation was applied to discs at doses of 1 g/mL and 1.5 g/mL, with ciprofloxacin 20 µg serving as the standard. Results indicated that the concentration of the dry plant leaf drug, specifically 600 g dissolved in 400 mL of sesame oil, displayed a significant zone of inhibition. These findings underscore the potential of utilizing *Blepharis maderaspatensis* for the treatment of acute bacterial conjunctivitis [112].

Preparing and using herbal remedies

Herbal eyewashes and compresses

Eyewashes and compresses are utilized to alleviate ocular discomfort, enhance visual clarity, and address various ocular complications. In cases of conjunctivitis, they can effectively reduce hyperemia by providing a cooling and soothing effect, which helps decrease tear secretions and inflammation of the conjunctival epithelium. Cold compresses are particularly beneficial in reducing watery eyes, discomfort, and gritty sensations associated with conjunctivitis; while warm compresses are preferred for treating bacterial conjunctivitis and easing discomfort caused by pus accumulation around the eyelids [113]. Moreover, intermittent application of saline irrigation onto the ocular surface has been noted to accelerate the healing process in cases of contact-lens papillary conjunctivitis and hyperacute conjunctivitis [114,115]. Additionally, frequent irrigation of the conjunctival fornices with normal saline solution has proved to be beneficial for bacterial conjunctivitis [116]. The Ayurvedic remedy Triphala churna combines unique parts of three potent fruits: black myrobalan (*Terminalia chebula Retz.*), Indian gooseberry (*Phyllanthus emblica* L.), and beleric myrobalan (*Terminalia bellerica* (Gaertn.) Roxb.) [117]. A promising study explored the potential of triphala churna, an ayurvedic herbal blend, as an eye rinse. Researchers tested a decoction (a boiled concentrate) of the formula on 68 eyes of 51 patients with eye issues. The rinse was administered twice daily for four days. Interestingly, a remarkable 40% of patients achieved complete resolution of their symptoms; while over 70% saw improvements in their condition [118]. Rose infusion, also known as rose water, represents one of the most cost-effective and soothing astringents available, and can be applied as a compress to provide soothing and cooling effects, resulting in a remarkable reduction in tearing, nociception, inflammation, and discomfort. Additionally, the antimicrobial activity of rose petals provides an added advantage [119,120]. A randomized, double-blind clinical trial was conducted to evaluate the efficacy of non-pharmaceutical therapy for acute seasonal allergic conjunctivitis in 18 individuals allergic to grass pollen. Participants were deliberately exposed to grass pollen to induce an allergic reaction in the eyes, after which they received various treatments: artificial tears, cold compress, a combination of both, and epinastine hydrochloride alone or with a cold compress. A control group received no treatment. The severity of conjunctival hyperemia, ocular surface temperature, and symptoms were assessed before treatment and at regular intervals for one hour afterward. Results indicated that non-pharmaceutical treatments effectively reduced conjunctival inflammation and normalized ocular surface temperature compared to the control group. Moreover, the combination of cold compress, artificial tears, and epinastine hydrochloride significantly lowered the heightened ocular surface temperature induced by allergen exposure. Cold compress, combined with either artificial tears or epinastine hydrochloride, demonstrated similar cooling and soothing effects [121].

Safety cautions

Administering a saline solution requires caution due to the potential pro-inflammatory stress resulting from high salt concentration. Hyperosmolarity can trigger signaling cascades that stimulate the expression and production of pro-inflammatory cytokines like IL-1β, TNF-α, and MMP-9. It also activates JNK, ERK, and p-38 MAPK signaling pathways on the ocular surface in mice. The thesis posits that hyperosmolar stress, which may lead to dry eyes, exacerbates inflammation of the ocular surface [122,123]. Caution should be exercised when using both cold and warm compresses. Hyper-cold compresses may impede blood circulation around the eyes; while warm compresses can elevate skin temperature and potentially lead to the removal of dermal layers around infected eyes. Additionally, the use of herbal eye irrigation and herbal infusions requires careful consideration, as they can be absorbed systemically and have both local and systemic effects, potentially resulting in adverse effects. Herbal remedies like chamomile and turmeric may interact with medications such as blood thinners [124,125]. For children, pregnant women, and individuals with allergies, there is a heightened risk of adverse reactions. Older adults with thin skin or glaucoma could be more susceptible to irritation or pressure changes from eye treatments. It is advisable to consult a medical practitioner before using herbal remedies.

Efficacy and Research

In recent years, there has been significant advancement in our understanding of botanical medicines, encompassing aspects such as safety, efficacy, quality control, marketing, and regulatory considerations. Phytotherapeutic agents represent standardized herbal preparations containing complex mixtures of plants as active ingredients. However, there remains insufficient data for most plants to guarantee their quality, efficacy, and safety. It is important to dispel the misconception that herbal drugs are devoid of side effects. While adverse effects from herbal drugs are less common compared to synthetic drugs, well-controlled clinical trials have confirmed their occurrence. This review also delves into clinical trials of herbal drugs for conjunctivitis, incorporating patient experiences and testimonials (Table 2). For over 70 years, eye drops derived from *Euphrasia rostkoviana* Hayne have been utilized in anthroposophical medicine to facilitate fluid organization in the eye. In a clinical trial involving 65 patients with conjunctivitis, Euphrasia eye drops were administered 1-5 times daily. The trial evaluated outcomes such as redness, swelling, secretion, burning sensation, and foreign body perception. The drops demonstrated good efficacy and were well-tolerated, with 81.5% of patients experiencing complete restoration and 17.0% showing improvement. Only one patient exhibited minor regression, and no serious adverse events were reported. Both patients and physicians rated the drops as "good" to "very good," achieving an 85% satisfaction rate. Euphrasia eye drops emerge as a safe and effective option for managing conjunctival conditions. Euphrasia has anti-inflammatory properties that may be linked to the inhibition of pro-inflammatory cytokines such as TNF-α and IL-6. By reducing the production of these cytokines, Euphrasia can help alleviate symptoms associated with conjunctival inflammation. [126,127]. Qatoor Ramad (QR), an ophthalmic formulation rooted in Unani medicine, is renowned for its efficacy in addressing eye inflammation. Comprising *Cassia absus* L., *Cydonia oblonga* Mill., and *Berberis aristata* DC., QR was subject to a clinical trial involving 70 patients with varying forms of conjunctivitis (mucopurulent, phlyctenular, and allergic). Over a span of 14 days, QR eye drops were applied to the affected eyes, and its efficacy was gauged based on conjunctivitis signs and symptoms. The trial revealed remarkable outcomes, particularly in mucopurulent conjunctivitis; while also arresting deterioration in phlyctenular and allergic conjunctivitis cases. Patients exhibited no side effects and displayed good tolerance to the eye drops. QR emerges as a valuable therapeutic option for the diverse spectrum of conjunctivitis conditions studied [128].

In a double-blind, randomized clinical trial involving 60 patients with Vernal Keratoconjunctivitis (VKC), the efficacy and safety of honey eye drops were investigated. Patients were randomly assigned to receive either honey eye drops or a placebo. Throughout the trial, participants were assessed for redness, papillae, and eye pressure at baseline and follow-up visits. Results indicated that the honey group exhibited reduced redness and papillae, along with increased eye pressure compared to the placebo group. At the trial's conclusion, one patient in the honey group and seven in the placebo group still had papillae. The findings suggest that honey eye drops, when used in conjunction with other eye drops, could be beneficial in managing VKC [130]. In a clinical study focusing on keratoconjunctivitis sicca in postmenopausal patients, supplementation with GLA (Gamma-Linolenic Acid) and n-3 PUFAs (Omega-3 Polyunsaturated Fatty Acids) was found to reduce disease-related inflammation in chronic dry eye. The study involved 38 patients with tear dysfunction who were randomly assigned to either the supplement or a placebo group for duration of 6 months. Various disease parameters, including the Ocular Surface Disease Index, Schirmer test, tear breakup time, conjunctival fluorescein and lissamine green staining, and topographic corneal smoothness indexes, were evaluated at baseline and at 4, 12, and 24 weeks. Results indicated that the supplement improved symptoms and corneal smoothness, and it inhibited dendritic cell maturation. Conversely, placebo treatment led to an increase in inflammation markers. However, tear production and corneal/conjunctival staining remained unaffected. The findings suggest

Table 2. Clinical studies of various herbal drugs and preparation for conjunctivitis

Plant source/ Herbal Formulations/ Phytometabolites	Design	Intervention	Outcomes	Ref.
Euphrasia rostkoviana Hayne	Prospective, open label, one-armed, multicentered, multinational cohort trial done in 65 patients	One drop of *Euphrasia* single-dose eye drops 1–5 times a day	During the trial, 53 patients experienced full recovery, while 11 patients showed clear improvement. Only one patient exhibited slight worsening in the second week of treatment. Throughout the trial, no serious adverse events were observed.	[126]
Qatoor Ramad (QR) is an ophthalmic formulation of Unani medicine	Double-blind, randomized, prospective, placebo-controlled clinical trial, conducted in 70 patients (20–60 yrs) suffering from different types of conjunctivitis, namely mucopurulent, phlyctenular and allergic conjunctivitis	Local application of two drops; 3–4 times/day to the affected eyes for up to 14 days	QR exhibited excellent results in treating mucopurulent conjunctivitis. For the cases of phlyctenular and allergic conjunctivitis, it effectively controlled deterioration and showed signs of improvement. Throughout the study, no side effects were observed, and the eye drop was well tolerated by all patients.	[129]
Topical honey eye drops	Double-blind, randomized, placebo-controlled, clinical trial, conducted in 60 patients who had mild, moderate, or severe kinds of keratoconjunctivitis, had no other ocular diseases	First group received fluorometholone drop (1%) and sodium cromolyn along with honey drops (60% honey in artificial tears) and patients in second group received fluorometholone and sodium cromolyn along with artificial tear; 1 drop from each of the mentioned treatments every 6 hours for 1 month	The honey drop-in honey group showed a significant increase in eye pressure and a reduction in redness and limbal papillae compared to the placebo control group.	[130]
Parietaria Judaica L.	Double-blind, placebo-controlled, parallel-group study, conducted in 41 children with *Parietaria* –induced rhinoconjunctivitis	Sublingual standardized *Parietaria judaica* extract (n = 20) or placebo (n = 21) for 2 years	The active treatment group exhibited a significant reduction in rhinitis symptoms and an increase in the threshold dose for the conjunctival allergen provocation test. Immunotherapy was well tolerated.	[131]
Berberis aristata DC.	Randomized, conducted in 52 clinically established cases of acute/ chronic allergic conjunctivitis	Topical application of 10 to 15 drops of medicated decoction into conjunctival sac for 5 days and repeated the procedures for the same period at an interval of one week	In 38 cases (73%), complete relief from presenting symptoms such as itching was observed. The response may be attributed to the anti-allergic, anti-inflammatory, and antibacterial properties of the drug.	[132]
Gamma-linolenic acid (GLA) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs)	Multicenter, double-masked placebo-controlled clinical trial enrolled 38 patients (both eyes) with moderate-to-severe keratoconjunctivitis sicca in postmenopausal patients	Supplemental GLA + n-3 PUFAs or placebo for 6 months	Supplementation led to a notable improvement in the Ocular Surface Disease Index score, which was significantly lower than the placebo group after 24 weeks. The surface asymmetry index was also significantly reduced in subjects receiving the supplement. However, neither treatment affected tear production, tear breakup time, or corneal and conjunctival staining.	[133]
Nimbadi eye drops	Prospective, single-blind, randomized, and drug-controlled trial established in sixty eyes of thirty patients, diagnosed with infectious conjunctivitis	Two groups were randomised, each to receive either *Nimbadi* eye drops or Levofloxacin (0.5%) in a dose of 2 drops 4 times a day for 10 days	The symptoms of conjunctival discharge, burning sensation, itching, ocular discomfort, and photophobia were effectively managed with *Nimbadi* eye drops in comparison to the control medication.	[134]

that supplemental GLA and n-3 PUFAs effectively improved symptoms and maintained corneal smoothness in postmenopausal patients with keratoconjunctivitis sicca [133]. A prospective, single-blind, randomized, controlled trial was conducted involving sixty eyes of thirty patients diagnosed with infectious conjunctivitis. The participants were divided into two groups, with each group receiving either Nimbadi eye drops or Levofloxacin (0.5%) at a dosage of two drops four times daily for ten days. The results showed that Nimbadi eye drops effectively managed symptoms such as conjunctival discharge, burning sensation, itching, ocular discomfort, and photophobia compared to the control medication [134].

Limitations and future perspectives

While research on herbal treatments for conjunctivitis is promising, some limitations must be addressed for a balanced understanding. Many studies involve small sample sizes, which limit the generalizability of results, emphasizing the need for larger, multi-center trials to confirm efficacy. Furthermore, the reliance on *in vitro* and animal studies highlights the scarcity of human clinical trials, underscoring the need for more robust research in human populations. Variability in preparation methods and sources of herbal ingredients can also affect treatment consistency, making standardization essential for reproducibility. Although high patient satisfaction is frequently reported, subjective outcomes may introduce bias; therefore, future studies should prioritize objective, quantifiable measures. Long-term safety data on herbal treatments are still limited, indicating the need for follow-up studies to monitor potential side effects. Direct comparisons with standard therapies, such as antihistamines and corticosteroids, as well as additional randomized controlled trials, would further clarify the relative efficacy and safety of these herbal alternatives in managing conjunctivitis.

Conclusion

Integrating natural remedies into conjunctivitis management protocols could undoubtedly offer patients alternative treatment options with potentially fewer side effects and greater patient satisfaction. *Camellia sinensis* and *Heliotropium indicum* are known to ameliorate allergic conjunctivitis by reducing total serum IgE levels. The phytocompound catechin is particularly effective in inhibiting histidine decarboxylase enzyme activity, leading to a significant decrease in histamine levels within the conjunctival hyperemia. *Aloe vera* is recognized for its ability to alleviate keratoconjunctivitis, and so on. In conclusion, while conventional medications remain the primary treatment modality for conjunctivitis, the exploration of herbal substitute holds promise for the future. Herbal remedies, when complemented with innovative technology like nanosplanlastic nanovesicles for drug delivery, offer coherence and definite benefits in conjunctivitis handling. However, the efficacy of herbal treatments for conjunctivitis requires further substantiation through additional research, including preclinical and clinical trials. To strengthen future research, it would be beneficial to specify patient demographics, such as age, gender, and underlying health conditions, as well as to recommend suitable study designs, should focus on exploring the efficacy and safety of herbal treatments for conjunctivitis to provide patients with comprehensive and effective therapeutic options.

Conflict of Interests

None

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None.

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