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The Potential Therapeutic Effect of Green Tea in Treatment of Vernal Kerato-conjunctivitis

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Abstract

Vernal keratoconjunctivitis is a chronic, recurrent and severe ocular allergic disease, which is characterized by persistent allergic inflammation of the conjunctiva. It can be accompanied by ocular discomfort and visual disturbance. All forms are characterized by intense itching, tearing, mucous secretions and a severe photophobia, which often forces children to live virtually in dark places. Conjunctival proliferative changes, such as the formation of giant papillae are the characteristic findings of affected individuals. Giant papillae develop as a result of infiltration of inflammatory cells, changes in the epithelial layer, and increased deposition of extracellular matrix molecules such as collagen and proliferation of conjunctival fibroblasts. Currently several therapeutic options such as corticosteroids, mast cell stabilizers and cyclosporine are applied for treatment of Vernal keratoconjunctivitis , but in long-term, the chronic and recurrent nature of this problem leads to failure or appearance of side effects of current treatment in many patients. Recently, Green tea extract and its principal active ingredient, epigallocatechin gallate , are gaining attention and increased usage due to its healthful properties. It has considerable anticatactogenic effect by inducing apoptosis in lens epithelial cells and antioxidant effects. Also its great benefits were achieved in attenuation of damaging influences to the retina caused by ischemia/reperfusion. Based on evidences supported beneficial effects of green tea, we hypothesize that local administration of green tea and its extract seems to be a proper substitute or adjunct to current treatments of Vernal keratoconjunctivitis. This plant contains a series of antioxidants that can abolish the process of allergic cascade. Moreover, by suppressing TNF-alpha potentially, it can reduce proinflammatory reaction, as well as fibroblast proliferation and subsequently decrease giant papilla formation ;however, its potency should be evaluated in multiple clinical trial studies.

Keywords
Vernal keratoconjunctivitis, Green tea, Treatment

Introduction

Vernal keratoconjunctivitis is a chronic, recurrent and severe ocular allergic disease which is characterized by persistent allergic inflammation of the conjunctiva. It is accompanied by ocular discomfort and visual disturbance. (1, 2) In majority of cases, the disease is seasonal, which lasts from the beginning of spring to autumn. Nevertheless, perennial cases that are persistent throughout the year are not rare, especially in patients living in warm sub-tropical or desert climates. Its predominance during the high pollen season lends credence to the widely accepted hypothesis that Vernal keratoconjunctivitis is an immunologically mediated hypersensitivity reaction to environmental antigens. (3) Recent evidence indicates that activated fibroblasts play a central role in the induction and amplification of ocular allergic inflammation and the consequent development of giant papillae and corneal disorders in individuals with Vernal keratoconjunctivitis. The activation of corneal and conjunctival fibroblasts is induced by proinflammatory cytokines such as TNF-α and the Th2 cytokines such as IL-4 and IL-13. Corneal fibroblasts are able to express the chemokines TARC and eotaxin as well as the adhesion molecules ICAM-1 and VCAM-1, all of which together promote the activation and infiltration of eosinophils and Th2 cells. The proliferation of and extra cellular matrix deposition by conjunctival fibroblasts contribute to the activation and survival of various immune cells with resultant inflammation and oxidative damage consequences which ultimitately leads to pathologic and clinical manifestations of Vernal keratoconjunctivitis. (1,2,3)

All Vernal keratoconjunctivitis forms are characterized by intense itching, tearing, mucous secretions and a severe photophobia, which often forces the children to stay virtually in dark places. Conjunctival proliferative changes, such as the formation of giant papillae are the characteristic findings of affected individuals. Giant papillae develops as a result of infiltration of inflammatory cells, changes in the epithelial layer, increased deposition of extracellular matrix molecules such as collagen and proliferation of conjunctival fibroblasts. (2) These corneal lesions often develop in the patients with Vernal keratoconjunctivitis which can permanently reduce the quality of vision. Treatment of vernal keratoconjunctivitis remains a significant clinical challenge. Currently several therapeutic options such as corticosteroids, mast cell stabilizers and cyclosporine are applied for treatment of Vernal keratoconjunctivitis. But the chronic and recurrent nature of this problem leads to failure or appearance of side effects of current treatment in many patients in long-term. (1, 2)

Hypotheses:

Based on evidences support the beneficial effects of green tea, we hypothesize that local administration of green tea and its extract seems to be a proper substitute or at least an adjunct to the current treatments of Vernal keratoconjunctivitis. Clues to build of this theory are as follows:

1- This plant contains a series of antioxidants (e.g, among others, vitamin C, vitamin E , β-carotene, polyphenols, or selenium) which act as potent radical scavengers that can abolished the process of allergic cascade in Vernal keratoconjunctivitis.

2-While Giant papillae develop as a result of infiltration of inflammatory cells and deposition of extra cellular matrix molecules such as collagen and proliferation of conjunctival fibroblasts , in vivo polyphenol-containing herbal drugs such as emodin inhibites proinflammatory and fibrogenic reactions by suppressing TNF-alpha-induced stimulation of proinflammatory reaction.(4, 5)

3-In a mouse ocular alkali burn model, green tea herbal component lessened inflammation and scarring.(4)

4- Tear TNF- alpha levels in patients with Vernal keratoconjunctivitis.

are significantly increased and these increases in tear TNF- alpha levels are correlated with the severity of the disease. (6) Also, TNF- alpha positive cells are increased in conjunctival tissues obtained from patients with Vernal keratoconjunctivitis. It has been shown that Epigallocatechin-3-gallate (the most active polyphenol in green tea) down-regulates TNF-α expression. (7, 8)

Evaluation of Hypotheses and Experimental data:

In exprimental studies in Rabbits, Epigallocatechin gallate, an active ingredient from green tea, attenuates damaging influences to the retina caused by ischemia/reperfusion.(9). The role of green tea extract Epigallocatechin-3-gallate in the growth inhibition of rabbit lens epithelial cells through cytochorom oxidase pathway(P 38 pathway) was also documented in previous studeis (10) Moreover, proliferation of the cultured rabbit lens epithelial cells was shown to be inhibited by adding Epigallocatechin-3-gallate in a dose and time dependent manner. This promising effect was inserted by mechanism of inducing epithelial cell apoptosis , which indicates that it is possible to prevent posterior subcapsular cataract by using this green tea extract..(11) Despite the increasing demand for these products, few studies have examined their safety. The toxicity of purified green tea extracts containing high concentrations of Epigallocatechin-3-gallate have been evaluated in a

series of studies, in order to define the safety of Teavigo, a high-concentration of Epigallocatechin-3-gallate extract produced by the same novel method. Topical Epigallocatechin-3-gallate preparations caused minor dermal irritation in rats and guinea pigs, but not rabbits, and were a moderate dermal sensitizing agent in the guinea pig maximization test. A rabbit eye irritation test produced a strong enough response to not warrant any further testing in this assay. (12) Furthermore, 0.1% Green tea extracts results in down-regulation of TNF-α, IL-1β, and IL-10 expression, indicating that green tea inhibits both TNF-alpha and the cytokines induced by TNF-alpha in organs. This effect of green tea can prevent (modulate) the mentioned pathophysiologic changes of Vernal keratoconjunctivitis which is associated with TNF-α. (5) According to the safety profile of topical green tea as it was mentioned above, in a clinical trial study the topical provide of 0.1% GX can be administrated as eye-drops four times daily for 4 weeks in both eyes of patients with moderate Vernal keratoconjunctivitis. Clinical signs (conjunctival hyperemia, chemosis, secretion, Trantas dots, superficial punctuate keratitis) and symptoms (itching, photophobia, burning, tearing) will be evaluated and scored from 0 to 3 at the baseline, after 2 and 4 weeks of treatment. Total sign (TSS) and symptom (TSyS) scores will be finally calculated.

Discussion:

Green tea has long history and many health benefits, with curative properties recognized in Chinese medicine for thousands of years. It is made from unfermented leaves and is reputed to contain the highest concentration of the potent antioxidants called polyphenols. (4) Tea polyphenols are classified as catechins that among them, epigallocatechin gallate is considered to be the most active component in green tea. (2) Recently, Green tea extract and its principal active ingredients, epigallocatechin gallate, are drawing attention and increased usage due to their healthful properties. (9) This substance also has several antibacterial properties. (13) Even in the field of ophthalmology, green tea was shown to have interesting properties. It reduces damaging influences to the retina caused by ischemia/reperfusion. (9) Moreover , oxidative-induced retinal degeneration is attenuated by epigallocatechin gallate.(14)

Subsequently , aqueous extracts of green and black tea were shown to eleminate reactive oxygen species such as singlet oxygen, superoxide and hydroxyl radicals, prevent the oxidative cross-linking of proteins and DNA damage. Even ,They were also seen to be able to counteract the oxidative insult mounted by cigarette smoke. (15) As was mentioned , Green tea was also shown to have main benefits in prevention and retardation of cataract. (16) Cataract was induced to the rats by subcutaneous injection of selenite as well, administration of green or black tea extracts led to a retardation of the progression of lens opacity, suggesting the potential cataracto-static ability of tea. (15) Consequently in Vernal keratoconjunctivitis as a recurrent allergic ocular disease, long term treatment especially in moderate to sever form, remain to be a sophisticated entity till now. The currently available topical drugs are effective in treating only acute phases of Vernal keratoconjunctivitis. However, there is a lack of evidence to support the recommendation of one specific type of medication for treating this disorder. There is a need for standard criteria to assess diagnosis and therapy based on severity. (1,17) There is also a need for multiple clinical trial studies assessing long-term effects of single drugs to control the disease.(17) Moreover , usage of synthetic drugs in long term are still associated with many harmful toxicities that even may mask their benefits. So , it is wise to look for natural substances that give us the proper effect without causing major complications .(18)

As it was mentioned , this plant contains a series of antioxidants (e.g, among others, vitamin C, vitamin E, β-carotene, polyphenols, or selenium) which act as potent radical scavengers that can abolished the process of allergic cascade in Vernal keratoconjunctivitis. (4) Recent evidence indicates that activated fibroblasts play a central role in the induction and amplification of ocular allergic inflammation and the consequent development of giant papillae and corneal disorders in individuals with Vernal keratoconjunctivitis. (2) Mast cell–derived TNF-α has been implicated in the promotion of fibroblast proliferation and collagen expression in a co-culture system of mast cells and fibroblasts.(7, 8)

Green tea extract results in down-regulation of TNF- α which have a main role in presentation of allergic problem especially in Vernal keratoconjunctivitis. (7, 8) So that , Green tea seems to be potentially effective to be used as an alternative treatment or at least as an new adjutant in treatment of vernal keratoconjunctivitis.

Conclusion:

It seems that topical application of green tea and its extracts may be effective in modulating different forms of allergic conjunctivitis especially in Vernal keratoconjunctivitis. However, the potency of Green tea extract should be evaluated in multiple clinical trial studies.

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