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REVIEW

Green tea consumption: an alternative approach to managing oral lichen planus

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Abstract Oral lichen planus (OLP) is a T-cell-mediated inflammatory autoimmune disease, whose pathogenesis includes both antigen-specific and non-specific mechanisms. Antigen-specific mechanisms in OLP consist of antigen presentation, lymphocyte activation, proliferation and migration as well as keratinocyte apoptosis mediated by $CD8^+$ cytotoxic T-cells, whereas non-specific mechanisms include mast cell degranulation and matrix metalloproteinase (MMP) activation in OLP lesions. Deficient antigen-specific transforming growth factor-β (TGF-β)-mediated immunosuppression may also contribute to the pathogenesis of OLP. In addition, OLP is considered to be a potentially malignant disorder with a malignant transformation rate of 0–5.3%. Green tea, especially epigallocatechin-3-gallate, possesses anti-inflammatory and chemopreventive properties. It can inhibit antigen presentation, T-cell activation, proliferation and migration, keratinocyte apoptosis, nuclear factor-kappaB (NF-κB) activation and MMP-9 activity, as well as regulated on activation, normal T-cell expressed and secreted (RANTES) expression, and can modulate the imbalance between TGF-β and interferon-γ signaling, all of which are involved in the pathogenesis of OLP. Thus, our hypothesis is that green tea consumption may decrease OLP incidence and provide a neoteric, nontoxic and inexpensive therapeutic strategy for OLP. Furthermore, green tea might be a possible agent for preventing malignancies in OLP.

Keywords Green tea · Epigallocatechin-3-gallate (EGCG) · Oral lichen planus · Pathogenesis · Treatment

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Introduction

Oral lichen planus (OLP) is a common T-cell-mediated inflammatory autoimmune disease with the features of disease chronicity, adult onset, female predilection, depressed immune suppressor activity and the presence of auto-cytotoxic T-cell clones in lichen planus lesions [1]. OLP is characterized by T-cell accumulation in the superficial lamina propria, basement membrane disruption, intraepithelial T-cell migration and keratinocyte apoptosis, resulting from both antigen-specific and non-specific mechanisms [2]. Antigen-specific mechanisms in OLP consist of antigen presentation, lymphocyte activation, proliferation and migration as well as keratinocyte apoptosis mediated by $CD8^+$ cytotoxic T cells, whereas non-specific mechanisms include mast cell degranulation and matrix metalloproteinase (MMP) activation in OLP lesions [2]. Moreover, deficient antigen-specific transforming growth factor (TGF-β)-mediated immunosuppression may contribute to the pathogenesis of OLP [3]. OLP is considered to be a potentially malignant disorder and carcinogenesis in OLP may be modulated by the integrative signal from various tumor inhibitors and promoters [2, 4].

Green tea, a popular, tasty and inexpensive beverage, is consumed throughout the world and has been suggested to

have many potential health benefits. Green tea is a rich source of the polyphenols known as catechins, including epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG) [5]. EGCG is the most biologically active catechin in green tea and accounts for 50–80% of the total tea catechins [6]. It has been investigated in recent years because of its anti-inflammatory and immunomodulatory activities [7, 8]. Findings indicated that EGCG supplementation may be beneficial to those with abnormally excessive T-cell function such as in autoimmune and inflammatory disorders [9]. Evidence has also suggested that green tea could be therapeutically beneficial for autoimmune disease such as osteoarthritis, rheumatoid arthritis, autoimmune diabetes, Sjögren's syndrome and lupus erythematosus [10–13]. However, research on the connection between green tea consumption and OLP is still inconclusive. In addition, present therapies for OLP are far from satisfactory because of various side effects [14]. Thus, we speculate that green tea consumption, through its anti-inflammatory and immunomodulatory activities, may affect OLP at multiple levels.

Based on the anti-inflammatory and chemopreventive properties of green tea, we here surmise that green tea consumption may have a potential to manage OLP by modulating antigen-specific and non-specific mechanisms involved in the pathogenesis of OLP. In addition, green tea consumption may prevent OLP from malignant transformation.

Effect of green tea consumption on antigen-specific mechanisms in OLP

Inhibition of antigen presentation

In antigen-specific mechanisms of OLP, antigen presentation as the first step can activate T cells and trigger a subsequent autoimmune reaction [15]. To stimulate a T-cell response, dendritic cells (DCs) and presumably Langerhans cells (LCs) must undergo a process of terminal differentiation called maturation [2]. After maturation, antigen-presenting cells (APCs) endocytose apoptotic basal keratinocytes, activate self-reactive $CD4^+$ T cells and then promote autoimmune reactions against basal keratinocytes [1]. EGCG, at 4–10 times higher doses than its daily intake from green tea (2.5 mmol/L), can inhibit the differentiation, terminal maturation and antigen-presenting function of DCs, and induce their apoptosis, possibly by increased production of interleukin (IL)-10 [7, 16]. Accordingly, we propose that treatment of OLP may profit from the inhibitory effects of EGCG on DCs.

Effects of EGCG on T cells

Subsequently, T-cell activation, proliferation, migration and keratinocyte apoptosis mediated by $CD8^+$ cytotoxic T cells involve in antigen-specific mechanisms of OLP. In OLP, most lymphocytes in the lamina propria are $CD4^+$ T cells, while the majority of lymphocytes within the epithelium and adjacent to damaged basal keratinocytes are activated $CD8^+$ T cells [3]. Helper $CD4^+$ T cells may be activated by antigen associated with major histocompatibility complex (MHC) II presented by Langerhans cells or keratinocytes, and secrete T-helper-1 (Th1) cytokines such as IL-2 and interferon-γ (IFN-γ) which bind their respective receptors on $CD8^+$ T cells [2, 17]. With the combination of antigen associated with MHC I on basal keratinocytes and Th1 cytokines, cytotoxic $CD8^+$ T cells are activated and trigger basal keratinocyte apoptosis, possibly via secreted tumour necrosis factor-α (TNF-α), resulting in the clinical and histological appearance of OLP [2, 3, 18]. Notably, studies showed that both in-vivo and in-vitro supplementation with EGCG at physiologically relevant concentrations of 2.5–10 μM can reduce T-cell proliferation [19]. One possibility is that EGCG may reduce expression of IL-2R in T cells rather than decrease IL-2 synthesis to impair IL-2/IL-2R signaling, which may in turn, through corresponding downstream pathways, affect cell cycle regulatory proteins and lead to inhibition of cell cycle division and progression [19]. Another possibility is that EGCG may function as a proteasome inhibitor to suppress T-cell activation and proliferation [20, 21]. In addition, green tea catechin, especially EGCG, can decrease adhesive and migratory properties of $CD8^+$ T cells to sites of inflammation by downregulating CD11b expression on $CD8^+$ T cells [22]. Therefore, EGCG supplementation may be beneficial for OLP by inhibiting T-cell activation and proliferation as well as modulating the migration of $CD8^+$ T cells to sites of inflammation.

Influence of EGCG on NF-κB signaling pathway

EGCG has been shown to inhibit nuclear factor-kappaB (NF-κB) activation in intestinal epithelial cells, respiratory epithelial cells, endothelial cells and mast cells [23–26]. Our previous study indicated that there was strong nuclear expression of p65, which may represent NF-κB activation, both in epithelial keratinocytes and infiltrated lymphocytes in OLP but not in normal oral mucosa [27]. EGCG has been reported to inhibit NF-κB activation through inhibition of p65 phosphorylation [24]. Similarly, higher NF-κB nuclear expression was demonstrated in oral LP than in cutaneous LP and was associated with significantly increased numbers of cytotoxic lymphocytes within the infiltrate [28]. Increased NF-κB activity might correlate with the severity of OLP and contribute to the long-lasting course and relapse of OLP [28]. NF-κB, a master switch or control point for the expression of a large number of pro-inflammatory genes, can induce the production of several

proinflammatory cytokines such as TNF-α, IL-1β, IL-2 and IL-6, chemokines (IL-8), and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), which can ultimately cause a dysregulated inflammatory cascade that results in significant autoinjury to the host [29]. It is indicated that pro-inflammatory NF-κB-dependent cytokines, including TNF-α, IL-1α, IL-6 and IL-8, may be elevated to various degrees in serum, oral keratinocytes, tissue-infiltrated mononuclear cells and various oral fluids (i.e., whole saliva, saline rinse and tissue transudate) in patients with OLP [30]. To sum up, all data confirm that increased NF-κB and NF-κB-dependent inflammation contribute to the outcome of OLP and strongly support the concept of therapeutic strategies targeting the NF-κB pathway, thereby limiting the inherent redundancy of the inflammatory cascade. For example, EGCG potently inhibits production of TNF-α by inhibition of NF-κB activation to protect keratinocytes in OLP from TNF-α-induced apoptosis, whereas EGCG may decrease ICAM-1 by inhibition of NF-κB activation to reduce tissue infiltration of T cells in OLP [1, 31]. Thus, green tea polyphenols, especially EGCG, potentially become a novel therapeutic strategy for OLP by inhibiting NF-κB activation and subsequent production of proinflammatory cytokines, chemokines and adhesion molecules in OLP.

Effects of EGCG on non-specific mechanisms in OLP

Inhibition of MMP-9 and RANTES expression

Non-specific T cells in OLP may contribute to disease pathogenesis by secreting matrix metalloproteinase-9 (MMP-9) and regulated on activation, normal T cell expressed and secreted (RANTES) [2]. MMPs are a family of zinc-containing endo-proteinases whose main function is the proteolytic degradation of connective tissue matrix proteins. The gelatinases (MMP-2 and -9) cleave type IV collagen and the stromelysins (MMP-3 and -10) cleave collagen IV and laminin. MMPs or proMMPs can form complexes with tissue inhibitor metalloproteinases (TIMPs) which are involved in regulating MMP proteolysis [32]. Since MMPs play an essential role in immune cell migration into inflammatory sites, tumor spread and connective tissue destruction, an imbalance in their expression or activity may have important consequences in various pathologies such as rheumatoid arthritis, multiple sclerosis and the development of cancers [11, 33, 34]. A previous study indicated that relative overexpression of MMP-9 (compared with TIMP-1) may cause T-cell migration and basement membrane disruption which further facilitate intra-epithelial $CD8^+$ cytotoxic T-cell migration in OLP [32]. T-cell-derived MMP-9 may therefore play a central role in disease pathogenesis and novel therapies may include blocking MMP-9 activity in OLP. Demeule et al. indicated that EGCG was the most potent inhibitor of MMP-2, MMP-9 and MMP-12, followed by ECG [35]. EGCG has also been shown to inhibit MMP-9 activity and MMP-9 expression [34]. Studies have documented that EGCG not only decreased the level of MMP production but also increased the expression of TIMP-1 in vitro [36]. RANTES secreted by OLP lesional T cells may attract mast cells into the developing OLP lesion and subsequently stimulate mast cell degranulation, which would release TNF-α and chymase, in turn upregulating OLP lesional T-cell RANTES secretion. EGCG has been shown to downregulate IL-1β-induced RANTES [37]. Overall, consumption of green tea or EGCG may inhibit the expression of MMP-9 and RANTES involved in the non-specific mechanisms of OLP and this may have a therapeutic benefit for OLP.

Modulation of the imbalance between TGF-β and IFN-γ signaling

Weak expression of TGF-β1 has been found in OLP and its chronicity may be due, in part, to a defect in the TGF-β1 immunosuppressive pathway [1]. TGF-β1 activity is mediated via the TGF-β II receptor, with subsequent phosphorylation of the TGF-β I receptor [2]. In addition, local overproduction of IFN-γ by Th1 $CD4^+$ T cells in OLP lesions would downregulate the immunosuppressive effect of TGF-β1 and upregulate keratinocyte MHC class II expression and $CD8^+$ cytotoxic T-cell activity [1]. Recently, EGCG was shown to exert a stimulatory effect on expressions of TGF-β1, TGF-β I receptor, TGF-β2, and TGF-β II receptor in the presence of IL-1 in mice [38]. It is found that EGCG interrupts TGF-β signaling in activated hepatic stellate cells by suppressing gene expression of TGF-β I receptor and TGF-β II receptor [39]. EGCG also can reduce IFN-γ production [9]. This suggests that EGCG has the potential to treat OLP by upregulating TGF-β1 expression associated with its receptors and downregulating IFN-γ production, which promotes the balance between TGF-β and IFN-γ signaling.

Potential of green tea consumption to prevent malignancies in OLP

OLP carries a malignant potential, and its malignant transformation rate is 0–5.3% [40]. The integrated signal from various tumor inhibitors and promoters may determine the sensitivity of oral keratinocytes to exogenous mutagens and may regulate tumor growth and metastasis following cancer formation in OLP. Some direct evidence was reported on the role of green tea in the protection of oral pre-cancerous mucosa lesions [41]. EGCG was also

found to inhibit the migration and invasion of human oral cancer cells by inhibiting the activation of MMP-2, MMP-9 and urokinase plasminogen activator (uPA) in a dose-dependent manner [34]. Dietary supplements of tea may serve that purpose in vivo, although 10 cups (120 ml/cup) of green tea daily supplemented with green tea tablets have been recommended to the general population for the prevention of cancer [42]. Overall, green tea might be a possible agent for preventing malignancies in OLP.

Conclusion

In conclusion, green tea, especially EGCG, is likely to be a suitable therapeutic candidate for OLP, as a result of its inhibition of antigen presentation, T-cell activation, proliferation and migration, keratinocyte apoptosis, NF-κB activation and MMP-9 activity as well as RANTES expression and its modulation of the imbalance between TGF-β and IFN-γ signaling. Furthermore, green tea might be a possible agent for preventing malignancies in OLP. Green tea consumption in general has not displayed any acute or chronic toxic effects, and in fact is health promoting [43]. EGCG has been showed to have markedly anti-allergic, anti-diabetic, anti-obesity, anti-cardiovascular disease, anti-bacterial, anti-viral, anti-periodontal gum diseases and anti-cariogenic/cariostatic effects [12, 44–49]. However, harmful effects of green tea overconsumption could be due to two main factors: caffeine content and the presence of aluminum [50]. Overconsumption of green tea may cause nervousness, sleep disorder, vomiting, headaches and tachycardia, but green tea presents low toxicity and high tolerance in human subjects, even when given in doses of EGCG as high as 1,600 mg [50]. It seems likely that much higher doses than the daily intake of EGCG from green tea are necessary for the immunosuppressive effects of EGCG to develop. Thus, pharmaceutical formulations of green tea would be necessary to achieve these plasma levels and caution should be taken in consuming large amounts of green tea. In any case, oral green tea consumption could provide a neoteric, nontoxic and inexpensive therapeutic strategy for OLP.

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