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REVIEW

Black pepper and its bioactive constituent piperine: promising therapeutic strategies for oral lichen planus

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Abstract

Oral lichen planus (OLP) is a common T cell-mediated chronic inflammatory disease with malignant potential and unclear etiology. The present study suggests that antigen-specific mechanisms in which dentritic cells, T lymphocytes and NF-κB signaling pathway play critical roles, are involved in the pathogenesis of OLP. Additionally, it has been indicated that altered expression of cyclooxygenase 2 (COX-2) and imbalanced oxidant-antioxidant status as well as psychological issue may act as promoters to the development of OLP. Therapies for OLP are primarily aimed to control symptoms and a specific cure is not yet available. Black pepper and its principle bioactive compound piperine have been reported to possess remarkable pharmacological activities. Not only has piperine been evidenced to exhibit repressive effects on the maturation of dentritic cells, the proliferation, activation and function of T lymphocytes as well as the NF-κB signaling pathway, but also to suppress the overproduction of COX-2 and weaken the oxidative stress. Furthermore, piperine might be a possible agent for alleviating psychological disorders and preventing carcinogenesis. Given all these into consideration, piperine may be a novel and effective therapeutic strategy for OLP.

Keywords Black pepper · Piperine · Oral lichen planus

Introduction

Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease with unknown etiology (Roopashree et al. 2010; Payeras et al. 2013; Nogueira et al. 2015), affecting approximately 0.1–4% of the adult population with a female predilection (Edwards and Kelsch 2002). It carries a malignant potential, being labeled as a potentially malignant disorder of the oral region by the World Health Organization in 2005 and being reported to at an overall transformation rate of 1.09% in 2014 (van der Waal 2009; Fitzpatrick et al. 2014). Clinically, the buccal mucosa, tongue and gingiva are commonly affected by OLP, presenting as a symmetrical and bilateral lesion or multiple lesions and occurring in six clinical variants as reticular, papular, plaque-like, erosive, atrophic and bullous (Roopashree et al. 2010). Antigen-specific mechanisms are believed to play crucial roles in the pathogenesis of this disease, which consists of antigen presentation, lymphocyte activation, proliferation and migration as well as keratinocyte apoptosis mediated by CD8+ cytotoxic T cells (Roopashree et al. 2010). Psychological issue has been linked with the occurrence and progression of OLP (Alrashdan et al. 2016). In addition, latent influences of COX-2 and oxidant-antioxidant status on the progression of OLP have been raised up (Battino et al. 2008; Abdel et al. 2012; Payeras et al. 2013). Treatment of symptomatic OLP varies considerably, ranging from elimination of precipitating or provoking factors to long-term pharmacological therapies, but there is no cure (Jungell 1991; Crincoli et al. 2011; Alrashdan et al. 2016). Hence, it is necessary to develop new, safe and effective therapeutics.

Black pepper (*Piper nigrum* L., family piperaceae)—one of the most worldwide used spices not only in human dietaries but also for other purposes such as medical research—is well known for its pungent alkaloid constituent piperine

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(1-[5-[1,3-benzodioxol-5-yl]-1-oxo-2,4-pentadienyl] piperidine; Srinivasan 2007). Piperine is the principle bioactive compound of black pepper, whose biological properties have been extensively explored in recent decades (Butt et al. 2013). Among the important pharmacological activities reported, the immunomodulatory, anti-inflammatory, anti-cancer and anti-depressive properties are characteristics closely related to the treatment of OLP (Srinivasan 2007; Bae et al. 2010; Butt et al. 2013; Meghwal and Goswami 2013; Derosa et al. 2016). Owing to its promising therapeutic potential, efforts are being made to apply this naturally occurring compound to drug discovery programs as a feasible template for the development of new chemical entities. The aim of this review is to give a deep insight to the therapeutic potency of piperine or black pepper for OLP on the basis of comprehensive reviews and experimental results.

Potential effects of piperine on the antigen-specific mechanisms in OLP

Potential effects of piperine on dentritic cells in OLP

For the beginning, dendritic cells (DCs), predominantly langerhans cells (LCs), might play an essential role in the initiation of adaptive immune response occurring in OLP by taking up epithelial antigens (Upadhyay et al. 2013). Subsequently, antigens presented by class II major histocompatibility antigen (MHC) are processed by antigen-presenting cells (APCs) (mainly LCs or keratinocytes) through an endosomal cellular pathway (Roopashree et al. 2010). Notably, a significant increase of MHC II antigen expression in LCs has been identified in OLP lesions (Sloberg et al. 1984; Farthing et al. 1990). High level of antigen expression accompanied by enhanced expression of CD40 and CD80 as well as secretion of interleukin (IL)-12 by MHC II APCs in OLP are thought to promote a Th1 CD4+ T cell response with IL-2 and interferon (IFN)-γ release (Alrashdan et al. 2016). Eventually, these DCs induce not only an initial sensitivity to the antigen (primary immune response), but also a subsequent secondary immune response which permits the appearance of the disease clinical signs (Barrett et al. 1996; Payeras et al. 2013).

Piperine has been discovered to suppress the maturation of LPS-induced bone-marrow-derived dendritic cells (BMDCs) by efficiently suppressing the expression of DCs surface molecules involved in DC-T cell interactions, such as MHC II, CD40 and CD86, and the generation of tumor necrosis factor alpha (TNF-α), IL-12 as well as monocyte chemoattractant protein-1 (MCP-1) in a dose-dependent manner (Bae et al. 2012; Rodgers et al. 2016). Consequently, those piperine-treated DCs retained phenotypically and functionally immature and thus were in deficiency of T cell-activation, performing a selective reduction of synthesis of Th1 cytokines: IFN-γ and IL-2, as well as the inhibition of T cells proliferation (Rodgers et al. 2016). Accordingly, it is sensible to assume that treatment of OLP may profit from the inhibitory effects of piperine on DCs.

Effectively inhibitory impacts of piperine on T cells

Following antigen presentation, lesional CD4+ Th cells and CD8+ cytotoxic T cells (CTLs) are activated. CTLs can be activated by antigen presented by MHC I on basal keratinocytes, while Th cells are activated by antigen presented by MHC II on LCs or keratinocytes and in turn activate CTLs by IL-2, IFN-γ and request for cytotoxic activity (RCA) receptors (Sugerman et al. 2002; Roopashree et al. 2010). Activated lesional CD8+ CTLs secrete many cytokines such as IL-2, TNF and IFN- a, which not only lead to the expression of HLA-DR in basal keratinocytes, but also the activation of DCs, thereby attracting more lymphocytes (Nogueira et al. 2015. It is noteworthy that our group have found a high expression of PD-1 and B7-H1 along with a significantly higher T-bet mRNA level and T-bet/GATA-3 mRNA ratio in OLP patients, which manifested the presence of a Th1 CD4+ T lymphocytes dominant inflammatory environment in OLP that may stimulate the activities of CD8+ CTLs (Lu et al. 2011; Zhou et al. 2012; Lu et al. 2015). Ultimately, activated CD8+ CTLs trigger basal keratinocytes apoptosis, possibly via secreted TNF-α, resulting in the clinical and histological appearance of OLP (Sugerman et al. 2000, 2002; Lodi et al. 2005).

Studies have documented that piperine may prominently inhibit T cells (TCs) proliferation, activation and function (Maraskovsky et al. 1989; Chuchawankul et al. 2012; Kannan et al. 2012; Bayer et al. 2013; Doucette et al. 2015a, b). First of all, piperine has been reported to suppress T cells proliferation by impeding expression of CD25 and synthesis of IL-2 (Bayer et al. 2013; Doucette et al. 2015a), or by causing a partial block in cell cycle progression at the G0/G1 phase (Doucette et al. 2015a, b). Additionally, piperine has been observed to impact the activation and function of T cells via hindering the synthesis of cytokines including IFN-γ, IL-2, IL-4, and IL-17A and the induction of cytotoxic effector cells (Chuchawankul et al. 2012; Doucette et al. 2015a). Importantly, the synthesis of IL-2 and IFN-γ was of most sensitivity to piperine-mediated inhibition, implying that the greatest impact of piperine is on overall T cells proliferation and Th1 effector function, thereby disturbing the induction of CTLs which require both IL-2 and IFN-γ (Maraskovsky et al. 1989). One possible mechanism for these effects was mediated by piperine-induced suppression of Akt, ERK, and NF-κB activation, hence inhibiting the critical TCR/CD3 signaling pathway (Kannan et al. 2012; Doucette et al. 2015a). Another explanation proposed a direct

inhibition of piperine to IL-2-driven T cells expansion and attributed this effect to the suppression of IL-2R signaling events, including the phosphorylation of STAT5, STAT3, ERK1/2, and also Akt (Doucette et al. 2015a).

Piperine may act on OLP via NF-κB signaling pathway

The significant inhibitory effects of piperine on NF-κB signaling pathway have been substantiated in inflammation-related disease models, such as lipopolysaccharide (LPS)-induced acute lung injury in murine model and IL-β-induced inflammatory mediators in human osteoarthritis chondrocytes (Vaibhav et al. 2012; Lu et al. 2016; Ying et al. 2013a, b). Our previous studies have revealed a strong nuclear expression of p65 (a subunit of NF-kB), which may symbolize the activation of NF-κB both in OLP lesional epithelial keratinocytes and infiltrated lymphocytes but not in normal oral mucosa. We also indicated that a positive regulatory loop between NF-κB and TNF-α existing in OLP may aggravate the inflammation of this disease (Zhou et al. 2009).

Concerning the well-recognized roles that NF-κB play in the pathogenesis of OLP along with the typical anti-NF-κB feature of piperine, it is reasonable to hypothesize that piperine might function as an adjunct to the management of OLP. For one thing, piperine priorly or simultaneously administered with different stimuli can almost dose-dependently inhibit the activation and translocation of NF-κB partially through decreasing the degradation or phosphorylation of NF-κB inhibitor (IκB) (Kumar et al. 2007; Vaibhav et al. 2012; Ying et al. 2013a, b; Lu et al. 2016; Zhai et al. 2016; Verma et al. 2017), and thus reduced the overproduction of TNF-α, IL-β and IL-6 (Vaibhav et al. 2012; Lu et al. 2016; Zhai et al. 2016; Verma et al. 2017) and increased the secretion of anti-inflammatory factor IL-10 (Zhai et al. 2016). For another, piperine was found to suppress the expression of NF-κB via blocking the phosphorylation or translocation of p65 subunit of NF-κB from the cytosol to the nucleus (Pradeep and Kuttan 2004; Ying et al. 2013a, b; Zhai et al. 2016).

Given the above, we can propose that piperine or black pepper consumption might alleviate the clinical syndromes of OLP by targeting the antigen-specific mechanisms, namely, the maturation of DCs, the proliferation, activation and function of T cells and the NF-κB signaling pathway (Fig. 1).

An assumption of piperine's efficacy based on its repressive effects on COX-2

Recently, potential impacts of COX-2 on the pathogenesis of OLP have attracted researchers' attention. COX-2, a 72-kDa enzyme induced by hypoxia, inflammatory cytokines, growth factors and other stress factors, is directly connected with inflammation, catalyzing synthesis of prostaglandins (PG), PGE2 in particular, and thromboxanes from arachidonic acid (Smith et al. 1996). The increased level of the COX-2 has been identified not only in a variety of cancers (Kawanishi et al. 2006; Misra and Sharma 2014; Cortés-Ramírez et al. 2010), but also in autoimmune diseases (Myers et al. 2000; Suzuki et al. 2006; Zhang et al. 2007; El-Rifaie et al. 2015) and OLP lesions, being considered to be implicated in the chronic inflammatory process or immunopathogenesis of OLP (Lysitsa et al. 2008; Abdel et al. 2012; Danielsson et al. 2012; Li and Cui 2013; Nogueira et al. 2015; Singh

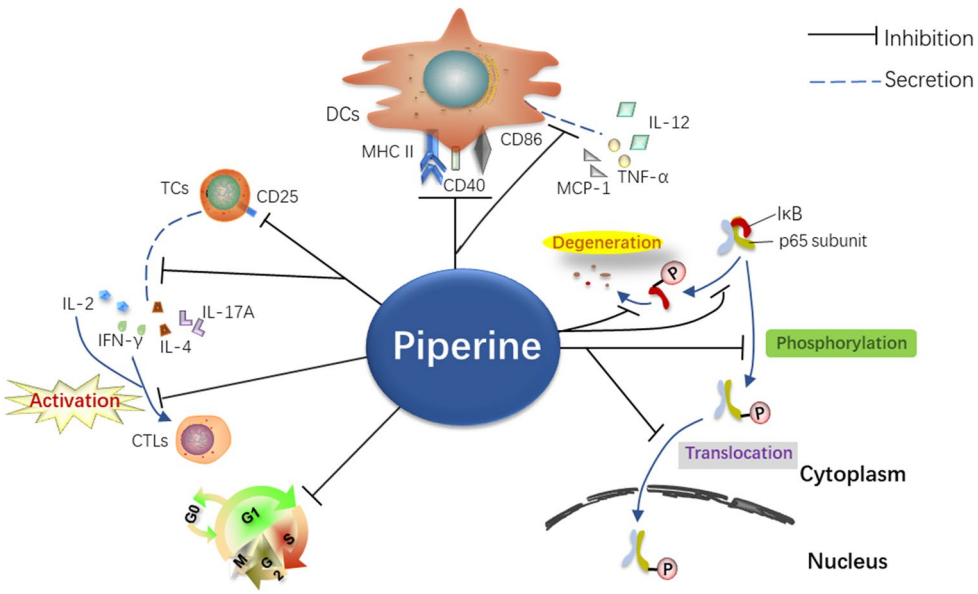

Fig. 1 Potential effects of piperine on the antigen-specific mechanisms in OLP. Piperine might help to alleviate OLP by suppressing the expression of DCs surface molecules (MHC II, CD40 and CD86) involved in DC-T cell interactions and the generation of TNF-α, IL-12 as well as MCP-1; impeding expression of CD25 and hindering the synthesis of cytokines (IFN-γ, IL-2, IL-4, and IL-17A) and the induction of CTLs, and also causing a partial block in cell cycle progression at the G0/G1 phase; decreasing the degradation or phosphorylation of IκB and blocking the phosphorylation or translocation of p65 subunit

et al. 2017). It is suggested that interaction between up-regulation of COX-2, mast cell and basement membrane sets a vicious cycle relating to the chronic nature of OLP (Singh et al. 2017). Another research observed the increased level of COX-2 and the decreased expression of COX-2 inhibitor miR-26b in OLP lesions, which might together support an autoimmune cause of OLP and contribute to the development of this disease (Danielsson et al. 2012). Therefore, the use of COX-2 inhibitors as an alternative therapeutic approach for OLP deserves due consideration.

Piperine was found able to suppress cerebral ischemia–reperfusion-induced inflammation to some extent via the repression of COX-2 in rat model (Vaibhav et al. 2012). Besides, piperine dose-dependently decreased PMA-induced PGE2 production, COX-2 expression together with COX-2 promoter-driven luciferase activity in murine macrophages (Kim et al. 2012). Similar suppressive function on COX-2 and PGE2 was shown in rat arthritis models and human osteoarthritis chondrocytes (Bang et al. 2009; Ying et al. 2013a, 2013b). The mechanisms underlying these activities were largely associated with the inhibition of NF-κB pathway, though exact mechanism varies to some degree depending on different conditions (Kim et al. 2012; Vaibhav et al. 2012; Ying et al. 2013a, 2013b). Accordingly, it is plausible to speculate that piperine might become a possible candidate relievable to the inflammatory condition of OLP since it has the capability to suppress COX-2 expression.

A probable improvement of OLP by piperine's anti-oxidative property

Oxidative stress is referred to an imbalance between the production of reactive oxygen species (ROS) and anti-oxidative status, which is involved in the pathogenesis of inflammatory diseases and cancer (Federico et al. 2007; Buczko et al. 2015). OLP, a common chronic inflammatory oral mucosal disease, is also in connection with oxidative stress. Researchers have proven the existence of elevated oxidative stress and relatively lowered antioxidant capacity in OLP by detecting alterations of corresponding biomarkers, and found that oxidative stress in erosive form tended to be more severe than reticular ones (Nagler et al. 2002; Sezer et al. 2007; Battino et al. 2008; Agha-Hosseini et al. 2009; Upadhyay et al. 2010; Scrobotă et al. 2011; Azizi and Farshchi 2012; Vlková et al. 2012; Abdolsamadi et al. 2014; Shirzad et al. 2014; Amirchaghmaghi et al. 2016; Darczuk et al. 2016; Rekha et al. 2017; Tvarijonaviciute et al. 2017). Recently, it has been suggested in the literature that the attack by ROS on the oral mucosa may cause various alterations in a wide spectrum from benign oral disorders such as periodontitis caused by bacterial infection, autoimmune disorder Sjøgren's syndrome to lethal head and neck cancers (Kesarwala et al. 2016). Thus, the need for exogenous antioxidants to augment the endogenous antioxidant machinery in OLP is worth thinking.

The anti-oxidative ability of piperine has been verified in vast vitro experiments. For instance, piperine could partly protect against diabetes-induced oxidative stress when intraperitoneally administered for 2 weeks, and dietary black pepper or piperine was found able to reduce high-fat-diet-induced oxidative stress via diminishing lipid peroxidation and restoring activities of antioxidant enzymes and glutathione (Rauscher et al. 2000; Vijayakumar et al. 2004; Srinivasan 2007). Although it may result in increased generation of hydroxyl radicals via activating the Fenton reaction at high concentrations, piperine in general is a powerful antioxidant since it could prevent oxidative damage through suppressing or quenching free radicals and ROS and inhibit lipid peroxidation. It therefore might be helpful for OLP management (Mittal and Gupta 2000; Srinivasan 2007).

Possible relievable functions of piperine on psychological disorders

The influences that psychological disorders have on OLP merit serious attention as indicated by lots of clinical trial-based evidence (Pippi et al. 2016). Some clinical investigations have shown that patients with OLP especially those with erosive form (Vallejo et al. 2001; Ivanovski et al. 2005; Lundqvist et al. 2006; Alves et al. 2015), were under a higher prevalence of anxiety, depression and psychological stress (Prolo et al. 2002; Koray et al. 2003; Ivanovski et al. 2005; Lundqvist et al. 2006; Girardi et al. 2011; Alshahrani and Baccaglini 2014; Gavic et al. 2014; Nadendla et al. 2014; Pippi et al. 2016; Tadakamadla et al. 2017). Psychological problems have been suggested in association with immune dysregulation, pain severity and tolerance as well as the development of OLP (Prolo et al. 2002; Gavic et al. 2014; Nadendla et al. 2014). Moreover, this notion was favored by higher levels of serum and salivary cortisol (a indicator of stress and associated with the HPA axis) in OLP patients when compared with healthy individuals (Prolo et al. 2002; Ivanovski et al. 2005; Shah et al. 2009; Nadendla et al. 2014; Pippi et al. 2014).

Importantly, the anti-depressant quality of piperine has been validated in murine models (Li et al. 2007a, b; Wattanathorn et al. 2008; Zaugg et al. 2010; Mao et al. 2011; Huang et al. 2013; Mao et al. 2014a, b). Within these studies, rats or mice initially pretreated to be either depressive or anxious by depression-inducing chemicals or physical stimulus showed a variety of abnormalities in behavioral tests and biochemical parameter assays. However, subsequent piperine administration effectively ameliorated those

depressant-like syndromes, presented as reduced duration of immobility in forced swimming test, reversed chronic mild stress (CMS)-induced changes in sucrose consumption and plasma corticosterone level (Li et al. 2007a, b; Wattanathorn et al. 2008; Mao et al. 2014a, b; Hritcu et al. 2015). One probable mechanism responsible for piperine's antidepressant-like effects may be the inhibition of monoamine oxidase activity together with the increasement of monoamine neurotransmitters levels (Kong et al. 2004; Lee et al. 2005; Li et al. 2007a, b; Huang et al. 2013). Moreover, in mice exposed to CMS, these effects of piperine were linked to up-regulation of hippocampal progenitor cell proliferation (Li et al. 2007a, b), or mediated by brain-derived neurotrophic factor signaling (Mao et al. 2014a, b). Besides, synthesis enhancement or reuptake inhibition of serotonin in mouse brain (Li et al. 2007a, b; Mao et al. 2011, Mao et al. 2014a, b) and modulation of γ-aminobutyric acid (GABA) type A (GABAA) receptors (Zaugg et al. 2010; Khom et al. 2013), as well as attenuation of the neuronal oxidative stress in the rat amygdala may together lead to the anxiolytic and anti-depressive efficacy of piperine (Hritcu et al. 2015). Overall, OLP might benefit from piperine application for its alleviative effects on psychological disorders.

Potential of piperine administration to prevent malignancies in OLP

Although the mechanism for the malignant transformation of OLP is not well-understood, several factors might be implicated in this change. One aspect may be the close relationship between chronic inflammation and carcinogenesis, where oxidative stress and cytokines such as TNF-α and IL-6 might participate in the formation of the inflammatory environment which belongs to the tumor-like microenvironment in OLP as we previously described (Balkwill and Mantovani 2001; Mignogna et al. 2004; Peng et al. 2017). Other transformation-related factors might in association with the overexpression of COX-2 and the imbalance between MMPs and tissue inhibitor of metalloproteinases (TIMPs),

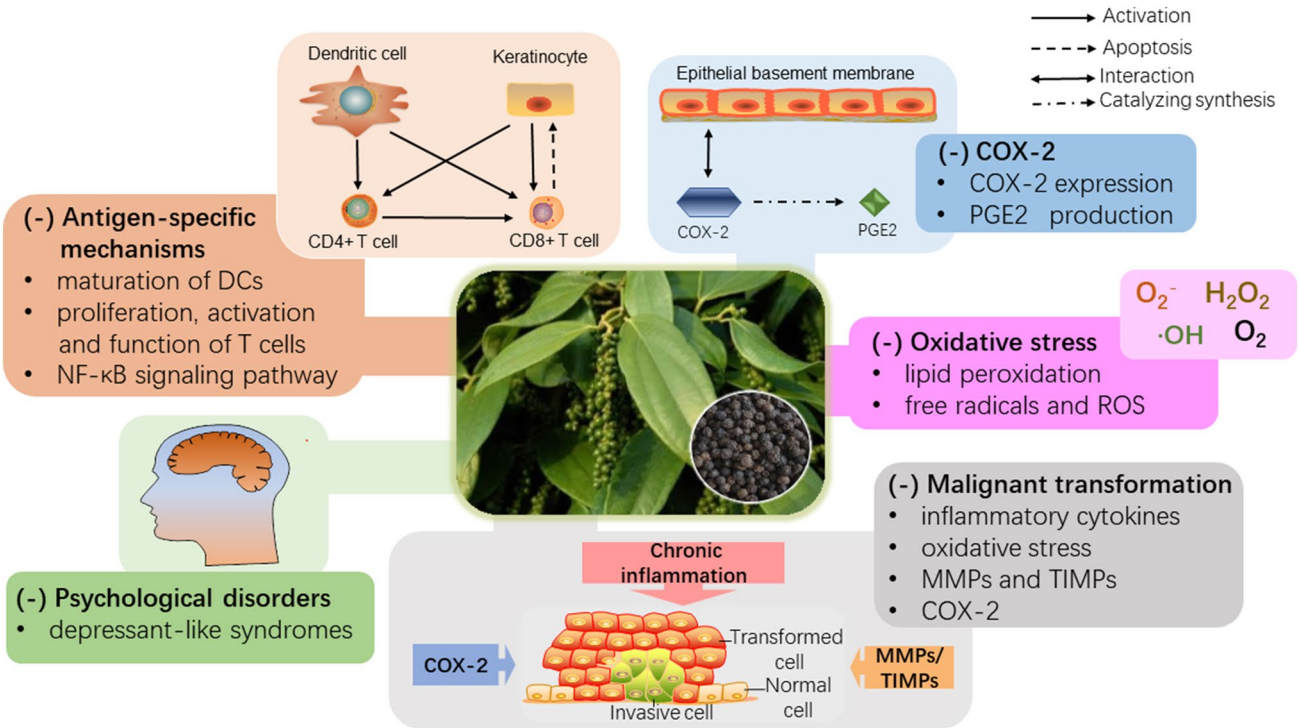

Fig. 2 An overview of black pepper or piperine' potential therapeutic efficacy on OLP in combination with factors related to the development of OLP. The antigen-specific mechanisms of OLP encompassing the intercellular interaction among dentritic cells, CD4+T cells, CD8+T cells and keratinocytes, while black pepper or piperine might suppress these mechanisms through inhibiting the maturation of DCs, the proliferation, activation and function of T cells and the NF-κB signaling pathway. COX-2 may contribute to the development of OLP by interacting with the basement membrane and catalyzing synthesis of PGE2, whereas expression of COX-2 and production of PGE2 could be hampered by piperine. Overexpression of oxidative stress in OLP may be associated with the progression of OLP, while black pepper or piperine might reduce it by suppressing or quenching free radicals and ROS and inhibiting lipid peroxidation. Moreover, black pepper or piperine might benefit OLP by ameliorating psychological disorders occurring in OLP patients. Furthermore, OLP has been recognized to carry malignant potential in which chronic inflammation status, upregulated expression of MMPs (compared with TIMPs) and activities of COX-2 are involved, however, black pepper or piperine may prevent malignancies in OLP via impacting these factors

especially relative higher expression of MMP-9 (compared with TIMP-1) which may cause lesional T cell migration and basement membrane disruption (Zhou et al. 2001; Mignogna et al. 2004; Chen et al. 2008; Lysitsa et al. 2008; Roopashree et al. 2010; Li and Cui 2013; Payeras et al. 2013).

Black pepper or piperine has been confirmed to possess anti-cancer potentiality by preclinical studies (Manayi et al. 2017). It was able to down-regulate the PMA-enhanced expression of MMP-9 at the protein, mRNA and transcriptional levels through the suppression of NF-κB and AP-1 activation, thereby inhibiting human fibrosarcoma cell invasion and metastasis (Hwang et al. 2011). The anti-cancer capacity of piperine was also identified in breast cancer rats and breast cancer cell lines as it could up-regulate p53, and down-regulate E-cadherin (Ecad), MMP-2/-9, and vascular endothelial growth factor (VEGF) levels (Deng et al. 2016). Moreover, a suppression on MMP-2/-9 expression and a promotion on TIMP-1/-2 expression induced by piperine were considered to inhibit proliferation of human osteosarcoma cells (Zhang et al. 2015). Taken together, piperine might make contributions to prevent malignancies in OLP owing to its beneficial impacts on the balance between MMPs and TIMPs on the one hand (Liu et al. 2010; Hwang et al. 2011; Lai et al. 2012; Zhang et al. 2015; Deng et al. 2016). And also because of its suppressive actions upon oxidative stress, cytokines released by inflammatory cells and COX-2 as mentioned earlier on the other hand (Fig. 2).

Conclusion

In conclusion, black pepper and especially its active principle piperine may be a potential supplementary therapy to OLP by virtue of its inhibitory effects on antigen-specific mechanisms and the overproduction of COX-2 as well as enhanced oxidative stress. Furthermore, piperine might be a possible agent for alleviating psychological disorders and preventing carcinogenesis in OLP. Adverse effects of black pepper consumption including gastric mucosal injury might be induced when consumed at much higher doses, and consumers using at an extreme dosage may be at higher risk (Koleva et al. 2012; Vardell 2015). However, a daily consumption of 0.33 g of black pepper by a 60-kg person would only result in an intake of 16.5–29.7 mg piperine/person/day, which is far less from harmful dose (Uma et al. 1993; Srinivasan 2007; Vardell 2015). Thus, oral consumption of black pepper in amounts commonly found in foods is safe to human health.

Intriguingly, various formulation approaches such as nanoparticles, liposomes, microspheres and solid dispersions have been developed to improve the aqueous solubility and oral bioavailability of piperine, which efficiently maximized the therapeutic benefits and broadened the clinical applications of piperine (Lee et al. 2018). Nevertheless, pharmacological activities belonging to black pepper or piperine are till now proven in either animal models or cell cultures, whereas experiments designed for OLP are still void. Thus, there is a necessity to conduct controlled randomized trials in human subjects, cohort studies, and meta-analyses, and especially researches specialized to OLP. Whatever, these findings support further study of piperine as a promising therapeutic agent in the treatment of oral lichen planus.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest regarding the publication of this paper.

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