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REVIEW ARTICLE

CURCUMIN - A NOVEL AYURVEDIC TREATMENT FOR ORAL LICHEN PLANUS

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ABSTRACT

Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease of unknown etiology, but it is believed to result from abnormal T-Cell mediated immune responses in which basal epithelial cells which are recognized as foreign body because of changes in the antigenicity of their cell surface. The treatment modalities in oral lichen planus are still empirical. Corticosteroids remain the mainstay of OLP therapy because of their activity in diminish cell-mediated immune activity. Corticosteroids are administered topically, intra-lesionally or systemically depending on the severity of disease. The prolong use of topical steroids for a period of greater than two weeks continuous use may results in mucosal atrophy and secondary candidiasis, and may increase the potential of systemic absorption. Herbal medicines can be suitable alternatives to synthetic drugs. Application of topical Curcumin can be suggested for treatment of OLP because of its desirable anti- inflammatory effects and insignificant side effects. This review enlightens the treatment of Oral Lichen Planus by means of Curcumin therapy.

INTRODUCTION

Lichen planus derives its name from symbiotic algae and fungal colonies on surface rocks termed as lichens. Lichen planus was first described by Eramus Wilson in 1869 as chronic, non-infectious, inflammatory disease involving skin and mucous membrane. The females are most commonly affected with a period of onset in the middle age. The most common site is buccal and vestibular mucosa followed by lateral borders of tongue and gingiva. The Clinical appearance present in various manifestations such as reticular, papular, plaque, atrophic and ulcerative patterns. The characteristic sign of OLP is "Wickham's striae" which appears as fine white lines with lace like pattern. OLP frequently occurs bilaterally on buccal mucosa. Minority of diseases that closely mimics lichen planus both clinically and histologically is termed as lichenoid lesions. Few examples are lichenoid drug reactions, lichenoid reactions seen in close proximity to amalgam restorations and chronic graft versus host disease. Eisen suggested that the mechanical trauma of dental procedures, mucosal trauma from sharp cusps and oral habits are koebnerogenic factors that can exacerbate OLP. The Koebner phenomenon is present in both cutaneous and OLP.[1, 2]

Etiology and Pathogenesis

The exact etiology of OLP is not well understood. It is believed to result from antigen specific mechanism which causes deregulation of T-Cell mediated immune response in which autocytotoxic $CD8^{+}$T Cells trigger the apoptosis of oral epithelium which occurs as a result of migration and activation of T lymphocytes. The lymphocytic infiltrate is present in OLP is composed almost exclusively of T-Cells and the majority of T-Cells within the epithelium and adjacent to damaged basal keratinocytes which are activated CD8+ lymphocytes. It is also believed that there is increased expression of heat shock protein by exogenous agents like viral and bacterial infections and contact allergens on oral mucosa keratinocytes in oral lichen planus but still antigen is unknown. The deficient antigen-specific transforming growth factor (TGF-β1) control pathway may result in hyper -proliferation of keratinocytes, thereby causing the white lesions in oral lichen planus. The non-specific mechanisms include mast cell degranulation and matrix metalloproteinase activation in OLP lesions. These mechanisms may combine to cause T cell accumulation in the superficial lamina propria, basement membrane disruption, intra-epithelial T cell migration and keratinocytes apoptosis in OLP. A major role in the pathogenesis of long-lasting inflammatory processes is played by the activation of nuclear factor kappa B (NF-κB), a primary transcription factor which upon translocation to the nucleus, binds to promoter regions of different genes encoding immune and pro-inflammatory mediators.[3,4,5,6]

Treatment

The treatment modalities in oral lichen planus are still experimental. In general, reticular and plaque form doesn't require any pharmacological intervention because usually they are asymptomatic. There is no single recommended therapy for oral lichen planus but Steroids remain the mainstay of oral lichen planus therapy because of their activity in dampening the cell-mediated immune activity. They are administered topically, intra-lesionally or systemically depending upon the severity. Alternative treatments are retinoids, ultraviolet phototherapy, steroid sparing agents (hydroxychloroquine, azathioprine, mycophenolate mofetil) and pimecrolimus. Although the above-mentioned drugs have shown positive results in the treatment of OLP, resistance to treatment, recurrence of lesion and a high risk of toxicities limit their use. The disadvantage of prolonged use of topical and systemic steroids may results in mucosal atrophy, secondary candidiasis and systemic toxicity with relapses and remissions. So to avoid systemic toxicity, herbal medicines can be suitable alternatives to synthetic drugs.[7,8,9] The Curcumin is fared better in reducing pain, erythema, and ulceration. Thus, Curcumin can be used as an alternative to steroid in the management of signs and symptoms of OLP with minimal side effects as compared to steroids with similar efficacy. The Curcumin is found to be an effective treatment in oral lichen planus even in the cases where topical steroids have been used and recurrence was seen. The high expectations towards the therapeutic usage of Curcumin are related to the various positive properties and simultaneous low toxicity of the compound.[10]

Herbal medicine known as turmeric is believed to strengthen the overall energy of the body. The most important chemical components of turmeric are a group of compounds called curcuminoids, which include curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin. The Curcumin which is best studied and is comprised of 0.3-5.4% of raw turmeric. As a natural product, Curcumin is nontoxic and has diversified effects in various oral diseases. Curcumin exhibits antioxidant, anti-inflammatory, antimicrobial, and anti-carcinogenic activities, antiproliferative, antimutagenic, neuroprotective, and immune-system modulating properties, which have been well documented in literature to date.

Both in vivo and in vitro animal studies have shown that curcumin inhibits the cancer cell growth process at the stage of forming, suppresses tumour promotion and expansion of cancerous changes Moreover, Curcumin is safe even at very high doses. [11,12,13,14]

Curcumin mediates its anti-inflammatory effects through the down regulation of inflammatory transcription factors (such as nuclear factor-kappa B), enzymes (such as cyclo-oxygenase 2 and 5, lipoxygenase) and cytokines (such as TNF-α, IL-1, IL-6 and IL-8). Furthermore, Curcumin produces its antioxidant effect through inhibition of free radicals and nitric oxide. It is currently clear that even a single 12g dose does not result in toxic effects. Due to its anti-inflammatory, anti-tumour, and anti-diabetic properties and positive therapeutic effects in liver problems, studies on the influence of Curcumin on other parts of the gastrointestinal tract are developing rapidly. Because of the suppression of INF-γ, TNF cytokines and COX inhibition that reduces the production of prostaglandins, Curcumin can be used in the treatment of oesophageal and gastric, colorectal. Thus Curcumin suppresses Tumor Necrosis Factor, Cytotoxic Activity Receptor, T Cell Receptor, FAS-FASL- Ligand Interaction, IL2, IL12 - Interleukin and Ifn-ϒ- Interferon gamma in Oral Lichen Planus (Figure 1). Curcumin does not exhibit any activity in cells in non-affected areas. Curcumin is a strong anti-oxidant agent, comparable to vitamins C and E, which has significant preventive and curative effects in a number of diseases. It acts as a potent scavenger of various Reactive Oxygen Species (ROS) including superoxide anion radicals and hydroxyl radicals. Application of topical Curcumin can be suggested for treatment of OLP because of its desirable anti- inflammatory effects and insignificant side effects. Curcumin also shows antifungal effects which would thus prevent the development of Candida infection over the OLP lesions which is a well-known side effect of topical corticosteroid therapy.[15, 16,17,18,19,20]

Curcumin in Oral Lichen Planus

The first study of Curcumin as an antibacterial agent was published in 1949 in Nature and the first clinical trial was reported in The Lancet in 1937. Although the current database indicates that there are almost 9000 publications on Curcumin, until 1990 there were less than 100 papers published.

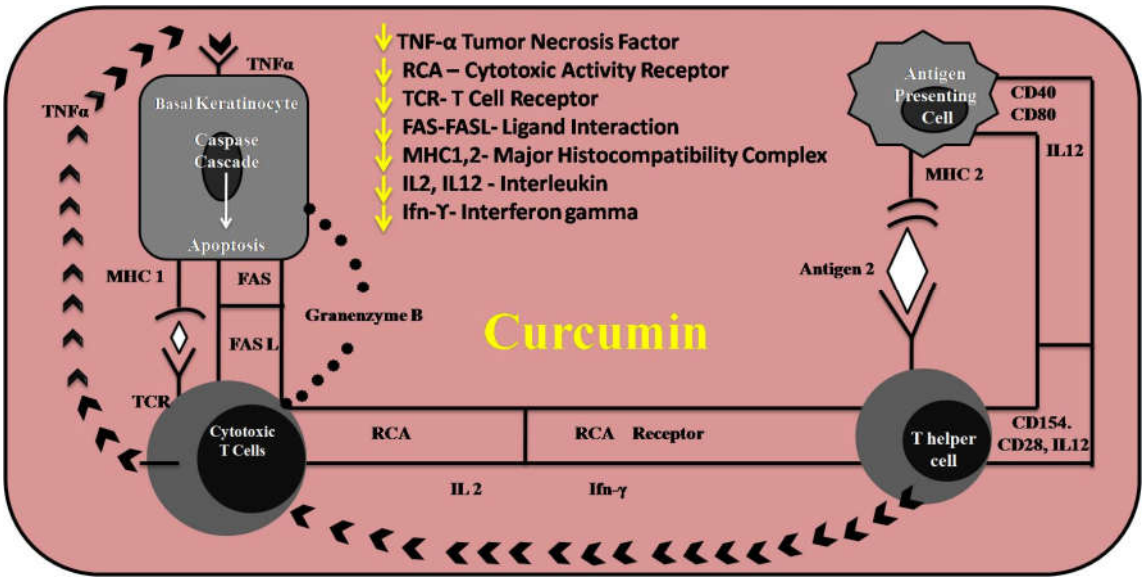

Figure 1 Molecular Targets of Curcumin in Pathogenesis of OLP

The interest in Curcumin has increased significantly since the findings about its anti-tumor and therapeutic effects in pre cancerous lesion were presented. Thus, as many as 1,000 research papers on Curcumin were written in 2008, which constitutes only a quarter of the papers written in 2011.[21,22,23,24,25]

In 2003, Chainani-Wu N was first to report the safety and anti-inflammatory activity of Curcumin. He studied 1 human trial with 25 subjects using up to 8000 mg of Curcumin per day for 3 months and found no toxicity. Five other human trials using 1125-2500 mg of Curcumin per day have also found it to be safe.[26]

In 2006, Sharma C *et al* conducted experiment on Curcumin down regulates smokeless tobacco-induced NF-kappa B activation and COX-2 expression in human with oral premalignant and cancer cells. In his study, he concluded that the down-regulates of STE (khaini) or NNK-induced NF-kappa B and COX-2 was found in oral premalignant and cancer cells using Curcumin in vitro.[27]

In 2007, Chainani-Wu N *et al* conducted a clinical trial of curcuminoids in oral lichen planus regarding the efficacy of Curcumins in which subjects were randomized to receive either placebo or Curcumins at 2000mg/day for 7 weeks. Curcumins at this dose were well tolerated and the results suggest that for future studies should have larger sample size, a higher dose and/or longer duration of Curcumins administration should be considered.[28]

In 2010, Rai *et al*. conducted a study on patients aged 17-50 years with 25 patients of lichen planus. The evaluation of oxidative stress in saliva, serum in salivary glands (malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine (8-OHd), and the level of vitamin C and E was made before administering Curcumin to the patients, a week later, and after recovery. It was noted that the markers in saliva, serum and vitamin level increased, whereas MDA and 8-OHd levels decreased simultaneously in patients suffering from lichen planus. The study showed that the received data was statistically significant after complete recovery.[29]

In 2011 Chainani-Wu N *et al* studied the use of curcuminoids in a cohort of patients with oral lichen planus, an autoimmune disease. According to his study total of 22/37 (60%) of patients reported a reduction of symptoms with curcuminoids with mild Side-effects included abdominal discomfort and diarrhea.[30]

In 2012, Chainani-Wu N *et al* conducted experiment in which high-dose Curcumin are efficacious in the reduction in symptoms and signs of oral lichen planus. According to his study, doses of 6000 mg/d in 3 divided doses are well tolerated and may prove efficacious in controlling signs and symptoms of oral lichen planus with minimal side effects, which are usually dose related. Whereas the smaller doses of Curcumin (< 2,000 mg/day) have proved to be less effective.[31]

In 2013, Vibha Singh *et al* conducted a pilot study on use of turmeric for lichen planus. The study was conducted on 10 patients who were clinically diagnosed and histopathologically confirmed as patients of oral lichen planus. In their study, extract of turmeric as an ointment was used for local application twice/day for a period of 3 months. The improvement in clinical symptoms of oral lichen planus were observed after 15 days.[32]

In 2015, Seid Javad Kia *et al* conducted a experiment on efficacy of topical Curcumin and triamcinolone for oral lichen planus. In their study, he found that all the parameters studied namely pain, erythema, and ulceration associated with OLP showed statistically significant improvement with topical Curcumin therapy.[33]

In 2015, Deepika K *et al* studied of 27 adult OLP patients was divided and was treated with triamcinolone acetonide 0.1% and the other group with commercially available topical Curcumin ointment each to be applied thrice daily for 2 weeks. The patients were reviewed every week. He concluded that curcumin can be used as an alternative to steroid in the management of signs and symptoms of OLP with minimal side effects as compared to steroids with similar efficacy.[34]

In 2015, Maryam Amirchaghmaghi *et al* performed a randomized controlled- trial on 27 and 20 OLP patients respectively to evaluate the efficacy and safety of topical Curcumin in the management of OLP. They concluded that Curcumin can be used as an alternative to steroid in the management of signs and symptoms of OLP with minimal side effects as compared to steroids with similar efficacy.[35]

The available forms of Curcumin are paste form and mouth wash. It is recommended to rub the mucosa with this paste twice daily. Turmeric mouthwash prepared by dissolving 10 mg of curcumin extract in 100 ml of distilled water and 0.005% of flavoring agent peppermint oil with pH adjusted to 4 is found to be as effective. Turmeric extract and turmeric oil have demonstrated onco preventive activity in vitro and in vivo animal experiments. The local symptoms of burning sensation and pain were reduced in oral Lichen Planus.[36,37,38,39]

Curcumin suffers limitations that hold it back from clinical application such as low solubility, rapid metabolism, and hence low bioavailability. Various strategies have been taken to overcome the limitations of the use of Curcumin and to allow its therapeutic application, including the incorporation in delivery systems. Using different drug delivery systems based on nanotechnology, such as polymeric nanoparticles, solid lipid nanoparticles (SLN), liquid crystal systems, precursor systems for liquid crystals, liposome's and micro emulsions, is an interesting approach to improve a formulation's most desirable properties. Curcumin increased the local level of vitamin C and E, while it decreased lipid peroxidation and DNA damage for patient suffered precancerous lesions. The safety of Curcumin is evaluated by numerous animal and human trials. The studies performed so far do not suggest any significant toxicity. Curcumin is found to be well tolerated even at high doses. The side effects are though rare, mainly include gastric irritation, stomach upset, nausea and diarrhea.[40,41,42,43,44]

CONCLUSION

The Curcumin was found to be safe at the prescribed dose and efficacious in controlling the signs and symptoms of OLP. It can be used as an alternative to the standard corticosteroid therapy in the management of OLP and thus alleviate the need for drugs with more serious adversities including corticosteroids. Curcumin may be the new hope for reducing the sign and symptoms and may eradicate the OL. It could be concluded that Curcumin holds a promising future in local therapeutic applications specific for oral diseases such as precancerous lesions. This review highlighted that Curcumin is safe, non-toxic, effective and economical alternative with no

side effects for many traditional drugs used. The fight against oral lichen planus is immensely important, and through the study of the therapeutic promise of Curcumin it has become clear that Curcumin may be the new hope for reducing the incidence of oral lichen planus. Future studies with larger sample sizes and the drug in the form of mouth rinse are recommended.

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