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International Journal of Current Research
Vol. 9, Issue, 03, pp.48119-48124, March, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

EFFICACY OF TURMERIC IN THE MANAGEMENT OF ORAL LICHEN PLANUS

***Bramara Kumari K., Satya Bhushan N. V. V., Sunil T., Siva Kalyan U., Kho Chai Chiang, Srinivas Saketh G., and Bharat Prakash M.**

Department of Oral and Maxillofacial Surgery, GITAM Dental College and Hospital

ARTICLE INFO

Article History:
Received 09th December, 2016
Received in revised form
16th January, 2017
Accepted 26th February, 2017
Published online 31st March, 2017

Key words:

Oral lichen planus, Curcumin, Inflammatory markers, Interleukins, Tumour necrosis factor-alpha, High sensitivity C-reactive protein, Pain, Erythema, Ulceration, Burning sensation.

ABSTRACT

The Purpose of this study was to evaluate the efficacy of Curcumin, a component of turmeric in the management of Oral lichen planus. A total of 30 patients were included in the study who were administered oral curcumin of dosage 300mg used thrice daily for three months in the management of clinical symptoms such as pain, burning sensation, erythema, ulceration and in reduction of inflammatory markers level interleukin-2, interleukin-6, interleukin-10, Tumor necrosis factor-alpha, high sensitivity C-reactive protein. Assessment of patients was done at 15th day, 30th day, 60th day and 90th day. Symptomatic effect of pain evaluation- there was a significant reduction in pain by using VAS score and burning sensation. Similarly, there was also significant reduction in the degree of Erythema and ulceration by using Oral mucositis assessment scale. There was a reduction in the level of inflammatory markers in the patient serum. Oral administration of curcumin showed a reduction of symptoms and inflammatory markers level in Oral lichen planus.

Citation: Bramara Kumari, K., Satya Bhushan, N. V. V., Sunil, T. *et al.* 2017. "Efficacy of turmeric in the management of oral lichen Planus", *International Journal of Current Research*, 9, (03), 48119-48124.

INTRODUCTION

Oral lichen planus (OLP) is a common chronic inflammatory disease associated with cell-mediated immunological dysfunction affecting mucosal and cutaneous tissue. Oral forms are more common than the cutaneous form (Sugarman *et al*., 2002). When the oral mucosa is involved, white lace-like patterns, red atrophic changes, ulcerations can occur. There is an increase in the level of the inflammatory markers such as Interleukins, Tumor necrosis factor-alpha and high sensitivity C-reactive protein in lichen planus patients. Symptoms can range from burning sensation to severe pain, interfering with speaking, eating and swallowing. Lichen planus is a relatively common disorder, estimated to affect 0.5% to 2.0% of the general population (Singh *et al*., 2013). It appears as white striations, papules, plaques, erythema, erosions or ulcers in the mouth and mostly affects the buccal mucosa, tongue and gingiva (Keshari *et al*., 2015). Oral lichen planus tend to be more resistant to any treatment as the patients are often subjected to medical treatment for long periods.Various treatment regimens have been improved in the management of oral lichen planus such as topical Corticosteroids, topical Calcineurin Inhibitors, retinoids, photo chemotherapy and traditional medicines. The primary goal of treatment of OLP is the reduction and preferably elimination of symptoms and to decrease the inflammatory markers level in the serum with limited adverse effects. As a result of side effects produced by the drugs, a natural remedy curcumin which is a component of turmeric used in this study. The purpose of this study is to determine the efficacy of turmeric in the treatment of oral lichen planus.

Corresponding author:* **Bramara Kumari, K.
Department of Oral and Maxillofacial Surgery, GITAM Dental College and Hospital

MATERIALS AND METHODS

This study was conducted in Oral and Maxillofacial surgery department, GITAM Dental College & Hospital, Visakhapatnam. A total of 100 patients among them 60 were males and 40 were females diagnosed with "Oral lichen planus" clinically and confirmed histo-pathologically through incisional biopsy under local anaesthesia after detailed case history of the patient and a thorough examination was recorded on a standard proforma. The study was approved by local institutional ethics committee and an informed consent was obtained from all the patients.

Inclusion Criteria: Patients were clinically and histo-pathologically diagnosed with oral lichen planus and who are willing to participate in the study.

Exclusion Criteria: Patients on long term corticosteroids and retinoids, Pregnancy & Lactation, Uncontrollable systemic diseases, Radiotherapy. Patients were instructed to take tablets orally of curcumin 300mg and piperine5mg thrice daily for 15 days. The patients were instructed to make a note in a diary if they skipped the dose on any particular day. All the patients were recalled on 16th day for 1st follow up and recorded the clinical parameters such as pain by visual analog scale. The scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 [100-mm/10 cm scale]). Patients were made to rate their burning sensation, erythema and ulceration by oral mucositis assessment scale. An intensity score for erythema, ranging from 0 to 3, was used (0 = normal, 1= mild erythema, 2 =moderate erythema, 3 =severe erythema). The score for ulcerations was based on area of ulceration (0 = no ulcerations, 1 =between 0-0.25 cm^2, 2 = between 0.25-1 cm^2, 3 =1 cm^2 or greater). Laboratory parameters such as Interleukins-2, 6, 10 (IL-2, 6, 10), Tumour necrosis factor-alpha (TNF-alpha), high sensitivity C-reactive protein (hs-CRP) in serum by taking blood through venipuncture during every follow-up were recorded by using ELISA kit. Further follow ups were at 30th day, 60th day and 90th day where in the above mentioned parameters were noted. 10 cases were not reported for follow ups.

Statistical analysis

All the statistical data was collected and tabulated using ANOVA test. ANOVA, a parametric test was performed in all the variables and $p<0.01$ was accepted as statistically significant. By taking baseline measurements as reference, intra-group comparisons were made by using ANOVA test.

RESULTS

In the present study, there was a relief for the patients from burning sensation after usage of curcumin tablets for a period of 90 days and no significant difference (P-value > 0.72) was observed between follow ups. Similarly, there was a marked reduction of ulceration and pain and were highly significant (P-value < 0.01) between follow ups. There was a reduction of erythema after 15 days of usage of curcumin tablets and at the end of 90 days most of the patients have shown no Erythema, where there was a highly significant difference seen (P-value < 0.01). There was a marked reduction in the inflammatory markers such as interleukin-2 (normal range is 0-5pg/ml) [Fig 1], interleukin-6 (normal range is 5-15pg/ml) [Fig 2], interleukin-10 (normal range is 0-7.8pg/ml) [Fig 3], TNF-alpha (normal range is 0-16pg/ml) [Fig 4] and hs-CRP levels (normal range is 0-3pg/ml) [Fig 5] in the serum and were highly significant (P-value < 0.01) between follow ups. From the above observations in this study, it can be concluded that after oral intake of curcumin and piperine (900mg dosage) in three divided doses for 3 months, there was a reduction of symptoms and signs score [Fig 6,7,8,9,10] and also the inflammatory markers level in the serum. None of the cases in this study had side effects like diarrhea, vomiting, gastritis, local and systemic irritation in follow-up visits.

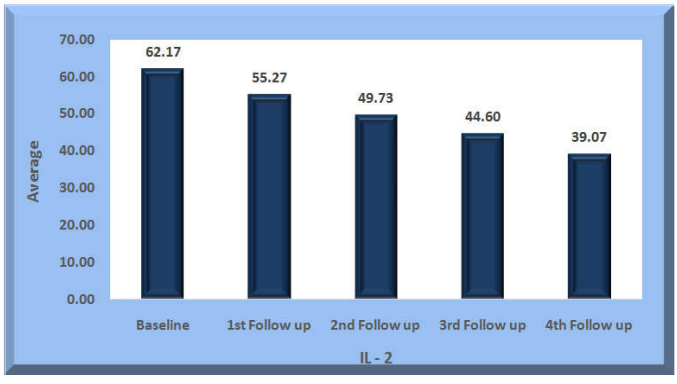

Fig.1. Bar diagram showing mean values of Interleukin-2

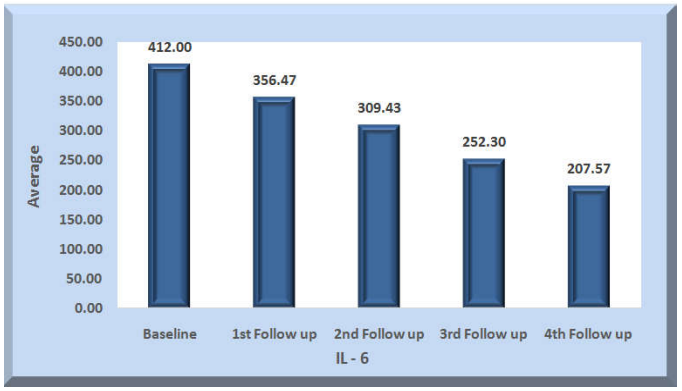

Fig.2. Bar diagram showing mean values of Interleukin- 6

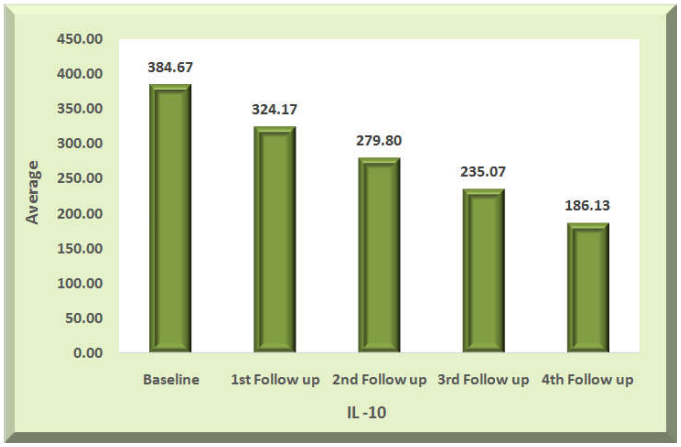

Fig.3. Bar diagram showing mean values of Interleukin-10

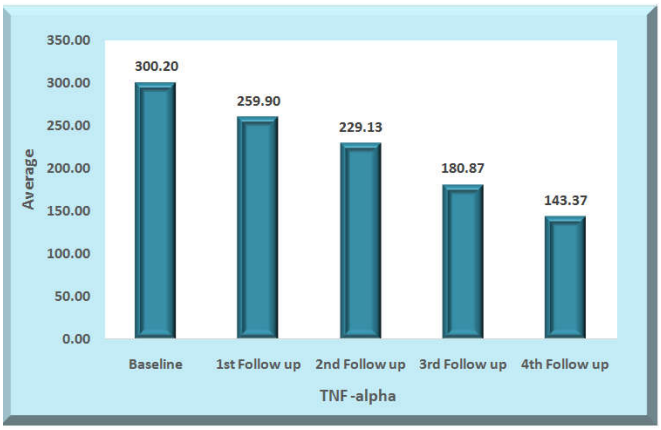

Fig.4. Bar diagram showing mean values of Tumour Necrosis Factor- Alpha

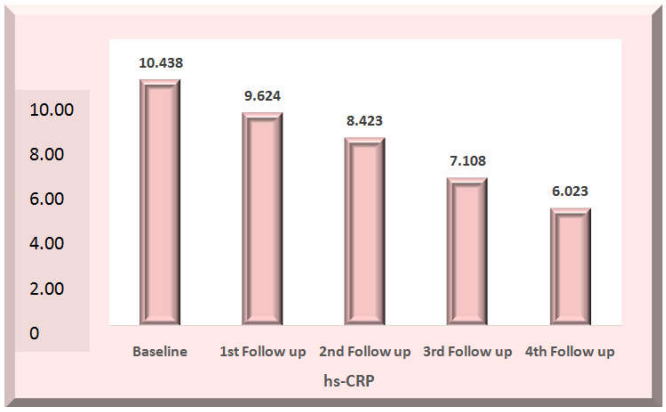

Fig. 5. Bar diagram showing mean values of high Sensitivity C- Reactive Protein

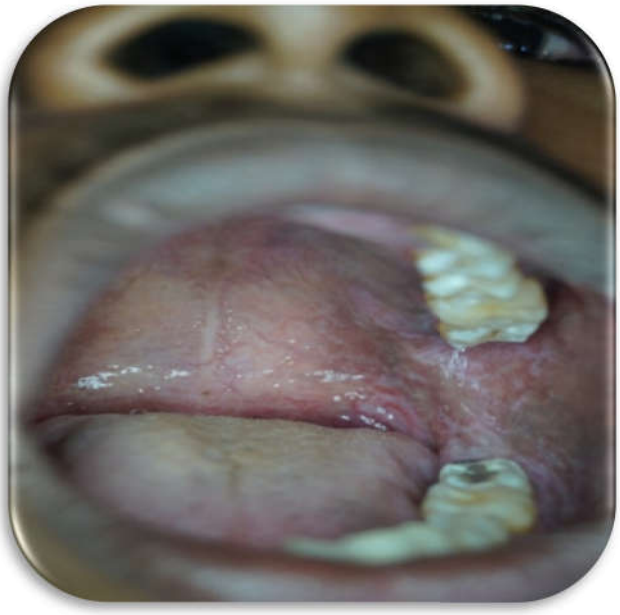

Fig.6. Clinical photograph of OLP: Pre-operative

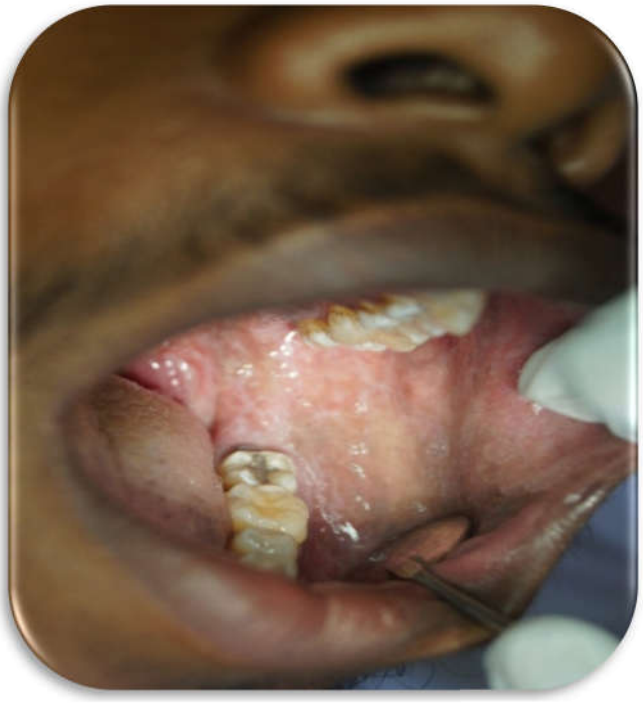

Fig.7. Clinical photograph of OLP: 1st follow up (15th day)

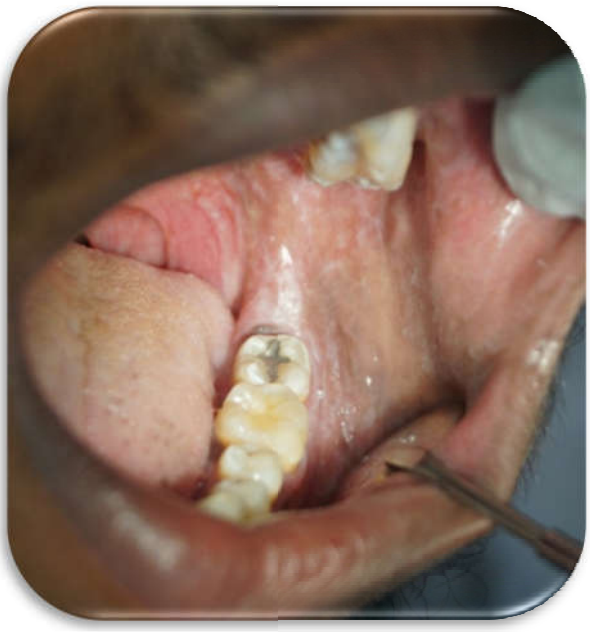

Fig.8. Clinical photograph of OLP: 2nd follow up (30th day)

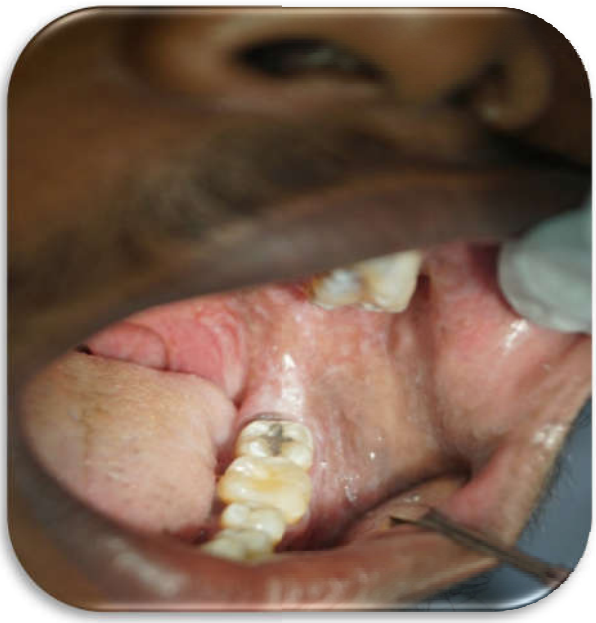

Fig.9. Clinical photograph of OLP: 3rd follow up (60th day)

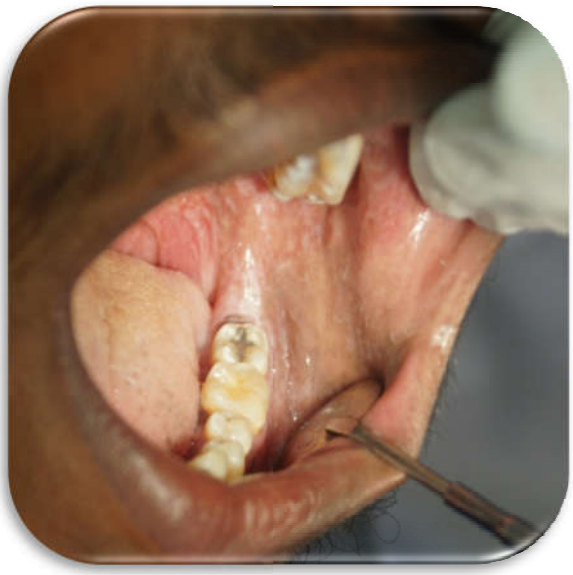

Fig.10. Clinical photograph of OLP: 4th follow up (90th day)

DISCUSSION

Oral lichen planus is a T-cell mediated chronic inflammatory mucocutaneous disease (Sugarman *et al*., 2002) which can alter the skin, oral mucosa and other mucous memberanes (Cardova *et al*., 2014). Today, oral lichen planus is considered as a disease of obscure etiology (Cardova *et al*., 2014) although various triggers are proposed. Various etiological factors are endogenous and exogenous factors like systemic medications, stress, dental materials (Kumari *et al*.,2016), irritants like maloccluded teeth (Prakash *et al*.,2017), ill-fitting dentures, amalgam filings (Gujjar *et al*., 2015), chronic liver disease, genetics, tobacco chewing, hepatitis C virus, graft versus host disease. Systemic medications such as anti malarial drugs, non steroidal anti-inflammatory drugs, anti hypertensive agents, diuretics, oral hypoglycemic drugs, beta blockers, pencillins (Saketh *et al*.,2016), sulfonamides, tetracyclines, heavy metals, thyroid preperations, anti retroviral medication have been reported to cause OLP. All these predisposing factors lead to the activation of cell-mediated immunity and play a major role in the pathogenesis of OLP (Gangashetty and Kumar, 2015). The prevalence rates of oral lichen planus reported vary from 0.5% to 2.2% of the population (Vander Waal, 2009). It affects mainly women more than men in a ratio of 1.4:1 (Singh *et al*., 2013; Gangashetty and Kumar, 2015) and occurs most frequently at typical age of presentation usually the fifth and sixth decades of life (Cardova *et al*., 2014) which is similar to this study. Lichen planus seen in two forms which are oral and cutaneous forms (Cardova *et al*., 2014). It affects oral mucosal surfaces such as buccal mucosa, tongue, gingival and non oral mucosal surfaces such as genitals, nails, scalp, anus, pharynx, conjunctiva and oesophagus. In this study, lesions seen in more than one site apart from buccal mucosa, the other sites involved were gingiva, mucobuccal fold and tongue which was similar to the studies done by Eisen *et al*. (2005), Ingafou *et al*. (2006), Thongprasom *et al*. (2009) and Xue *et al*. (2005). The clinical forms of oral lichen planus are reticular, plaque, papular, erythematous, ulcerative and bullous types. Various treatment regimens are being used for the treatment of oral lichen planus of which corticosteroids is the most common choice. Other treatment options include topical calcineurin inhibitors, retinoids, antimetabolites, photosensitizing psoralen drugs, ultraviolet A radiation, Photodynamic therapy, CO_2 laser, Cryotherapy, neodymium-doped yttrium aluminium garnet laser[5]. All these modalities of treatment have ended up with some side effects. To overcome these side effects, a natural way of treatment curcumin which is a component of turmeric has been used extensively in ayurvedic medicine for centuries, as it is non-toxic and has a variety of therapeutic properties including analgesic, antioxidant, anti-inflammatory, anti-septic activity and anti carcinogenic property (Keshari *et al*., 2015).

Curcumin has shown theurapeutic efficacy in human diseases but the major concern about curcumin is poor oral bioavailability, high rate of metabolism and rapid systemic elimination from the body. Curcumin is capable of interacting with numerous molecular targets involved in inflammation. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin -1, 2, 6, 8, and 12, monocyte chemo-attractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases. COX-2 and iNOS inhibition are likely accomplished via curcumin's suppression of nuclear factor kappa B (NF-κB) activation.NF-κB, a ubiquitous eukaryotic transcription factor, is involved in regulation of inflammation, cellular proliferation, transformation, and tumorigenesis. Curcumin is thought to suppress NF-κB activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor I-kappa B kinase (IκB). Suppression of NF-κB activation subsequently down-regulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis. Curcumin also inhibited arachidonic acid metabolism and inflammation via downregulation of the cyclooxygenase (COX-2) and lipoxygenase pathways (LOX) (Singh *et al*., 2014) COX-2 and LOX are two enzymes involved in inflammation. Cytokine induced COX-2 transforms arachidonic acid in to prostaglandins during acute inflammatory episodes. COX-2 is also the prevalent isoform during chronic inflammations. Lipoxygenase transforms arachidonic acid in leukotrienes, which take part in leukocytes recruiting and plays a role in inflammation (Jacob *et al*., 2007). Curcumin also protects keratinocytes and fibroblasts against H_2O_2- induced damages and allow reduction of oxidative and inflammatory stress (Jacob *et al*., 2007). Curcumin exhibits low systemic bioavailability after oral dosing and may undergo intestinal metabolism (Jacob *et al*., 2007). The reasons for reduced bioavailability of any agent within the body are low intrinsic activity, poor absorption, high rate of metabolism, inactivity of metabolic products and / or rapid elimination and clearance from the body. Hence, co-administration of curcumin with piperine, a compound found in pepper vine and peppers increased the bioavailability of curcumin following oral dosing presumably due to the inhibition of xenobiotic glucuronidation by piperine. It appears to inhibit different cytochrome P450 isoforms, UDP- glucuronyltransferase and hepatic arylhydrocarbon hydroxylase involved in drug and xenobiotic metabolism.

Other mechanisms for the bioenhancer activity of piperine have been proposed including DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump, drug metabolizing enzymes, stimulates absorption by stimulating gut amino acid transporters inhibits the cell pumpresponsible for drug elimination from cells and inhibits intestinal production of glucuronic acid, thus permitting a more active form of drug to enter the body It may increase the absorption of drug in the GIT, or inhibit enzymes responsible for drug metabolism, especially in the liver when the drug passes through the liver after absorption from GIT. Thus it enhances the action of curcumin. The result of this study indicated 900 mg of curcumin per day is very effective orally and safe with minimal side effects as compared to the previous drug regimens in which 2000 mg curcumin per day was given where gastric irritation was a major side effect seen in the study of chinani-wu *et al*. Previous studies of Chinani-wu *et al*. (2012, 2008 & 2007) demonstrated that high doses of curcumin are needed in oral lichen planus due to the poor bioavailability of curcumin following oral administration. Addition of small amounts of piperine (Patil *et al*., 2011; Shoba *et al*., 1998; Bhardwaj *et al*., 2002; Panda and Kar, 2003; Singh *et al*., 2011; Kumar *et al*., 2007; Pathak and Khandelwal, 2009; Bhat and Chandrasekhara, 1987; Desai *et al*., 2008) has shown to greatly improve the bioavailability of curcumin as described by shobaet, al was followed later by chinani-wu et.al and also in this study with good results. Hence, good bioavailability of curcumin was obtained even with a low dosage of 900mg / day by the addition of piperine indicating the synergistic effects of

piperine and curcumin as well as decreased side effects to the patients following a low dosage therapy. In this study, curcumin plus piperine 900mg per day in three divided doses for 12 weeks were administered. There was a statistically significant difference (p-value < 0.01) observed for pain, erythema and ulceration when baseline and intra follow ups were compared. There was no statistically significant difference (p-value > 0.72) observed in burning sensation when baseline and intra follow-ups were compared. No patient with oral lichen planus using 900mg dosage of curcumin and piperine per day for 12 weeks have shown gastritis, diarrhea, vomiting, local and systemic irritation. Blood tests were done to record the levels of inflammatory markers such as interleukin-2, interleukin-6, interleukin-10, Tumor necrosis factor-alpha and high sensitivity C-reactive protein in serum for 30 patients pre-operatively, at 15th day, 30th day, 60th day and 90th day. There was a high significant difference (p-value < 0.01) observed in the levels of inflammatory markers when baseline and intra follow-ups were compared

Conclusion

In the present study, Curcumin 300 mg and piperine 5mg administered orally thrice daily for 90 days reduced the subjective symptoms of pain, erythema and ulceration and is by showing statistically significant reduction when preoperative and intra follow-ups were compared, where as there was no significant difference observed in relation to burning sensation. Patients did not report any adverse effects like vomiting, gastritis, diarrhea, local irritation or any discomfort during the three months follow up after oral administration of curcumin. Steroids are considered as a gold standard for treatment of OLP but their long-term use has known to cause side effects. Hence, curcumin, a component of turmeric, which is relatively safer, can be considered as a treatment option for the management of Oral lichen planus.

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