

# A comparative study to evaluate the therapeutic effects of nutraceuticals in oral leukoplakia:- A randomized clinical trail

## ABSTRACT

**Background:** Oral leukoplakia, usually white changes in the oral mucosa, is one of the most common conditions affecting the oral cavity. Oral leukoplakia can occur anywhere in the mouth and is usually asymptomatic. Clinical diagnosis is reliant on visual inspection and manual palpation. It has a global prevalence of 2.6% and a malignant transformation rate of 0.13–34%. In India, OL has a higher prevalence (0.2–5.2%) but a lower malignant transformation rate (0.13–10%).

**Methodology:** It was a randomized control trial in which study was conducted on clinically diagnosed 300 oral leukoplakia patients. All patients were randomly categorized in three groups of 100 each. Group-A: Patients were given commercially available curcumin 500 mg. daily orally. Group-B: Patients were given 4 mg of oral lycopene daily. Group-C: Patients were treated with 4 mg of lycopene + 500 mg curcumin daily by oral route. After recording the pre-treatment clinical findings, all the participants were evaluated regularly after 30 days, 60 days and 90 days of active treatment and once in a month for another 3 months of post-treatment follow-up and to evaluate concomitant medication, lesion(s), compliance, and adverse events. The clinical response was evaluated by bi-dimensional measurement of the lesions and color photography. Safety assessment measures: Physical examination and laboratory tests were performed at baseline, and every 30 days for 3 months after randomization.

**Result:** Number of participants cured after treatment with oral curcumin was 51%. Participants took lycopene tablets showed 63% cure rate and 72% participants cured after treatment with combination curcumin and lycopene.

**Conclusion:** Results showed that curcumin, lycopene, and a combination of the two are effective in the treatment of oral leukoplakia. When compared, we found that lycopene is a better nutraceutical as compared to curcumin. When both nutraceuticals were given to the participants, they showed better results than single nutraceuticals when the data were analyzed after 90 days of treatment. There is a significant difference in the response of curcumin and combinations of both nutraceuticals, although the difference between lycopene and combinations of curcumin and lycopene is insignificant.

**Keywords:** Curcumin, leukoplakia, lycopene, oral premalignant lesions

## INTRODUCTION

Oral leukoplakia is one of the most common potentially malignant disorder affecting the oral cavity. In India, the prevalence of leukoplakia varies from 0.2% to 5.2% and malignant transformation ranges between 0.13% and 10% according to various studies.<sup>[1]</sup> The main objective of oral leukoplakia management is to prevent malignant transformation of the lesion and early detection.

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As per the pathogenesis of leukoplakia is concerned, functional loss of multiple TSGs (tumor suppressor genes) is believed to be the main contributing factor leading to the development of malignancies.<sup>[2,3]</sup>

Several TSGs are involved in oral cancer specially the cyclin family, ras, PRAD1, cyclin dependent kinase inhibitors, p53, and RB1. TSG p53 is the most frequently mutated factor accounting for approximately 70% of adult solid tumors.<sup>[4]</sup> Not only TSG p53 but the members of its suppressor pathway, which themselves too are prone to be mutated, may prove the involvement of p53 in the majority of cases of cancers.<sup>[5]</sup>

Different surgical and non-surgical treatments have been discovered, but currently there is no universal consensus on the most appropriate one. Rigorous and conscious attempts are being continuously made to develop safe and effective chemo preventive agents for the treatment of leukoplakia. First illustration of the use of chemo preventive agents for leukoplakia dates back around 25 years ago.<sup>[6]</sup> The use of nutraceuticals as chemo-preventative agents have been studied, and promising results were obtained as per their ability to prevent and treat cancer.

Nutraceuticals, as the term has evolved from “nutrition” and “pharmaceutics,” are bioactive substances that are present in routine food or plant-based sources that can be delivered in the form of dietary supplements or health beneficial food, providing innumerable therapeutic effects in addition to the necessary nutritional requirement.<sup>[7]</sup> Nutraceuticals of different sources have been expressed anti-cancer activity in various studies. Plants such as garlic, ginseng, curcumin, ginger, and green tea extract express several mechanisms of action against oncogenesis. Such mechanisms include the inhibition of DNA alkylation, tumor initiation, proliferation, and metastasis, in addition to the promotion of autophagy and intrinsic apoptosis. Furthermore, nutraceuticals have been found to diminished cancer signaling pathways that are perceived to play a role in carcinogenesis.<sup>[8]</sup> Many studies have been conducted to evaluate the mode of action of nutraceuticals against various types of cancer. A wide range of nutraceuticals has been found to express anti-cancer properties against various types of cancers including oral cancer, prostate cancer, breast cancer, lung cancer, and colon cancers.<sup>[9,10]</sup>

Natural dietary nutraceuticals may justify being anticarcinogenic *via* several mechanisms of action like carotenoids that promote gap-junctional communication *in vitro* studies through augmentation of “connexin 43”,<sup>[11]</sup> or flavonoids which regulate phase I and II xenobiotic

detoxification, or vitamin E that hamper protein kinase C, a critical enzyme in tumor advancement of some types of cancer.<sup>[12]</sup> Advantageous Effects of Curcumin, Resveratrol (RES), and Berberine (BBR) have been examined in clinical trials of several pathologies such as cardiovascular diseases, colorectal adenoma reoccurrence, diabetes, defective endothelial function, glucose metabolism/metabolic syndrome, age-related macular degeneration, Alzheimer’s disease, different types of cancer and many others.<sup>[13]</sup> Many reports state that phytochemical compounds (e.g., from cumin, red pepper and ginger) can potentially prevent cancer by suppressing the pathway of Nuclear transcription factor- KB (NF- KB) correlated with cancer and many inflammatory diseases. NF- KB is a very attractive therapeutic target for plant-derived nutraceuticals and polyphenols.<sup>[14]</sup>

Curcumin a yellow colored plant derivative, obtained from the root of *Curcuma longa* (Turmeric) belonging to the ginger family with a wide range of therapeutic effects including anti-inflammatory, anti fibrotic, antioxidant, and anti carcinogenic properties assume it useful for medicinal purposes.<sup>[15]</sup> Clinicians show substantial enthusiasm in current years for the use of curcumin in OL, OSF and other OPMDs.<sup>[16-19]</sup> Curcumin induces apoptosis in various cancer cells by p53-dependent and p53-independent pathways. This effect of curcumin is maximum in p53-expressing cells, such as TR-7 and MCF-7. In addition, the expression of pro-apoptotic protein BCL2 associated X, (Bax) is also reported at its peak in curcumin treated MCF-7 cells. These results collectively support that curcumin induces the chemo preventive property mainly through a p53-dependent pathway.<sup>[20]</sup> Lycopene is a natural pigment synthesized by plants and microorganisms but not by animals. In 57 studies there was an inverse association between tomato intake or circulating lycopene levels and risk of several types of cancer; in 35 cases the association was statistically significant. None of the studies showed adverse effects of high tomato intake or high lycopene levels.<sup>[21]</sup> The inverse relationship between lycopene intake and cancer risk has been observed in particular for cancers of the prostate, pancreas, bladder, cervix, and oral leukoplakia’s because of its ability to modulate dysplastic changes.<sup>[22,23]</sup> New evidence has provided other explanations for the anticancer activity of lycopene by the upregulation of connexin and stimulation of gap junctional communication, an action that is independent of its role as an antioxidant.<sup>[24,25]</sup>

The constitutive compounds of garlic can selectively inhibit tumor proliferation by several factors, for example, controlling DNA repair mechanisms, chromosomal stability, and cell cycle regulation. Garlic constituents can suppress

carcinogen formation, carcinogen bioactivation, and tumor proliferation.<sup>[26,27]</sup>

Thymoquinone (TQ) induces apoptotic cell death in cancerous tissues by up-regulating expression of apoptotic genes (caspases and bax) and down-regulating expression of anti-apoptotic genes (e.g., bcl 2)<sup>[28]</sup>; TQ abating Akt activation by dephosphorylation and thus arrest cancer cell survival; TQ deactivates NF-kappa B pathway by inducing cytokine generation, and thus check oncogenic expression.<sup>[29,30]</sup>

## METHODOLOGY

After selecting, five nutraceuticals through an exhaustive survey of pertinent literature for having properties against malignancy and premalignant conditions like oral leukoplakia and oral sub mucus fibrosis. A feasibility study was done to figure out the most appropriate one among the five. Twenty persons were enrolled for the pilot study with four persons in each of the five groups. The trial was done for thirty days. Noticeable effect was recorded in two subjects who received lycopene and two subjects who received curcumin. No appreciable effect could be observed in groups receiving allicin, thymoquinone, and gingerol within thirty days and therefore allicin, thymoquinone, and gingerol were not selected to explore further.

Lycopene and curcumin were then given to the larger population to have a comparative analysis of both the drugs and also to appraise any synergy and coaction between the two. The study was conducted on 300 patients visiting the Faculty of Dentistry during 2019–2022 with a white patch in oral cavity, enrolled patients were physically healthy, were from age group 18–70 years, with no sex predilection, with a leukoplakic patch size not less than 1 cm. Patient with chronic illness, pregnancy or with history of any drug allergy and patients showing any potential malignant changes in the lesion were excluded from the study.

Oral leukoplakia was confirmed clinically in participating subjects. The aim and purpose of the study was explained to each patient thoroughly and written consent was obtained.

Also the habits like tobacco chewing and alcohol usage were enquired on each visit and the patients were encouraged to discontinue the same. Ethical clearance has been obtained from the Institutional ethical committee (proposal number 1/10/294/JMI/IEC/2020). Study was also registered with Clinical Trial Registry-India (CTRI/2021/05/033380). All the 300 patients were randomly allocated in three groups of 100 each. Group-A: Patients were given commercially available curcumin capsules 500 mg once a day. Group-B: Patients were given 4 mg of oral lycopene tablet once a day. Group-C: Patients were given 4 mg of lycopene along with 500 mg curcumin once a day. The study subjects were called regularly at 15 days intervals and therapeutic assessment was done once in a month for three months during treatment. Post study follow-up was also done once in a month for another three months to record any relapse, or adverse events if there were any. In case of any untoward reaction such as rash, allergy, etc., the patients were asked to report immediately. Safety assessment measures like Physical examination, and laboratory tests including complete blood count, serum biochemistry, and urine analysis, were performed at baseline, after one month, two months, and three months of randomization.

**Statistics:** For comparing the efficacy of test nutraceuticals between the three parallel groups, the Z' test was applied. If the value of 'Z' is greater than 1.96 or less than -1.96, the null hypothesis is rejected. In a test of hypothesis, the level of significance for the test is 0.05.  $P > 0.05$  is the probability that the null hypothesis is true.

## Outcome measures

An objective clinical response was evaluated by bi-dimensional measurement of the lesion, and by color photography. Outcome was classified as completely cured, partially cured (with a reduction in the size of the lesion), and not cured.

## RESULTS

Initially, 300 patients were enrolled in the study [Table 1] but 17 patients did not report back in follow ups at different stages of treatment and were considered drop out cases.

**Table 1: Randomization of participants**

| Age group | Number of patients (n=300) | Patients received curcumin (n=100) | Number of patients who received lycopene (n=100) | A number of patients received curcumin and lycopene together (n=100) | Dropout cases |
|-----------|----------------------------|------------------------------------|--|--|---------------|
| 18-30     | 39                         | 12                                 | 12   | 12   | 3             |
| 30-40     | 60                         | 19                                 | 18   | 20   | 3             |
| 40-50     | 96                         | 31                                 | 32   | 30   | 3             |
| 50-60     | 76                         | 23                                 | 22   | 23   | 8             |
| 60-70     | 29                         | 9                                  | 10   | 08   | 2             |

Patients in test group 'A' (100) were given curcumin as a single nutraceutical [Table 2]. It was observed that four patients got cured in the first one month. Another 21 patients were cured in two months and 26 more patients were relieved completely in three months. Total of 51 patients got cured in group 'A' at the end of therapy that is, after '90' days of treatment. Six patients remained untraceable and didn't turn up therefore were counted as dropout cases. Also, five cases showed relapse in post therapy follow up.

In test group B (100) patients were given only lycopene capsules orally [Table 3]. Improvement was recorded in seven patients who got cured in one month. Another 25 patients got cured in two months and 26 more patients got relieved completely in three months. The number of patients getting cured in group 'B' at the end of therapy that is, after '90' days of treatment was '63'. Five participants remained untraceable and were recorded as dropout cases. In post-therapeutic follow-up, relapse was also recorded in six cases.

In test group C (100) patients were given two nutraceuticals separately together, curcumin and lycopene [Table 4]. In this test group with a combination of nutraceuticals it was observed that 12 patients were cured in the one month. 37 more patients were cured in two months and another 23 patients got relieved completely in 90 days. A total of

72 patients got cured in three months with combination therapy. Six participants were untraceable and were counted as dropout cases. In post therapeutic follow-up, there found a relapse of symptoms in three cases.

For comparing the efficacy of test nutraceuticals between the three parallel groups, the 'Z' test was applied for the significance of curcumin and the combined effect of curcumin and lycopene, it was found that  $Z = 3.417006 (> 1.96)$  which is highly significant. When we compared data of curcumin and lycopene after 90 days of treatment, we found value of the  $Z = 1.849659 (< 1.96)$ . Therefore, this situation shows that there is no significant difference in the efficacy of lycopene and curcumin supplements in the treatment of oral leukoplakia. When using the "Z" score to compare the effect of lycopene with combined effect of both curcumin and lycopene as a dietary supplement, the "Z" value after 90 days of treatment was 1.5 (<1.96). So the difference is insignificant. When we compared the data showing the effects of curcumin as a nutraceutical with the combination of curcumin and lycopene after 90 days of treatment, the value of the "Z" obtained = 3.417006 (> 1.96). There is a significant difference between the efficacy of curcumin alone and the combined efficacy of curcumin and lycopene nutraceuticals. The combination of the two nutraceuticals was much more effective than curcumin alone [Table 5].

**Table 2: Results of patients who received curcumin only**

| Age group | Number of patients 94 | Cured after 30 days | Cured in 60 days | Cured in 90 days | Total patients cured after 90 days | Not cured | Relapse cases |
|-----------|-----------------------|---------------------|------------------|------------------|------------------------------------|-----------|---------------|
| 18-30     | 12                    | 00                  | 03               | 04               | 07                                 | 05        | 01            |
| 30-40     | 19                    | 00                  | 06               | 04               | 10                                 | 09        |               |
| 40-50     | 31                    | 02                  | 07               | 09               | 18                                 | 12        | 02            |
| 50-60     | 23                    | 02                  | 03               | 07               | 12                                 | 11        |               |
| 60-70     | 09                    | 00                  | 02               | 02               | 04                                 | 05        | 02            |

**Table 3: Results of patients who received lycopene only**

| Age group | Number of patients 95 | Cured after 30 days | Cured in 60 days | Cured in 90 days | Total patients cured after 90 days | Not cured | Relapse cases |
|-----------|-----------------------|---------------------|------------------|------------------|------------------------------------|-----------|---------------|
| 18-30     | 12                    | 01                  | 03               | 05               | 09                                 | 03        |               |
| 30-40     | 18                    | 02                  | 06               | 06               | 14                                 | 04        | 01            |
| 40-50     | 32                    | 02                  | 08               | 10               | 20                                 | 12        | 02            |
| 50-60     | 23                    | 02                  | 05               | 07               | 14                                 | 09        | 02            |
| 60-70     | 10                    | 00                  | 03               | 03               | 06                                 | 04        | 01            |

**Table 4: Results of patients who received curcumin and lycopene both simultaneously**

| Age group | Number of patients 94 | Cured after 30 days | Cured in 60 days | Cured in 90 days | Total patients cured after 90 days | Not cured | Relapse cases |
|-----------|-----------------------|---------------------|------------------|------------------|------------------------------------|-----------|---------------|
| 18-30     | 12                    | 02                  | 04               | 03               | 09                                 | 03        |               |
| 30-40     | 20                    | 03                  | 07               | 06               | 16                                 | 04        | 01            |
| 40-50     | 30                    | 04                  | 12               | 07               | 23                                 | 07        | 01            |
| 50-60     | 24                    | 02                  | 10               | 06               | 18                                 | 06        | 01            |
| 60-70     | 08                    | 01                  | 04               | 01               | 06                                 | 02        |               |

**Table 5: Comparison of results of curcumin alone lycopene alone and curcumin and lycopene both**

| Nutraceutical given            | Number of patients | Cured after 30 days | Cured in 60 days | Cured in 90 days | Total patients cured after 90 days | Not cured | Relapse cases |
|--------------------------------|--------------------|---------------------|------------------|------------------|------------------------------------|-----------|---------------|
| Curcumin alone                 | 94                 | 04                  | 21               | 26               | 51                                 | 42        | 03            |
| Lycopene alone                 | 95                 | 07                  | 25               | 31               | 63                                 | 32        | 04            |
| Curcumin and lycopene together | 94                 | 12                  | 37               | 23               | 72                                 | 22        | 02            |

**Discussion:** The main goal of oral leukoplakia treatment is to prevent the disease from turning into a malignancy. Self-treatment of leukoplakia is rare. Many surgical and non-surgical treatments have been discovered, but there is no general consensus about the most appropriate treatment. These surgical and non-surgical treatments have not been shown to be effective in preventing future malignant transformation.<sup>[8]</sup> Efforts are ongoing to develop safe and effective chemopreventive agents for the treatment of oral leukoplakia and other precancerous oral diseases. This study aims to evaluate the effects of oral curcumin and lycopene as single nutraceutical and the administration of curcumin and lycopene together in the participants with oral leukoplakia and to compare them. We found that curcumin and lycopene are effective nutraceuticals in the treatment of oral leukoplakia. By reviewing the literature, we found studies supporting the anti-cancer and anti-precancerous effects of curcumin and lycopene. A review by Ahmad T *et al.* (2021)<sup>[31]</sup> included 90 participants with a mean age of 32 and ranging from 17-60 years. Of the 90 participants, 70 were male and 20 were female. The results of this review showed that oral administration of curcumin and lycopene improved mouth opening, burning sensation, and cheek flexibility compared to placebo. Concluded that treatment of OL and OSF with oral curcumin and lycopene appears to be effective and safe Kuriakose MA *et al.* (2016)<sup>[32]</sup> found that the presence of pre-malignant diseases such as oral leukoplakia, submucosal fibrosis and lichen planus caused a decrease in blood and saliva vitamin C and E values compared to healthy individuals, which showed significant improvement when curcumin was administered. Based on these observations, the researchers concluded that curcumin mediates cancer prevention by increasing vitamins C and E and preventing lipid peroxidation and DNA damage. This study also shows that, in addition to the importance of curcumin's anti-cancerous and antioxidant activities, all patients improved their symptoms and decreased inflammation.<sup>[17]</sup> Other investigators reported that oral administration of 3.6 g/day of curcumin in comparison to placebo resulted in significant clinical and histological responses. They observed a response in 75 (67.5%) of 110 subjects.<sup>[32]</sup> Article (2001) concluded that curcumin has the potential to prevent cancer in patients with premalignant or high-risk diseases, including oral leukoplakia. This study also found that 8,000 mg of curcumin taken daily for three months was non-toxic to humans.<sup>[33]</sup> Observations in group B

are also following the results of the study which reported that Lycopene in doses 8 mg/day and 4 mg/day showed significant resolution of the leukoplakic lesion when compared to the placebo arm for three months of treatment results obtained 80%, 66%, and 12.5% respectively.<sup>[23]</sup> In a clinical study conducted on 58 patients concluded that lycopene brings appreciable histological changes of a significant degree in patients with OL.<sup>[34]</sup> In another study on researchers tried to investigate the association between serum micronutrient levels and OL. Serum levels of lycopene among men with OL were found significantly lower than in the participants of the control group further establishing positive impact of lycopene in the prevention of OL.<sup>[35]</sup> When data analyzed after 30 days we found that there is no significant difference in the therapeutic effect of single nutraceuticals in oral leukoplakia. Also, there is an insignificant difference between therapeutic effect of lycopene and combined therapeutic effect of both curcumin and lycopene. There is a significant difference in the therapeutic effect of curcumin and combined therapeutic effect of both curcumin and lycopene. When data analyzed after 60 days we found that there is no significant difference in the therapeutic effect of single nutraceuticals in oral leukoplakia. Also there is insignificant difference between therapeutic effect of lycopene and combined therapeutic effect of both curcumin and lycopene. There is a significant difference in therapeutic effect of curcumin and combined therapeutic effect of both curcumin and lycopene. When data analyzed after 90 days we found that there is no significant difference in the therapeutic effect of single nutraceuticals in oral leukoplakia. Also there is an insignificant difference between therapeutic effect of lycopene and combined therapeutic effect of both curcumin and lycopene. There is significant difference in therapeutic effect of curcumin and combined therapeutic effect of both curcumin and lycopene.

From above analysis we can say that the combined effect of nutraceuticals is better than single one. Therapeutic effect of Lycopene is better than than curcumin although it's not significant.

## CONCLUSION

Clinical trial in present study showed that curcumin is effective in premalignant conditions like oral leukoplakia. Study also observed the effectiveness of lycopene in oral leukoplakia

and the combined effect of curcumin and lycopene. Lycopene came out as a better nutraceutical in comparison to curcumin, although difference was not significant. Study also showed that the combined effect of both nutraceuticals is better than single nutraceuticals. When data was analyzed after 30 days, 60 days, and 90 days of treatment it was found that difference in the efficacy of curcumin and lycopene is insignificant, the difference between therapeutic effect of lycopene and the combined effect of curcumin and lycopene was also insignificant. But when we analyzed data to see the difference in therapeutic effect of curcumin and combined effect of both curcumin and lycopene in oral leukoplakia there was significant difference in the response. These novel findings indicated that lycopene and curcumin as single nutraceuticals and when given simultaneously could act as promising potential natural anticancer agents. Well-designed clinical trials of lycopene are expected to make new progress in the next decades. Although the safety evaluation of these nutraceuticals is being established, More clinical intervention trials are needed. These novel findings indicated that curcumin and lycopene could act as a promising potential natural anticancer agent. Well-designed clinical trials of combined effects and comparative studies are expected to make a new progress in the next decades. The definite potential efficacy of curcumin, lycopene, and the combined effect of these nutraceuticals as an anticancer agent remains unclear completely, which warrants further investigation. However, above mentions, nutraceuticals are still a potential agent due to their multiple antitumor mechanisms, which may contribute to the prevention and treatment of human premalignant conditions like oral leukoplakia.

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#### Conflicts of interest

There are no conflicts of interest.

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