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Herbal Treatment Modality for Management of Leukoplakia - A Systematic Review

Rakhi Chandak¹, Vidya Lohe², Manoj Chandak³, Rahul Bhowate⁴,
R.S. Sathawane⁵, Romita Gaikwad⁶, Dhiran Talatule⁶, Runal Bansod⁷,
Pranali Thakare⁷

¹Reader, Department of Oral Medicine & Radiology, SDKS Dental College & Hospital, Nagpur, Maharashtra, India; Ph.D Scholar at SPDC, DMIMSU Sawangi, Dental College & Hospital, Wardha, Maharashtra, India; ²Professor & Head of Department, Department of Oral Medicine & Radiology, SPDC, DMIMSU Sawangi, Dental College & Hospital, Wardha, Maharashtra, India; ³Professor, Department of Conservative Dentistry, SPDC, DMIMSU Sawangi, Dental College & Hospital, Wardha, Maharashtra, India; ⁴Professor, Department of Oral Medicine & Radiology, SPDC, DMIMSU Sawangi, Dental College & Hospital, Wardha, Maharashtra, India; ⁵Professor & Head of Department, Department of Oral Medicine & Radiology, SDKS Dental College & Hospital, Nagpur, Maharashtra, India; ⁶Senior Lecturer, Department of Oral Medicine & Radiology, SDKS Dental College & Hospital, Nagpur, Maharashtra, India; ⁷Post Graduate student, Department of Oral Medicine & Radiology, SDKS Dental College & Hospital, Nagpur, Maharashtra, India.

ABSTRACT

A systematic review was conducted using PRISMA guidelines. Studies, case series, clinical trials mentioning the treatment of leukoplakia with herbal modalities were included. Data are available on follow-ups of herbal treatment modalities for leukoplakia. 7 out of 10 studies were picked up for inclusion and were included in the systematic review. The effectiveness of various herbal treatment modalities for the management of leukoplakia was reviewed. With the help of abstracts and titles, the preliminary screening of the recovered studies was done. In studies whose results were found to be unclear, its corresponding full text was read. The studies were independently evaluated by authors and the results were discussed until a decision was made by a general agreement. 7 out of 10 studies were picked up for inclusion and were included in the systematic review. Several treatments exist for treating this “potentially malignant lesions” even including some surgical, as well as non-surgical treatment plans but the spectrum of herbal medicine surely, brings a new ray of hope. The most meritorious effect of herbal medicine is that it interacts with the specific chemical receptors within the body and has less side effect as compared to traditional medicines. Herbs are very good anti-oxidants, anti-bacterial agents, anti-inflammatory agents as well as good sedatives and anxiolytics hence play a very useful role in the treatment of oral diseases.

Key Words: Curcumin, Herbal, Leukoplakia, Malignant Disorder

INTRODUCTION

Diagnosing an oral white lesion is of great skill and challenge to the Oral Health Care practitioners mainly due to the varied appearances of the white lesions. Reactive lesions, various carcinomatous lesions as well as some dysplastic lesions may play in the field of making a differential diagnosis opposite these oral white lesions. Clinicians must take great efforts in deriving a final diagnosis and to prevent time delay in treating patients with some serious lesions.¹

Classification of oral white lesions consisting of red-white lesions, ulcerations, pigmentations and exophytic lesions.² Oral white lesions such as “leukoplakia, lichen planus, and proliferative verrucous leukoplakia” have a great malignant

potential of as high as 0.5–100% and these white lesions constitute only 5% of all the oral white lesions.³ Therefore, the appropriate clinical diagnostic approach of the white lesion is necessary to exclude the possibility of malignancy.¹ Amongst all the white lesions, oral leukoplakia secures the top place in being the most common “potential malignant disorder” which affects the oral cavity. The etiopathogenesis of “oral leukoplakia” involves two basis - first being oral leukoplakia due to tobacco consumption while the second being of idiopathic or unknown etiopathology.³

According to literature, “oral leukoplakia” is described as a white patch or lesion that cannot be clinically or histologically attributed as a definite lesion.^{4,5} The prevalence rate of oral leukoplakia among the general population is reported

Corresponding Author:

Dr. Rakhi Chandak, Reader, Department of Oral Medicine & Radiology, SDKS Dental College & Hospital, Nagpur, Maharashtra, India.
Contact: 9011071465; E-mail: rakhi.chandak@sdk-dentalcollege.edu.in

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to be 2.6% and is most commonly seen above the age of 50 years with the male predilection however a few studies do report of having a female predilection too. Approximately 16% to 62% of oral squamous carcinomas occur as a successor to a pre-existing oral leukoplakia.

Several factors such as tobacco, alcohol, sanguinary, UV radiation, trauma, betel nut use, genetic predisposition and microorganisms are known to have a strong and significant relationship with leukoplakia.⁵⁻⁷ Clinically it appears as a non-scrapable, irreversible and slightly raised white patch on plaque having wrinkled, leathery to having dry “Cracked mud appearance.” The “homogenous type of leukoplakia” has well-defined margins, a regular, smooth whitish surface. The “non-homogenous type of leukoplakia” occurs in various forms like nodular or erythematous, ulcerated, erosive or verrucous exophytic component. A type of leukoplakia called the “verrucous leukoplakia” has an elevated, proliferative or a corrugated surface while the nodular type of leukoplakia develops a small polypoid enlargement or a white rounded excrescences.^{4,7}

The histopathologic aspects of oral leukoplakia may vary from epithelial atrophy to hyperplasia to varying degrees of epithelial dysplasia.^{8,9,10} High-risk lesions of oral leukoplakia are situated on the floor of the mouth, soft palate and tongue while the low-risk lesions of oral leukoplakia are situated in other areas of the oral cavity. Annual malignant transformation rate of OL has an.1% to17%.¹¹⁻¹⁴ Epithelial dysplastic changes should be assessed while planning for the treatment of oral leukoplakia.

In cases of moderate or severe dysplastic changes surgery would be a treatment of choice, however lesions with a low to moderate malignant risk may or may not be removed completely but factors such as location, size, smoking habits should be taken into consideration.

Oral leukoplakia can be treated conservatively. Minimal adverse effects to patients in cases of widespread oral leukoplakia, in medically compromised patients, convenient application not requiring frequent hospital visits and low cost are some of the advantages of non-surgical modalities.^{8,15} Therefore this systematic review deeply describes and analyses the published data and compares the effectiveness of various herbal treatment modalities for the management of leukoplakia.

METHODOLOGY

Primary Question of Research

Which herbal treatment modality is the most fruitful in managing leukoplakia?

GOALS

1. Scrutinizing the data and studies available on various herbal treatments for leukoplakia.

2. Extracting the most efficacious herbal treatment options for leukoplakia.

METHODS

Eligibility Criteria

Inclusion criteria

1. Studies, case series, clinical trials mentioning the treatment of leukoplakia with herbal modalities.
2. Data available on follow ups of herbal treatment modalities for leukoplakia.
3. Published articles from January 2005 up to 31 December 2019 searched in Pubmed.
4. English written literature was included. (Table 1)

Exclusion criteria

1. Data available in some other linguistic forms
2. In vitro studies, editorials, abstracts, letters, and historical reviews were excluded from the searches. (Table 1)

PICO from PICO

P – Participants: Leukoplakic participants or participants with dysplasia.

I - Intervention: Herbal treatment options.

C-Comparison between various herbal treatment options.

O - Outcomes: Decrease in the lesion size and severity of epithelial dysplasia.

Procedure

This systematic review was conducted using the PRISMA guidelines statement. All the studies were carefully chosen after reviewing all the abstracts and text as per the inclusion and exclusion criteria and are explained below. During the review process, none of the authors of the manuscript was contacted.

Search strategy

The search strategy commenced by conducting searches from PubMed / Medline, web of science and Scopus to collect and identify the studies published in English irrespective of the year of publication. Keywords such as oral leukoplakia and therapy, oral leukoplakia and herbal modality, curcumins in oral leukoplakia, oral leukoplakia and its management, oral and potentially malignant disorders were used.

RESULTS

With the help of abstracts and titles, the preliminary screening of the recovered studies was done. In studies whose results were found to be unclear, its corresponding full text was read. The studies were independently evaluated by authors

and the results were discussed until a decision was made by a general agreement. 7 out of 10 studies were picked up for inclusion and were included in the systematic review. All the details and results of the search strategy along with the efficacy of various herbal treatment modalities for the management of leukoplakia were summarised in Table 2.

DISCUSSION

Oral leukoplakia is one of the most important disorders of the oral cavity having great malignant potential. The two important etiological factors for oral leukoplakia is tobacco in smoking and smokeless form. Oral malignancy develops from “potentially malignant disorders”, so early and prompt diagnosis and treatment are required to resist their progression towards malignancy. Current non-surgical treatment modalities include cessation of tobacco chewing habit, retinoids and lycopene. Various authors have tried a variety of herbal medicines for treating oral disorders including premalignant disorders. The present study aims at analysing various herbal treatment modalities for the management of oral leukoplakia.^{1,2}

Rai et al¹⁶ in 2010 conducted a study on 13 male patients and 12 female patients having oral leukoplakia, 11 male patients and 14 female patients having Oral Submucous Fibrosis and 13 female patients and 12 male patients having lichen planus along with 25 healthy participants who wear age between 17 years to 50 years. For the diagnosis of precancerous lesions of the oral cavity, all the Diagnostic test were thoroughly scrutinized. To ascertain the presence of systemic diseases a questionnaire-based Medical and Dental history was obtained from each subject along with the history of alcohol, smoking or drug consumption. A Caplet of 1 gm of curcumin containing curcumin (900 mg), desmethoxycurcumin (80 mg) and bisdemethoxycurcumin (20 mg) was approved from “Sabinsa Corporation”.

Markers of oxidation like “malonaldehyde (MDA), 8-hydroxydeoxyguanosine (8-OHdG), vitamin C and vitamin E” were measured in serum and saliva before the administration of curcumin, 1 week following the consumption of curcumin and once the precancerous lesions were cured clinically. It was found that the patients with “OL, oral submucous fibrosis & lichen planus” succeeding the administration of curcumin, the levels of MDA and 8-OHdG were found to be significantly decreased, while the levels of vitamin C and vitamin E were found to be increased in the saliva and serum. Statistically significant changes in the values were obtained post clinical cure of the disease and the p-value was found to be less than 0.05 (p<0.05). Hence, it was found that by increasing the levels of vitamin C and vitamin E and preventing DNA damage and peroxidation of lipids, curcumin radiates its pre-cancer activities.

Behura et al.¹⁷ in 2015 conducted a study by using a major polyphenol Epigallocatechin gallate (EGCG) mainly found in green tea possessing great antioxidant and chemopreventive properties. This Epigallocatechin gallate (EGCG) showed very promising results¹¹. In the present study, a total of 59 patients out of which 29 patients with oral leukoplakia were randomly asked to use mixed tea extract orally as well as topically. The oral lesions appeared to decrease in size in almost 40% of the treated patients which was also associated with a decrease in proliferation on histopathological examination after a 6-month trial.

Hazzah et al.¹⁸ in 2016 analysed qualitatively low dose curcumin based loaded mucoadhesive gel consisting of solid-lipid nanoparticle (CurSLN) for local application in the treatment of “oral precancerous lesions”. The Cur SLNs was formulated and then dispersed in a matrix of mucoadhesive gel for the application on the buccal mucosa. Using binary system a conventional mucoadhesive gel was adopted. Using chicken buccal mucosa the prepared gels were subjected to Vitro drug dialysis & ex-vivo permeation. A short clinical evaluation based on pain index and measurement of lesion size was carried out on 10 patients in a total of 10 patients who were suffering from OL. It was observed that the CurSLN loaded gel reflected good adhesion property. Hence it was concluded that using a low dose of Cur can be a promising option for treatment of precancerous lesions.

Singh et al.¹⁹ in 2017 analysed qualitatively, Calendula officinalis, the herbal medicines for the management of oral leukoplakia. She included 60 clinically and histopathologically confirmed case of homogenous leukoplakia based on the classification given by Warnakulasuriya S. et al. which randomly divided into two groups in which is each group consisted of 30 patients each. Group 1 patients were given C. Officinalis gel containing antioxidants 2 mg by weight, per gram of gel. Patients in Group II were dispensed lycopene gel containing lycopene antioxidant 2 mg by weight, per gram of gel.

The double-blinded protocol was followed; the therapy was followed up for the next 3 months. All the patients were examined in this study and all the 30 patients in C. Officinalis group showed a significant reduction in the size of the lesion. the size of the lesion within 1 month. The significant difference is obtained in group 1 imply that the extracts of C. Officinalis can efficiently be used in the treatment of oral leukoplakia.

Chhapparwal et al.²⁰ in 2018 carried out the clinical trial by including patients diagnosed clinically as well as histopathologically as having oral leukoplakia. Subjects were given 2% tetrahydro curcuminoid (THC) gel (Sami Labs, Bengaluru) to apply on the affected sites in the oral cavity and keep it in the mouth for 30 min, 5 times daily for 12 weeks. They were prohibited for eating or drinking anything and gargling for 1

hour after applying the medication and returned for a follow-up once in 3 weeks or earlier in the event of any adverse reaction associated with the application of the medicament. Of the 8 patients, six patients within the age range of 40 to 70 years were males with a mean age of 56 years. All the patients reported a reduction of burning sensation within 3 weeks of starting treatment and were completely asymptomatic by the completion of the study. The size of the lesion during the period of follow-up appeared to be significantly reduced. Reduction in thickness of the lesion was found in six of eight patients. Histological improvement was seen in three patients after completion of treatment. However, there was no histological improvement in four patients, and one patient progressed to mild dysplasia from hyperkeratosis without dysplasia. It is concluded that THD when topically applied in gel form is remarkably effective in alleviating clinical symptoms. The remarkable histological improvement was seen in 3 of 8 patients.

Bhagat et al²¹ in 2018 conducted a study by including 60 patients having oral leukoplakia after confirming the diagnosis clinically and histopathologically. Patients were divided into two groups, group A & B. Group A received placebo. Group B is given curcumin capsules for 3 months. Curcumin capsules were obtained from Himalaya, the trade name is Himalaya Haridra. Each capsule contains 400mg of curcumin. They are sealed in a plastic bottle containing 60 each. The patients selected for the study were instructed to take 1 capsule twice daily. The patients were recorded after every 15 days for their clinical evaluation and to collect the medications. All the patients signed informed consent before the study. The patient was kept on a 3-month treatment plan in which they were called upon after for every 15 days within 6 months follow-up period. A scoring system was used to evaluate severe clinical signs and symptoms. A decrease in the size of the lesion along with healing of the lesions was seen as a sign of significant improvement in group B patients. Hence, after a thorough inspection of the effect of curcumin, it can be suggested as a safe and effective medication for treating oral leukoplakia.

Kapoor et al.²² in the year 2019 conducted a study which consisted of 60 patients who were grouped into three groups. Group A included 20 patients having oral leukoplakia. Group B consisted of 20 diagnosed with oral lichen planus and group C consisted of 20 patients with OSMF. Each subject answered a questionnaire for evaluating the prevalence of diseases, smoking, alcohol and drug history. Two main clinical variables mainly pain control and healing of lesions were used for evaluating the cure of "leukoplakia", "lichen planus" and "OSMF". For the measurement of pain, a pain analogue was used ranging from "0.5 (very mild) to 5 (severe pain)". To check the healing, we measured the change in lesions size (five-point rating scale). For OSMF patients mouth opening was also taken

into consideration. In Group C, a marked increase in the mouth opening was seen, while in groups A, B, and C a marked decrease in the size of lesions was evident. It was concluded that curcumin is a potent, safe and inexpensive modality for the management of PMDS.

Patel et al²³ in 2020 conducted a study on 60 patients. Out of 60 patients, successful completion of trial of 41 patients was done along with a proper follow-up. These 41 patients were then further divided into two groups randomly as the Study group (Group A) consisting of 21 participants who were administered "lycopene (6mg) + vitamin E(400 I.U) + selenium (200 mcg)" in two equally divided doses. This study made use of a product named "Lyc-O-Mato" soft gels, manufactured by "Mano Pharmaceuticals", Chennai, India. The second was the Placebo group (Group B) consisting of 20 participants who were administered placebo capsules once a day. Before the treatment, once the clinical and histological findings were recorded, all the participants were then subjected to a thorough evaluation at a period of 15 days for 3 months regularly as active treatment and then once a month for another period of 3 months after the follow-up treatment. The investigation of clinical response was done using the bi-dimensional measurement of the lesions and with help of colour photography during each visit. It was seen that the union of "vitamin E and selenium with lycopene" was greatly efficient in improving the clinical and histological findings in the participants with "leukoplakia" and the result was significant statistically when compared to the placebo group. A reduction in the leukoplakic lesion/ keratosis was observed as a primary clinical finding, following a reduction in the lesion size and a pinkish hue of the mucosa. In lycopene receiving patients, a noteworthy histological response was noted and was identified by a reversal in the dysplastic changes.

The oral mucosa displays varied appearances, some personal habits being one of the etiological factors.²⁴ Excessive tobacco and alcohol consumption can result in irreversible, irreplaceable and an irreparable genetic injury. Hence it's very important to introspect these early potentially malignant disorders like oral leukoplakia before they start turning into malignancy as the human body tries to eliminate these cells which have got altered by these mechanisms but in case it fails or no longer can suppress their replication then the possibility of development of squamous cell carcinoma develops.²⁴ It's a belief that excessive tobacco consumption produces carcinogens which induce liberation of reactive species & free radicals of oxygen. These, in turn, are responsible for an increased oxidation or peroxidation rate of the polyunsaturated fatty acids.²⁵ Due to this peroxidation process there is the liberation of peroxide radicals. As a result of which the essential components of the cell membrane might get involved in carcinogenesis.²⁵

Dysplastic changes of the oral epithelium are more likely to give rise to oral malignancies. Though it is found that 50% of the oral squamous cell carcinomas begin in apparently normal mucosa, there are some most widely accepted oral lesions with severe malignant potency, leukoplakia being one of them.²⁶

CONCLUSION

In this systematic review, five in vivo studies showed that curcumin showed better results in the management of leukoplakia than green tea, calendula *Officinalis* gel and vitamin E and selenium with oral lycopene. One of the in-vivo studies compared all the herbal treatment modalities and showed that curcumin performed better in the management of leukoplakia. However, green tea and calendula *Officinalis* and a gel consisting of oral lycopene with vitamin E and selenium showed the same findings concerning the decrease in size of the leukoplakic lesion. One of the in-vitro and Vivo study stated that “curcumin solid–lipid nanoparticle loaded gels” showed good mucoadhesion property, a marked significant reduction in pain, and complete healing after 6 weeks of treatment was observed. The local use of a low dose Cur is a promising option in the treatment of leukoplakia than green tea, carotenoid, Calendula *Officinalis* extract gel and lycopene in oral leukoplakia. Reviewing all the studies, it can be concluded that “curcumin solid–lipid nanoparticle loaded gels” and tetrahydro curcuminoid is effective in the management of oral leukoplakia.

Table 1: Prisma flow diagram:

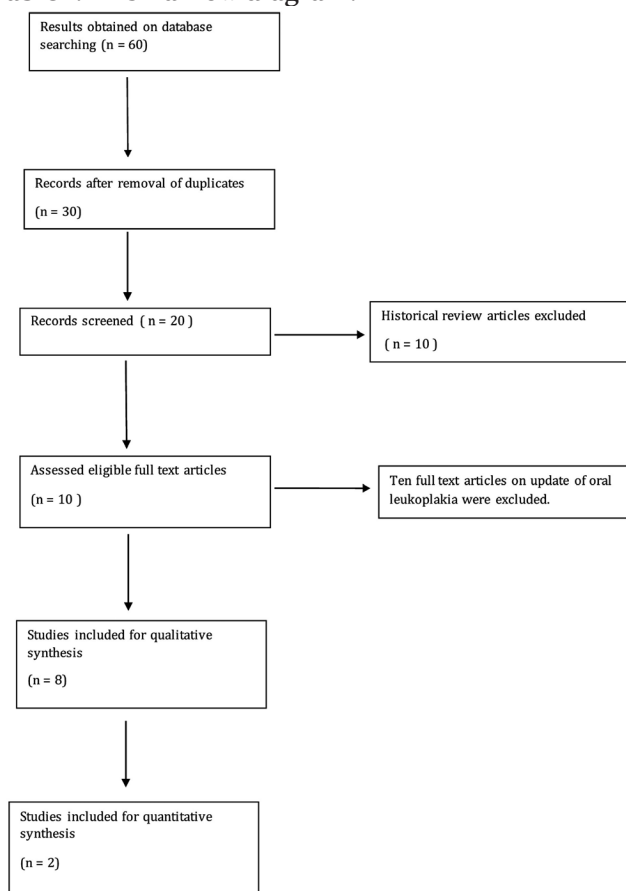


Table 2: Represents the reported efficacy of various herbal treatment modalities for management of leukoplakia.

First author	Year	Type of study	Herbal drug	Results
Rai et al. ¹⁶	2010	In vivo	curcumin.	Salivary and serum oxidation markers in leukoplakic patients were measured before and after the treatment with curcumin. Statistically significant changes in the findings were observed after the clinical cure of the disease.
Behura et al. ¹⁷	2015	In vivo	Green Tea Polyphenols	Use of a mixed tea extract was applied in patients with oral leukoplakia orally as well as topically. The size of the lesions appeared to decrease after a 6 month trial in almost 40% of the treated patients which in turn was associated with a decrease in the proliferation in the treatment group on histopathologic examination.
Hazzah et al. ¹⁸	2017	Vivo and vitro	Curcumin solid–lipid nanoparticle loaded gels.	The findings showed that CurSLN loaded gel showed

Singh and Bagewadi ¹⁹	2017	In vivo	Calendula officinalis extract gel with lycopene gel	good adhesion properties and there was a marked significant decrease in pain and complete healing after 6 weeks of treatment. Hence use of Cur in a low dose is a promising option for treatment of precancerous lesions.
Chhapparwal et al. ²⁰	2018	In vivo	Tetrahydrocurcuminoid.	There was a significant reduction in the lesion size due to C. officinalis extract gel and hence it can be implied that C. officinalis extract gel can be effectively used as an alternative to lycopene gel for treating oral leukoplakia.
Bhagat et al. ²¹	2018	In vivo	curcumin	The results showed that tetrahydro curcuminoid when used topically in gel form, shows remarkable effects in alleviating the clinical signs and symptoms such as the decrease in size and thickness of lesion and pain. A remarkable improvement was seen histopathologically in 3 out of 8 patients.
Kapoor et al. ²²	2019	In vivo	curcumin	On inspecting the effects of Curcumin, it can be concluded that it can be used in the treatment of leukoplakia.
Jyotsna Sandeep Patel et al. ²³	2020	"In vivo"	Oral lycopene with Vitamin E and Selenium	In this study, a marked decrease was seen in the size of lesions in patients with leukoplakia. This study suggests that for the management of leukoplakia, curcumin can be used effectively as it potent, safe and inexpensive.
				Statistically significant findings were seen in lycopene + vitamin E + selenium receiving patients in this study and also there were no side effects in those receiving placebo.

REFERENCES

- Mortazavi H, Safi Y, Baharvand M, Jafari S, Anbari F, Rahmani S. Oral white lesions: an updated clinical diagnostic decision tree. *Dentistry J.* 2019 Mar;7(1):15.
- Mortazavi, H, Safi Y, Baharvand M, Rahmani S, Jafari S. Peripheral Exophytic Oral Lesions: A Clinical Decision Tree. *Int. J. Dent.* 2017; 9193831.
- Mohammad A, Bobby J, Devipriya S. Prevalence of oral mucosal lesions in patients of the Kuwait University Dental Center. *Saudi Dent J* 2013; 25:111–118.
- Mortazavi H, Baharvand M, Mehdipour M. Oral potentially malignant disorders: An overview of more than 20 entities. *J Dent Res Dent Clin Dent Prospect* 2014; 8: 6–14.
- Parlatescu I, Gheorghe C, Coculescu E, Tovar S, Oral Leukoplakia—An Update. *Maedica* 2014; 9: 88.
- Neville B, Damm D, Allen C, Chi A. *Oral and Maxillofacial Pathology*, 4th ed.; Elsevier: Amsterdam, The Netherlands, 2016.
- Martorell-Calatayud A, Botella-Estrada R, Bagán-Sebastián J.V, Sanmartín-Jiménez O, Guillén-Barona C. Oral leukoplakia: Clinical, histopathologic, and molecular features and therapeutic approach. *Actasdermo- Sifiliográficas* 2009; 100: 669–684.
- Ribeiro AS, Salles PR, da Silva TA, Mesquita RA. A review of the nonsurgical treatment of oral leukoplakia. *Int J Dentist* 2010;21:1-10.
- Van der Waal KP, Schepman EH, Van der Meij, Smeele LE. Oral leukoplakia: a clinicopathological review. *Oral Oncol* 1997; 33(5): 291–301.
- Neville BW, Day TA. Oral cancer and precancerous lesions. *Cancer J Clin* 2002;52(4): 195–215.
- Schepman KP, Van der Meij EH, Smeele LE, Van der Waal I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncol* 1998;34(4):270-5.
- Saito T, Sugiura C, Hirai A, Notani KI, Totsuka Y, Shindoh M, Fukuda H. Development of squamous cell carcinoma from pre-

- existent oral leukoplakia: concerning treatment modality. *Int J Oral Maxillofac Surg* 2001;30(1):49-53.
13. Reibel J. Prognosis of oral pre-malignant lesions: the significance of clinical, histopathological, and molecular biological characteristics. *Crit Rev Oral Biol Med* 2003;14(1):47-62.
 14. Lodi G, Porter S. Management of potentially malignant disorders: evidence and critique. *J Oral Pathol Med* 2008;37(2):63-9.
 15. Epstein JB, Gorsky M, Wong FL, Millner A. Topical bleomycin for the treatment of dysplastic oral leukoplakia. *Cancer: Interdisciplinary. Int J Am Cancer Soc* 1998;83(4):629-34.
 16. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. *J Oral Sci* 2010;52(2):251-6.
 17. Behura SS, Singh DK, Masthan KM, Babu NA, Sah S. Chemoprevention of oral cancer: a promising venture. *Int J Oral Care Res* 2015;3(2):80-7.
 18. Hazzah HA, Farid RM, Nasra MM, Zakaria M, Gawish Y, El-Massik MA, Abdallah OY. A new approach for treatment of precancerous lesions with curcumin solid-lipid nanoparticle-loaded gels: in vitro and clinical evaluation. *Drug Deliv* 2016;23(4):1409-19.
 19. Singh M, Bagewadi A. Comparison of effectiveness of *Calendula officinalis* extract gel with lycopene gel for treatment of tobacco-induced homogeneous leukoplakia: A randomized clinical trial. *Int J Pharm Invest* 2017;7(2):88.
 20. Chhapparwal Y, Pai KM, Kamath MS, Carnelio S, Chhapparwal S. Efficacy and safety of tetrahydrocurcuminoid in the treatment of oral leukoplakia: a pilot study. *Asian J Pharm Clin Res* 2018;11(12):194-6.
 21. Bhagat V, Arora P, Ranjan V, Rastogi T. Efficacy Of Curcumin In The Treatment Of Oral Leukoplakia-A Prospective Study. *Int J Curr Med Pharm Res* 2018;4(12):3959-3962.
 22. Kapoor S, Arora P. Effect of curcumin in management of potentially Malignant disorders-A comparative study. *Onkologia I Radioterapia* 2019;13(1):1-4.
 23. Patel JS, Umarji HR, Dhokar AA, Sapkal RB, Patel SG, Panda AK. Randomized controlled trial to evaluate the efficacy of oral lycopene in combination with vitamin E and selenium in the treatment of oral leukoplakia. *J Indian Acad Oral Med Radiol* 2014;26(4):369.
 24. Lohe VK, Bhowate RR, Association of Socioeconomic Risk Factor with Oral Squamous Cell Carcinoma. *J Datta Meghe Inst Med Sci Uni* 2016;11(2): 243-246
 25. Lohe VK, Degwekar SS, Bhowate RR, Kadu RP, Dangore SB. Evaluation of correlation of serum lipid profile in patients with oral cancer and precancer and its association with tobacco abuse. *J Oral Pathol Med* 2010 Feb;39(2):141-8.
 26. Sune RV, Indurkar AD, Bhowate RR, Degwekar SS, Lohe VK. An evaluation of field cancerization in patients with oral cancer by "Mirror Image" biopsy. *Journal of Datta Meghe Institute of Medical Sciences University*. 2017 Apr 1;12(2):148.