Effectiveness of Antioxidants in Oral Submucous Fibrosis: A Retrospective Study

Manivasagam D[1], Muthukrishnan A[2*] and Chaudary Manjari[1]

[1]*Department of Oral Medicine and Radiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, India;* [2]*Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India*

Corresponding author: Muthukrishnan A, Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India, E-mail: arvindm@saveetha.com

Abstract

Background: Oral Submucous Fibrosis (OSMF) is defined as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although, occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic changes in lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and difficulty in eating. It is a condition with increased oxidative stress leading to free radical release. Thus, the aim of the study is to assess the therapeutic effectiveness of antioxidants in oral submucous fibrosis. **Materials & Methods:** Retrospective analyses of 52 clinically diagnosed OSMF patients were included in the study. The habit history was recorded. The patients were administered systemic antioxidants after habit cessation. Therapeutic effectiveness was assessed by analyzing the recorded inter incisal distance measurement and Visual Analog Scale (VAS) response at baseline, 15 days, 30 days and 45 days. **Results:** OSMF were reported maximum in 31 to 40 years (28.8%) with a male predilection (94%). Predominant site was right and left buccal mucosa (88.4%). Clinical grade II (44.2%) and grade III (38.5%) of OSMF were more prevalent. A paired t test performed for assessing mouth opening and Visual Analog Scale (VAS) preoperatively and postoperatively revealed significance value of $p<0.05$ and $p<0.01$ respectively. **Conclusion:** The study concludes that habit cessation with a combination of antioxidants, multivitamins and minerals rapidly decrease the burning sensation and a significant increase in mouth opening.

Keywords:

Antioxidants; Habits; Mouth opening; Oral Submucous Fibrosis (OSMF); VAS

Introduction

OSMF is defined as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx.

Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic changes in lamina propria, with epithelial atrophy leading to stiffness of oral mucosa causing trismus and difficulty in eating. [1]

OSMF is also called as 'diffuse oral submucous fibrosis, 'idiopathic palatal fibrosis, 'sclerosing stomatitis', 'juxta epithelial fibrosis'. [2]

OSMF has multiple etiological agents [3,4] with areca nut use being the most predominant. [5]

Arecodine, an active alkaloid found in betel nuts stimulates fibroblasts to increase production of collagen by 150%. [6]

Studies have shown association of OSMF with HLA-DR antigens. [7]

Antioxidants and cytokines, Glutathione S-transferase are part of the system. Increased association has been reported with GSTT1 and GSTM1, CYPIA phenotypes. [8]

Others lesser known proposed risk factors are hot spicy food like chillies, [9] HLA-AIO, HLA-BT, HLA-DR3 alleles and iron deficiency.[10,11]

They are more prevalent in Southeast Asian countries such as India, Bangladesh, Srilanka, Pakistan,and Taiwan. Prevalence rate in India is 0.2%-0.5%. [12]

OPMD has high risk of malignant transformation. [13,14]

Malignant transformation rate is 3%-7.6%. [15,16] Salivary micro RNA is used for early

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detection for OPMD. [17] Biopsy is the gold standard diagnostic aid. [18] Management of OSMF is by both medical and surgical measures. [19] Medical measures include steroids, antioxidants, [20] minerals, [21] vitamins, placental extracts, interferon gamma. Surgical management includes coronoidectomy, nasolabial flap, oral stent, CO_2 laser, buccal pad fat, [22] split thickness graft, therabite and excision upto anterior tonsillar pillar. [23]

Mechanism of action of antioxidants on OSMF is by separating the free oxygen radicals from susceptible molecules and also they lyse and inactivate the free radicals, thus boosting the body's multilevel defense system against them and also rapidly repair the damage caused by free radicals. [24-39] Previously our team has a rich experience in working on various research projects across multiple disciplines. Thus, the aim of the study is to assess the therapeutic effectiveness of antioxidants in oral submucous fibrosis.

Materials and Methods

A retrospective study was conducted in the oral medicine department from June 2019-May 2020. The following inclusion and exclusion criteria were used to retrieve data from the institutional database. The research was approved by the institutional ethical committee and Scientific Review Board (SRB). The ethical approval number for the study is SDC/SIHEC/2020/DIASDATA/0619-0320.

Inclusion criteria

- All clinical stages of OSMF.
- Patients who have come at least for 3 reviews.
- Patients records with habit cessation and antioxidant management.

Exclusion criteria

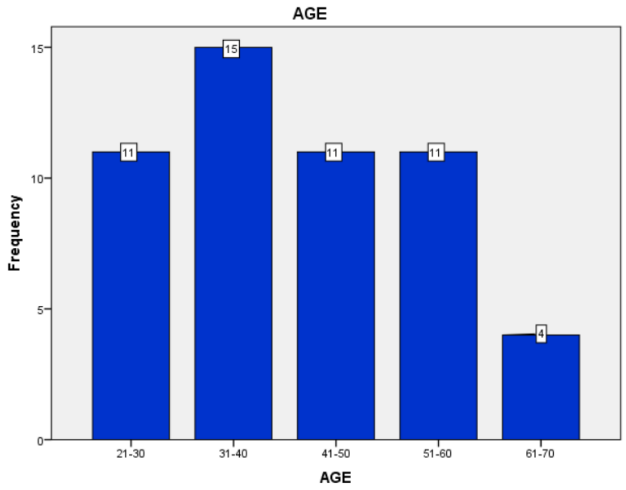
Patients who were previously under any other treatment like intralesional steroids or other medical and surgical management. Patients who have been under any combined treatment modality with antioxidants.

In this study, 52 patients were included in final analysis. Sampling bias was minimized as all stages (I-IVa) of OSMF were included. All demographic details, habit history with type of tobacco and habit duration were included. Staging of OSMF, type of antioxidant prescribed, interincisal distance measurements and VAS score which was measured preoperatively and subsequently at 15 days, 30 days and 45 days were obtained. The antioxidant prescribed was a combination of alpha lipoic acid, lycopene and selenium (commercially marketed as SM-Fibro). Retrieved data were first documented in an excel sheet then they were transferred to SPSS importing. The qualitative variables were sex, OSMF stage, type of tobacco used, habit cessation, antioxidant. The quantitative variables were age, duration of habit, mouth opening distance and VAS.

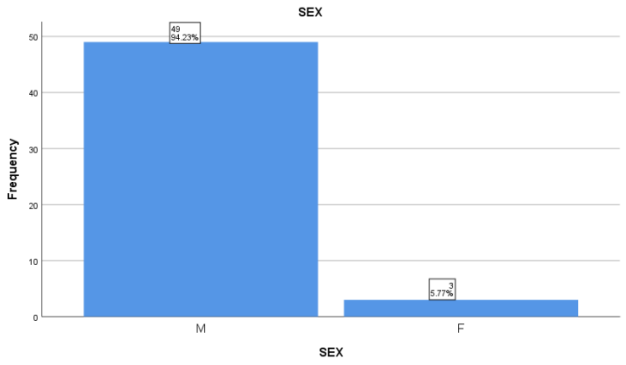
SPSS version IBM 20 was used. The independent variables were age, sex, stages of OSMF, habits, antioxidants. Dependent variables were mouth opening (interincisal distance) and VAS score. Correlation and association was analyzed using a Chi-square test for age, sex, habit with stage of OSMF. A paired t test used for assessing the interincisal distance preoperatively and postoperatively (15, 30, 45 days) and for VAS assessment, both preoperatively and postoperatively (15, 30, 45 days).

Results and Discussion

In this retrospective study, 52 OSMF patients of all clinical stages and who were treated with systemic antioxidants were included. The age group and gender of the study population was 31 to 40 years 28.8%; 211 to 30 years 21.2%; 41 to 50 years 21.2%; 51 to 60 years 21.2% and 61 to 70 years 7.7% [Graph 1] and OSMF was predominant in males 94.23% when compared to female 5.77% [Graph 2].



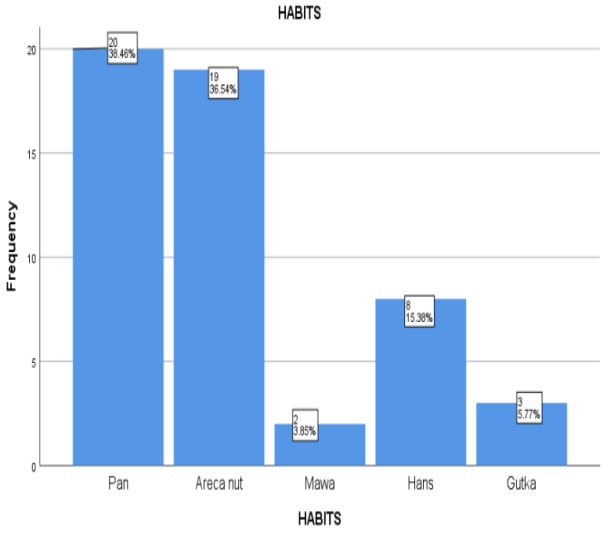
Graph 1: This bar graph represents the age distribution of the study population where the X axis represents the age group in years and Y axis represents the frequency in numbers of OSMF patients. In this study, the maximum patients (n=15) belonged to age group of 31 to 48 years (28.85%).



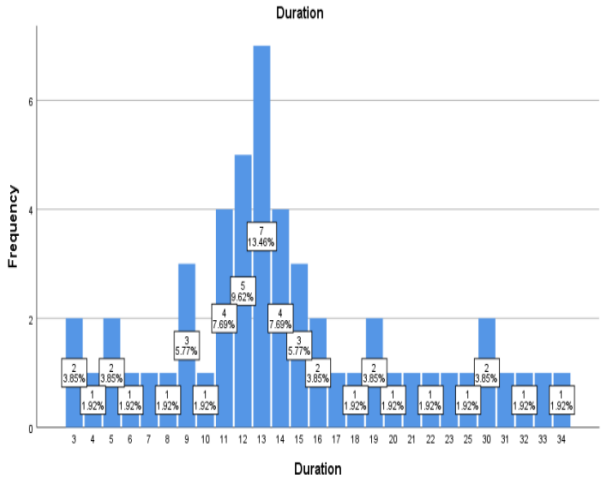
Graph 2: This bar graph represents the sex distribution of the study population where the X axis represents the sex (F: Female and M: Male) and Y axis represents the frequency in numbers of OSMF patients. Graph 2 shows that males (94.23%) were predominantly affected than females (5.77%).

The most common type of tobacco product used and duration of habit reveals pan chewing in 38.46% followed by areca nut

36.5%, hans 15.4%, gutka 5.8%, mawa 3.8% and maximum duration reported was 34 years 1.9%, minimum duration was 3 years 3.8% and most frequently reported duration was 13 years 13.5% [Graph 3, Graph 4].

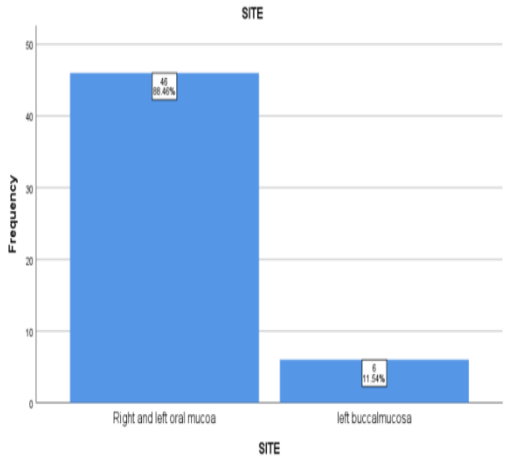


Graph 3: This bar graph represents the type of tobacco products used by the study population, where the X axis represents the tobacco products and Y axis represents the frequency of the number of OSMF patients. In this study, the maximum patients consumed pan (38.46%) followed by areca nut (36.54%).

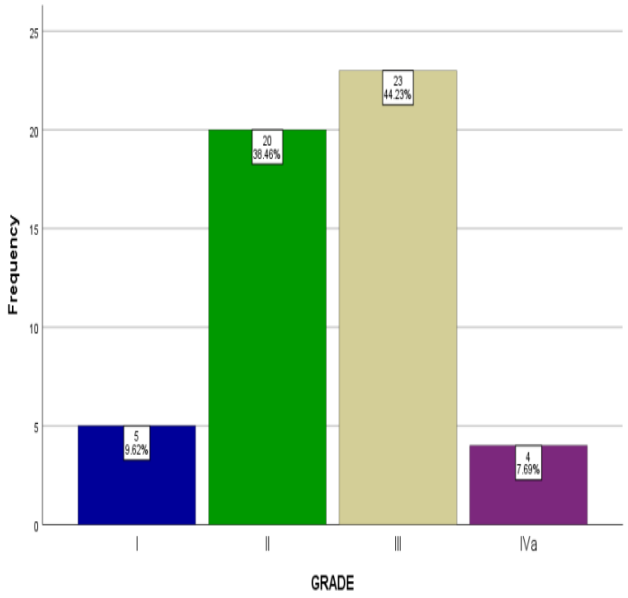


Graph 4: This bar graph represents the duration of tobacco products consumed by the study population where the X axis represents the duration in years and Y axis represents the frequency in numbers of OSMF patients. In this study, the maximum duration of tobacco consumption habit was 13 years (13.46%).

Frequency distribution of site and clinical grading of OSMF reveals the right and left buccal mucosa 88.4% was the commonest site and maximum reported clinical grade was III 44.2% followed by grade II 38.5%, grade I9.6%, grade IVa 7.7% [Graph 5, Graph 6].

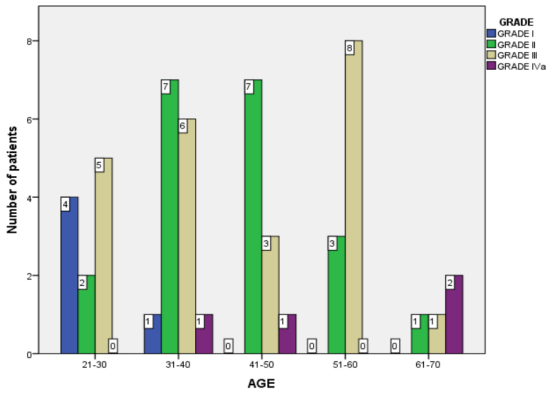


Graph 5: This bar graph shows the site involvement in the study population where the X axis represents the oral mucosa sites and Y axis represents the frequency in numbers of OSMF patients. In this study the maximum involved site was both right and left buccal mucosa (88.46%).

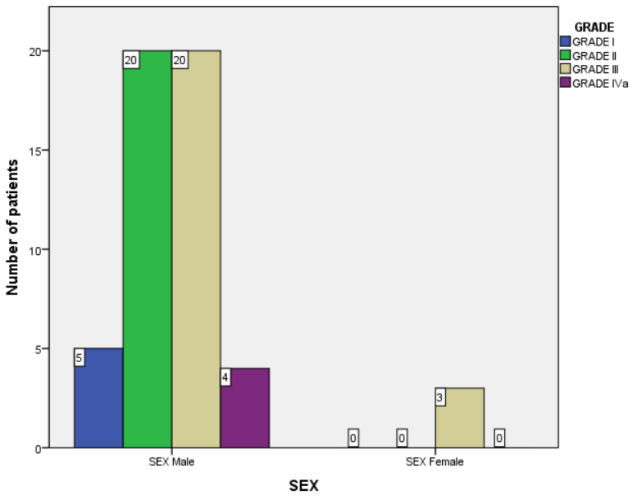


Graph 6: This bar graph represents clinical grading of OSMF in our study population where the X axis represents the clinical grading a (Grade 1: Burning, depapillation, blanching or leathery mucosa (disease triad) mouth opening >35 mm, Grade II: disease triad, mouth opening 20-35 mm, Grade III: Disease triad, mouth opening <20 mm, Grade IVa: Disease triad+Oral Potentially Malignant Disorder (OPMD) and Y axis represents the frequency in number of OSM patients. In this study, the maximum seen was Grade III (44.23%) followed by Grade II (38.46%).

Descriptive analysis for age and clinical grading of OSMF, sex and clinical grading using a chi square test revealed Grade II was more predominant in 31 to 40 years and 41 to 50 years, Grade III in 51 to 60 years with $p<0.01$ and Grade II and III more predominant in male gender; $p>0.05$ [Graph 7, Graph 8].

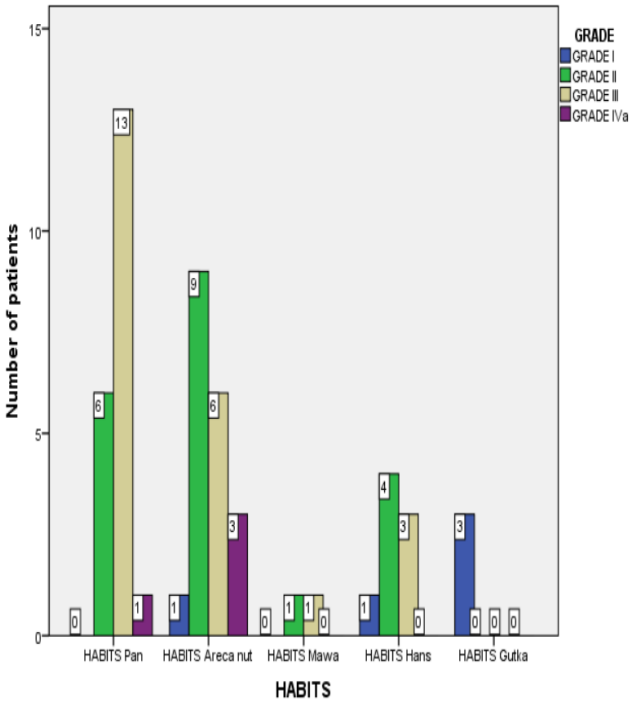


Graph 7: This bar graph represents the association of age and clinical grade where the X axis represents age group in years and Y axis represents the number of patients with different clinical grading of OSMF. Grade III was more commonly seen in 51 to 60 years and reticular Grade II was more frequently reported in 31 to 40 years and 41 to 50 years. Pearson chi square=2.801, p=0.004 (p<0.01) (chi-square test) denotes a significant association was found between age and clinical grading of OSMF.



Graph 8: This bar graph represents the association of gender and clinical grading where the X axis represents gender and Y axis represents the number of patients with different clinical grading of OSMF. Grade II and III were more common in males and grade III in females Pearson chi-square=4.014, p=0.260(p value>0.05), chi-square test reveals gender and clinical grading of OSMF were not statistically significant.

Descriptive analysis used for habit and clinical grading revealed that Grade II more commonly reported in areca nut chewing and Grade III more common in pan chewing patients; p<0.01 [Graph 9].



Graph 9: This bar graph represents the association of type of tobacco product and clinical grading of OSMF where the X axis represents tobacco product and Y axis represents the number of patients with different clinical grading of OSMF. Pan chewing was more associated with grade III and areca nut with grade II. Pearson chi square=37.18, p=0.000(p value<0.01), (chi-square test) reveals a statistical association between gender and clinical grading of OSMF.

A paired t test used to assess the statistical difference of mouth opening inter incisal distance preoperatively and first visit reveals a p>0.05 with a mean and standard deviation 2.365 ± 24.892 [Table 1]. The mean difference at first review and second review; second review and third review; preoperatively and postoperatively 45 days revealed p<0.01 with mean and standard deviation -2.327 ± 1.368; -2.269 ± 1.402 respectively; -2.231 ± 24.390 [Table 1].

Table 1: Showing mean difference of interincisal distance measured at baseline and first review (15 days), second review (30 days) and third review days (45 days) done using paired t test.

	Baseline	First review (15 days)	Second review (30 days)	Third review (45 days)
Mean and Std dev	26.65 ± 25.374	24.29 ± 7.039	26.62 ± 6.523	28.88 ± 6.404
Mean difference and Std dev	0	2.365 ± 24.892	-2.237 ± 1.368	-2.269 ± 1.402
p value	0	0.496	0	0

A paired t test used to assess the statistical difference of VAS preoperatively and first visit, first review and second review; second review and third review; preoperatively and postoperatively 45 days reveals a p<0.01 with a mean and standard deviation 3.538 ± 0.917; 0.750 ± 0.738; 0.577 ± 0.667 and 4.685 ± 1.205 respectively [Table 2]. Oral submucous

fibrosis was first reported in 1952 by Schwartz while examining 5 Indian women from Kenya and it was called as "A trophicaI diopathica Tropica Mucosae Oris". [40] In 1956, Paymaster first reported its precancerous potential. In 1966, Pindborg defined OSMF as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and or associated with vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic changes in lamina propria, with epithelial atrophy leading to stiffness of oral mucosa causing trismus and difficulty in eating. Altered keratinocyte and genomic instability have been reported to play an important role in malignant transformation. [41,42] Etiology of OSMF is multi-factorial [43] and areca nut plays a major role in the pathogenesis of OSMF.

Table 2: Showing mean difference of VAS score measured at baseline and first review (15 days), second review (30 days) and third review days (45 days) done using paired t test.

	Baseline	First review (15 days)	Second review (30 days)	Third review (45 days)
Mean and Std dev	5.02 ± 1.093	1.48 ± 0.852	0.73 ± 0.598	0.15 ± 0.364
Mean difference and Std dev	0	3.538 ± 0.917	0.750 ± 0.738	0.577 ± 0.903
p value	0	0	0	0

Areca nut and other tobacco products contain quinine/ hydroquinone from which hydrogen peroxide and hydroxyl free radicals are released. [44] These hydroxyl free radicals lead to lipid peroxidation which in turn leads to release of many damaging aldehydes malondialdehyde, propanedial, 4-hydioxynonenal 4-HNE. [45] MDA causes crosslinking of collagen by providing its aldehyde group to lysine and helps in lysine to lysine bridging in presence of enzyme lysyl oxidase. This crosslinking of collagen leads to stiffening of tissue and reduces their function. To neutralize these free radicals antioxidants enzymes like glutathione peroxidase, catalase and superoxide dismutase were consumed by the body which in turn results in decrease in antioxidant enzyme levels in OSMF patients. [46-53]

In our study the minimum age reported was 22 years and maximum age was 69 years with a mean age of 42 years with a male predilection. These results were similar to a study conducted by Ali FM et al in 2013. Pan and areca nut chewing was a more common tobacco product used and the mean duration was 15 years which was similar to a study conducted by Cai X et al in 2019. [54] Grading of OSMF was done by using Warnakulasuriya criteria which revealed Grade III was more common and the studies were similar to study by Ali et al. Treatment which is most commonly used for OSMF is habit cessation, intralesional steroids, human placental extracts, antioxidants, vitamins, minerals, and circuminoids. [55] Antioxidants prevent free radicals formation and delay or nullify the malignant transformation. Post operatively mouth opening has increased 3 to 4 mm after habit cessation and antioxidant therapy similar to the results obtained by Karemore et al. [56] and was also statistically significant. VAS shows progressive reduction in pain and burning sensation and post operatively the patients are asymptomatic and results are in association with previous study conducted by Mehrotra et al. in 2013.

Limitations of study are reduced sample size, lack of histopathological correlation, short follow up period and progression of disease not being assessed. Future scope of the study is to assess the effectiveness of antioxidants with intralesional steroids which may lead to more reduction in the fibrosis, a greater increase in mouth opening, relief from burning sensation and prevent a possible malignant transformation. [57-59]

Conclusion

OSMF is an oral potentially malignant disorder with increased oxidative stress leading to free radical release. Free radical release can be carcinogenic. Treatment should be aimed to prevent release of free radicals and to minimize the injury caused by them. Studies conducted by previous authors proves Vitamin A, lycopene to be more beneficial in treating OSMF and our study concludes that habit cessation with a combination of antioxidants, multivitamins and minerals rapidly decreases the burning sensation and a significant increase in mouth opening over a time period of 45 days.

References

1. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966;22(6):764-79.
2. Ali FM, Patil A, Patil K, Prasant MC. Oral submucous fibrosis and its dermatological relation. Indian Dermatol Online J. 2014;5(3):260-5.
3. Steele JC, Clark HJ, Hong CHL, Jurge S, Muthukrishnan A, Kerr AR, et al. World workshop on oral medicine VI: An international validation study of clinical competencies for advanced training in oral medicine. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(2):143-51.e7.
4. Subha M, Arvind M. Role of magnetic resonance imaging in evaluation of trigeminal neuralgia with its anatomical correlation. Biomedical and Pharmacology Journal. 2019;12(1):289-96.
5. Muthukrishnan A, Warnakulasuriya S. Oral health consequences of smokeless tobacco use. Indian J Med Res. 2018 Jul;148(1): 35-40.
6. Gupta S, Reddy MVR, Harinath BC. Role of oxidative stress and antioxidants in aetiopathogenesis and management of oral submucous fibrosis. Indian J Clin Biochem. 2004;19(1):138-41.
7. Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y. Oral submucous fibrosis: Newer proposed classification with critical

updates in pathogenesis and management strategies. Natl J Maxillofac Surg. 2017;8(2):89-94.
8. Ghosh T, Gupta S, Bajpai P, Agarwal D, Agarwal M, Gupta OP, et al. Association of CYP1A1, GSTM1, and GSTT1 gene polymorphism with risk of oral submucous fibrosis in a section of North Indian population. Mol Biol Rep. 2012;39(10):9383-9.
9. Kandasamy M, Anisa N, Rahman A, Rajan MA, Prakash A, Lal J. Etiopathogenesis of oral submucous fibrosis-review of literature. J Adv Med Dent Sci Res. 2015;3(3):53.
10. Bhardwaj D, Dinkar AD, Satoskar SK, Desai SR. Serum iron and haemoglobin estimation in oral submucous fibrosis and iron deficiency anaemia: A diagnostic approach. J Clin Diagn Res. 2016;10(12):ZC54-8.
11. Ganapathy KS, Gurudath S, Balikai B, Ballal S, Sujatha D. Role of iron deficiency in oral submucous fibrosis: An initiating or accelerating factor. J Indian Academy Oral Med Rad. 2011;23(1): 25.
12. Al-Omari M, Al-Samahi S. Detection of bacteria in endodontic samples and its association with defined clinical signs and symptoms of endodontic infection Saudi. J Oral Sci. 2014; p.83.
13. Misra SR, Shankar YU, Rastogi V, Maragathavalli G. Metastatic hepatocellular carcinoma in the maxilla and mandible, an extremely rare presentation. Contemp Clin Dent. 2015;6(Suppl 1):S117-21.
14. Muthukrishnan A, Bijai Kumar L. Actinic cheilosis: Early intervention prevents malignant transformation. BMJ Case Rep. 2017:bcr2016218654.
15. Mehrotra R, Nigam SK, Nigam N. Role of antioxidants on oral submucous fibrosis: A clinico-pathological study. J Evolution Med Dent Sci. 2013;2(47):9174-83.
16. Muthukrishnan A, Bijai Kumar L, Ramalingam G. Medication-related osteonecrosis of the jaw: A dentist's nightmare. BMJ Case Rep. 2016:bcr2016214626.
17. Maheswari TNU, Venugopal A, Sureshbabu NM, Ramani P. Salivary micro RNA as a potential biomarker in oral potentially malignant disorders: A systematic review. Tzu Chi Med J. 2018;30(2):55–60.
18. Dharman S, Muthukrishnan A. Oral mucous membrane pemphigoid: Two case reports with varied clinical presentation. J Indian Soc Periodontol. 2016;20(6):630-4.
19. Rohini S, Kumar VJ. Incidence of dental caries and pericoronitis associated with impacted mandibular third molar: A radiographic study. Res J Pharma Tech. 2017;10(4):1081-4.
20. Chaitanya NC, Muthukrishnan A, Babu DBG, Kumari CS, Lakshmi MA, Palat G, et al. Role of Vitamin E and Vitamin A in oral mucositis induced by cancer chemo/radiotherapy: A meta-analysis. J Clin Diagn Res. 2017;11(5):ZE06-9.
21. Subashri A, Uma Maheshwari TN. Knowledge and attitude of oral hygiene practice among dental students. Res J Pharma Tech. 2016;9(11):1840-2.
22. Patil SR, Maragathavalli G, Araki K, Al-Zoubi IA, Sghaireen MG, Gudipaneni RK, et al. Three-rooted mandibular first molars in a Saudi Arabian population: A CBCT study. Pesqui Bras Odontopediatria Clin Integr. 2018;18(1):4133.
23. Ray JG, Chatterjee R, Chaudhuri K. Oral submucous fibrosis: A global challenge. Rising incidence, risk factors, management, and research priorities. Periodontol 2000. 2019;80(1):200-12.
24. Chaitanya NC, Muthukrishnan A, Krishnaprasad CMS, Sanjuprasanna G, Pillay P, Mounika B. An insight and update on the analgesic properties of Vitamin C. J Pharm Bioallied Sci. 2018;10(3):119-25.
25. Ponnulakshmi R, Shyamaladevi B, Vijayalakshmi P, Selvaraj J. In silico and in vivo analysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. Toxicol Mech Methods. 2019;29(4):276-90.
26. Mathew MG, Samuel SR, Soni AJ, Roopa KB. Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns and surrounding gingival inflammation in primary molars: randomized controlled trial. Clin Oral Investig. 2020;24(9):3275-80.
27. Subramaniam N, Muthukrishnan A. Oral mucositis and microbial colonization in oral cancer patients undergoing radiotherapy and chemotherapy: A prospective analysis in a tertiary care dental hospital. J Investig Clin Dent. 2019;10(4):e12454.
28. Girija ASS, Shankar EM, Larsson M. Could SARS-CoV-2-induced hyperinflammation magnify the severity of coronavirus disease (Covid-19) leading to acute respiratory distress syndrome? Front Immunol. 2020;11:1206.
29. Dinesh S, Kumaran P, Mohanamurugan S, Vijay R, Singaravelu DL, Vinod A, et al. Influence of wood dust fillers on the mechanical, thermal, water absorption and biodegradation characteristics of jute fiber epoxy composites. J Polym Res. 2020;27(1).
30. Thanikodi S, Singaravelu D Kumar, Devarajan C, Venkatraman V, Rathinavelu V. Teaching learning optimization and neural network for the effective prediction of heat transfer rates in tube heat exchangers. Therm Sci. 2020;24(1Part B):575-81.
31. Murugan MA, Jayaseelan V, Jayabalakrishnan D, Maridurai T, Kumar SS, Ramesh G, et al. Low velocity impact and mechanical behaviour of shot blasted SiC wire-mesh and silane-treated aloevera/hemp/flax-reinforced SiC whisker modified epoxy resin composites. Silicon Chem. 2020;12(8):1847-56.
32. Vadivel JK, Govindarajan M, Somasundaram E, Muthukrishnan A. Mast cell expression in oral lichen planus: A systematic review. J Investig Clin Dent. 2019;10(4):e12457.
33. Chen F, Tang Y, Sun Y, Veeraraghavan VP, Mohan SK, Cui C. 6-shogaol, an active constiuents of ginger prevents UVB radiation mediated inflammation and oxidative stress through modulating NrF2 signaling in human epidermal keratinocytes (HaCaT cells). J Photochem Photobiol B. 2019;197:111518.
34. Manickam A, Devarasan E, Manogaran G, Priyan MK, Varatharajan R, Hsu C-H, et al. Score level based latent fingerprint enhancement and matching using SIFT feature. Multimed Tools Appl. 2019;78(3):3065-85.
35. Wu F, Zhu J, Li G, Wang J, Veeraraghavan VP, Krishna Mohan S, et al. Biologically synthesized green gold nanoparticles from induce growth-inhibitory effect on melanoma cells (B16). Artif Cells Nanomed Biotechnol. 2019;47(1):3297-305.
36. Ma Y, Karunakaran T, Veeraraghavan VP, Mohan SK, Li S. Sesame inhibits cell proliferation and induces apoptosis through inhibition of STAT-3 translocation in thyroid cancer cell lines (FTC-133). Biotechnol Bioprocess Eng. 2019;24(4):646-52.
37. Ponnanikajamideen M, Rajeshkumar S, Vanaja M, Annadurai G. In vivo type 2 diabetes and wound-healing effects of antioxidant gold nanoparticles synthesized using the insulin plant Chamaecostus cuspidatus in albino rats. Can J Diabetes. 2019;43(2):82-9.e6.
38. Vairavel M, Devaraj E, Shanmugam R. An eco-friendly synthesis of Enterococcus sp. mediated gold nanoparticle induces cytotoxicity in human colorectal cancer cells. Environ Sci Pollut Res Int. 2020;27(8):8166-75.
39. Paramasivam A, VijayashreePriyadharsini J, Raghunandhakumar S. N6-adenosine methylation (m6A): A promising new molecular

target in hypertension and cardiovascular diseases. Hypertens Res. 2020;43(2):153-4.

40. Schwartz J. Atrophia idiopathica (tropica) mucosae oris. Indian J Med Sci.1952;16:189-97.
41. Chole RH, Gondivkar SM, Gadbail AR, Balsaraf S, Chaudhary S, Dhore SV, et al. Review of drug treatment of oral submucous fibrosis. Oral Oncol. 2012;48(5):393-8.
42. Venugopal A, Uma Maheswari TN. Expression of matrix metalloproteinase-9 in oral potentially malignant disorders: A systematic review. J Oral MaxillofacPathol. 2016;20(3):474-9.
43. Choudhury P, Panigrahi RG, Maragathavalli, Panigrahi A, Patra PC. Vanishing roots: First case report of idiopathic multiple cervico-apical external root resorption. J Clin Diagn Res. 2015;9(3):ZD17-9.
44. Ranganathan K, Kavitha R. Proliferation and apoptosis markers in oral submucous fibrosis. J Oral Maxillofac Pathol. 2011;15(2): 148-53.
45. Ekanayaka RP, Tilakaratne WM. Oral submucous fibrosis: Review on mechanisms of pathogenesis and malignant transformation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):192-9.
46. Patel T, Kulkarni V. A study on antioxidant levels in non-smoke tobacco consuming Oral Sub Mucous Fibrosis (OSMF). Int J Med Res Health Sci. 2013;2(2):229-32.
47. Priyadharsini VJ. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. J Periodontol. 2019;90(12):1441-8.
48. Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. J Oral Pathol Med. 2019;48(2):115-21.
49. Ramesh A, Varghese S, Jayakumar ND, Malaiappan S. Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients: A case-control study. J Periodontol. 2018;89(10):1241-8.
50. Mathew MG, Samuel SR, Soni AJ, Roopa KB. Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: randomized controlled trial. Clin Oral Investig. 2020;24(9):3275-3280.
51. Sridharan G, Ramani P, Patankar S, Vijayaraghavan R. Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Oral Pathol Med. 2019;48(4):299-306.
52. Pc J, Marimuthu T, Devadoss P. Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study. Clin Implant Dent Relat Res. 2018;20(4):531-534.
53. Ramadurai N, Gurunathan D, Samuel AV, Subramanian E, Rodrigues SJL. Effectiveness of 2% Articaine as an anesthetic agent in children: Randomized controlled trial. Clin Oral Investig. 2019;23(9):3543-50.
54. Cai X, Yao Z, Liu G, Cui L, Li H, Huang J. Oral submucous fibrosis: A clinicopathological study of 674 cases in China. J Oral Pathol Med. 2019;48(4):321-5.
55. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: A review of the current management and possible directions for novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):232-41.
56. Karemore TV, Motwani M. Evaluation of the effect of newer antioxidant lycopene in the treatment of oral submucous fibrosis. Indian J Dent Res. 2012;23(4):524-8.