How to Cite:
Narang, D., Kaur, P., & Singh, A. (2021). Antihypertensives in oral submucous fibrosis. *International Journal of Health Sciences*, *5*(S2), 175–186.
https://doi.org/10.53730/ijhs.v5nS2.5629

Antihypertensives in oral submucous fibrosis

Deepak Narang
Reader, OMDR, Deshbhagat Dental College Mandigobindgarh Punjab

Prabhjot Kaur
Reader Oral Pathology / Deshbhagat Dental College Mandigobindgarh Punjab

Amandeep Singh
Prof & Head, Community Dentistry/ Deshbhagat Dental College Mandigobindgarh Punjab

***Abstract*---**Oral submucous fibrosis is a common pre-malignant condition affecting the oral mucosa with more prevalence among Indian population. Various treatment modalities have been elucidated in order to alleviate the symptoms associated with OSMF. Currently oral Anti-hypertensive has been proved to have beneficial result in treating OSMF because of its anti-inflammatory, fibrinolytic, immunomodulatory and rheologic modifying property. Several categories of drugs have been used in the treatment of OSMF but their effectiveness leaves much to be desired and no treatment regimen has afforded definitive cure. While Oral administration limits the concentration of drugs in lesional tissue and increases the potential for side effects, the Intralesional injections are associated with significant mechanical injury and noncompliance on the patient's part because of the accompanying discomfort and pain. The present study was done to evaluate the effectiveness of oral antihypertensives in the management of OSMF. Very few studies across world have showed that anti-hypertensive drugs showed significant improvement in mouth opening, reduction in burning sensation. Hence anti-hypertensive can be a good alternative in the management of OSMF for whom intralesional steroids or hyaluronidase are contraindicated, for those who cannot make frequent visit and to avoid pain due to injection. And most importantly anti-hypertensive is cost effective and more compliant to the patient.

***Keywords*---**anti hypertensives, Tobacco, OSMF.

***Corresponding author**: Narang, D.; Email: parasitology1979@gmail.com*
Manuscript submitted: 18 Sept 2021, Manuscript revised: 9 Nov 2021, Accepted for publication: 12 Dec 2021

Introduction

Health is multifactorial and multidimensional, influenced by various factors. Disease is generally an individual problem and infirmity is probably a result of genetic makeup and environmental influences. Several disorders that affect the oral mucosal health are acquired through various lifestyle practices. Addictions for any adverse habit merely represent man's unbounded weakness. Such adverse habits may follow the ladders of culture or mere addiction; which forms a platform for disease to show its synchronous presence. In day to day clinical practice Dentists often encounter a wide spectrum of oral mucosal alterations. These mucosal alterations may be in the form of changes in the colour, size, shape and texture. They range from innocuous mucosal alterations needing simple therapeutic remedies to more interventional procedures.

Many of these lesions are caused by habit of betel nut and tobacco use. Oral Submucous Fibrosis (OSMF) is one among them which is frequently encountered due to betel nut chewing. Schwartz in 1952 described a condition affecting the oral mucosa including the palate and faucial pillar, called "atrophia idiopathica (tropica) mucosae oris" among five Indian women from Kenya[1]. Later the term "Oral submucous fibrosis" was coined by S.G Joshi in 1953[2]. It was also called by the other names like "idiopathic scleroderma of the mouth", "idiopathic palatal fibrosis", "juxta-epithelial fibrosis". Paymaster (1956) observed the precancerous nature of OSMF, because of the slow onset of squamous cell carcinoma in one third of OSMF patients[3].

In 1966 Pindborg and Sirsat, defined OSMF as "an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat"[4]. The disease is predominantly seen in India among Asian countries, with a reported prevalence ranging up to 0.4% in Indian rural population. Based on study conducted in 2002, more than 5 million people in India suffer from OSMF (0.5 % of Indian population). OSMF is widely prevalent in all age groups and across all socioeconomic strata in India[5].

Several factors play a role in the etiopathogenesis of OSMF and current evidence suggests that arecoline in the areca nut is the key factor in initiating the disease[6]. The habit of betel quid chewing is widespread throughout India and South East Asia. And it is widely prevalent in teenagers and young adults[7]. Buccal mucosa, faucial pillar, soft palate are predominantly affected. Underlying muscles and the muscles of mastication can also be involved. The mucosa in the involved areas gradually becomes pale followed by progressive stiffness of subepithelial tissues. Increased incidence of malignancy is noted in OSMF patients which is around 8% in overall affected Indian population[8]. Many treatment protocols have been proposed for OSMF to alleviate the signs and symptoms which include intralesional steroids, hyaluronidase, placentrax, immunomodulatory drugs, immunised cow milk[9], colchicine[10], antioxidant, nutritional supplements,

physiotherapy, combined medical therapy and surgical therapy with varying degrees of benefits[11].

But none of them proved to be effective due to their own short comings. Currently anti-hypertensive, is reported to have satisfactory result in the management of OSMF due to their immune modulation, alteration of fibroblast physiology, rheologic modification and antiinflammatory property. Immunologic abnormalities have been primarily reported with OSMF which probably mediate local tissue damage and that they appear to be the final common pathway in the pathogenesis of OSMF. Anti hypertensive has immunomodulating effects which include increasing leucocyte adhesion, causing neutrophil degranulation and release of peroxides and decreasing production of tumour necrosis factor alpha[12]. The review of current literature shows that the use of Anti hypertensives in OSMF management has not been adequately explored and research in this area is very limited. Very few studies have been done so far, that too mainly involve subjective evaluation like mouth opening, blanching of oral mucosa, burning sensation. The purpose of the review is to evaluate the effectiveness of oral anti hypertensives for the treatment of OSMF

Pathogenesis of OSMF

Different hypotheses have been put forward so far in fully elucidating the pathogenisis of OSMF. The betel quid (BQ) chewing has been recognized as one of the important risk factors for OSMF as supported by the various experimental studies. The alkaloids and flavonoids from the BQ are absorbed and undergo metabolism which are the constant source of irritation to the oral mucosa during their contact. In addition, the fibres of areca nut also cause mechanical irritation to the oral mucosa which facilitates the diffusion of alkaloids and flavanoids into the subepithelial connective tissue, resulting in juxtaepithelial inflammatory cell infiltration[57]. Inflammation is characterized by the presence of activated T cells, macrophages and various chemical mediators. Persistent inflammation is crucial for the occurrence of tissue fibrosis. Thus, it can be considered that the induction of oral mucosal inflammation by BQ ingredients to be a critical event in the pathogenesis. Growth factors like transforming growth factor- β (TGF-β) are synthesized at the sites of inflammation. At the molecular level, the collagen production and degradation are regulated by TGF-β and flavonoids present in areca nut[58]

Collagen production pathway

The three main events which favours the collagen production are:

- Activation of procollagen genes
- Elevation of procollagen proteinases levels 3. Upregulation of lysyl oxidase (LOX) activity

TGF-β activates the procollagen genes, resulting in the production of more pro-collagen. In OSMF, there is increased cross-linking of the collagen, resulting in increased insoluble form of collagen. The flavanoids also increase cross-linking in

the collagen fibers. This is facilitated by increased activity and production of a key enzyme – LOX, which result in increased collagen production[59].

Collagen degradation pathway

There are two main events regulated by TGF-β which decreases collagen degradation:

- Activation of tissue inhibitor of matrix metalloproteinases gene (TIMPs).
- Activation of plasminogen activator inhibitor (PAI) gene.

TGF-β activates genes for TIMPs which inhibits the activated collagenase enzyme that is necessary for degradation of collagen. It also activates the gene for PAI, which is an inhibitor of plasminogen activator, results in absence of active collagenase. The flavanoids inhibit the collagenase activity. A reduction in the activity and levels of collagenase results in a decrease in collagen degradation[60]. Lysyl oxidase (LOX) is a copper activated enzyme critical for collagen crosslinking and organization of extracellular matrix (ECM), which has been shown to be ten times more resistant to digestion by collagenase.

A study was conducted to compare the LOX activity of fibroblasts derived from human normal mucosa and OSMF associated with betel nut chewing. The study revealed that OSMF fibroblasts showed reasonably more lysyl oxidase activity than normal mucosa fibroblasts and this was statistically significant (p Copper also has been implicated in the pathogenesis of OSMF. Areca nut has been found to have a high copper content and play an important role in the pathogenesis of OSMF. The possible role of copper functioning as a mediator of fibrosis in OSMF has been proved by the finding that raised copper levels in oral biopsies from patients with OSMF[62]. Plasminogen/plasmin system plays an important role in maintaining the equilibrium between synthesis and degradation of extracellular matrix (ECM). Plasminogen Activation inhibitor (PAI-1) inactivtes the plasminogen activators resulting in a decreased production of plasmin which is required for the degradation of ECM. Hence increased concentrations of PAI-1 leads to an accumulation of ECM[63].

OSMF is characterized by qualitative and quantitative alteration of collagen within the subepithelial layer of oral mucosa. The degradation of collagen by fibroblast phagocytosis is an important physiological remodeling of connective tissue. OSMF tissues exhibited 40% reduction of collagen phagocytic cells and a 48% decrease of fibronectin phagocytic cells as compared to normal fibroblasts. Normal fibroblast cultures incubated with areca nut alkaloids provided a dosedependent reduction in the proportions of phagocytic cells. Thus inhibition of fibroblast phagocytosis by alkaloids provide a mechanism for the development of OSMF[64].

A hypothesis that is commonly reported in OSMF patients is the epithelial alteration. The epithelium is considered to be “atrophic” and therefore vulnerable to the effects of oral carcinogens. “Atrophy” is explained to be arise as a result of stromal changes, which include decrease in cellularity and vascularity with resultant tissue ischemia and undergoes progressive hyalinization[67]. However the epithelium in OSMF failed to demonstrate an increased Absolute Cell Death Index

(ACI) often seen in tissue atrophy. An alternative hypothesis was proposed which state that hypoproliferation of epithelium was a factor which causes thinning of surface epithelium rather than atrophy in advanced cases of OSMF[68].

Recent study with regard to vascularity in OSMF was conducted to assess the degree of expression of nitric oxide (NO), a net vasodilator, in OSMF. The study concluded that enhanced expression of inducible nitric oxide synthase (iNOS) noticed in OSMF mucosa. NO has diverse properties of angiogenesis, vascular dilatation and increased permeability of vessels. These properties are all contrary to the concept of tissue hypoxia in OSMF and therefore the proposed "ischemic atrophy" of the overlying epithelium. This augments the earlier contention of an alternative explanation for thinning of the epithelium often noticed in clinically advanced cases. The thinning may be attributed to the defective replenishment of the desquamated epithelial cell pool probably due to decreased proliferation of the adult stem cell.

Based on this, hypoplasia being a more reasonable concept explaining epithelial "thinning" than that of "atrophy". The possible genotoxic and cytotoxic effects of NO on adult stem cells of epithelium and supporting stroma supports further impetus to this concept69. Regulation of transglutaminase-2 (TGM-2) by arecoline in oral fibroblasts have been found to play a major role in stabilizing the ECM proteins by cross-linking and making them highly resistant to protease degradation. This results in the accumulation of ECM, leading to fibrosis in OSMF cases. The expression of TGM-2 was studied in OSMF tissues by real-time RT-PCR analysis, and significant over expression was observed in most OSMF tissues ($p=0.0112$) compared with normal tissues[70].

Currently the pathogenesis of OSMF have focused on heme oxygenase-1 (HO-I) expression in fibrosis. HO-I, a microsomal enzyme, responsible for maintaining the cellular homeostasis. It plays an important protective role in the tissues due to reducing oxidative injury and attenuating inflammatory response. HO-I is consistently and dramatically upregulated in a variety of fibrotic diseases, such as benign prostatic hyperplasia and cystic fibrosis of lung. OSMF demonstratedsignificantly higher HO-I mRNA expression than normal buccal mucosa on immnuhistochemistry. Arecoline was also found to elevate HO-I mRNA expression in a dose-dependent manner[71]. As OSMF produces changes localized to oral cavity, it has been put forth that saliva may have a role in the pathogenesis of OSMF. Saliva of OSMF patients have shown increased pH, increase in salivary amylase, increase in alkaline phosphatase and potassium, low level of calcium and normal level of salivary immunoglobulin.

Formation of coagulum was observed in greater number of cases as the severity of the disease increased. It is thus postulated that the mechanical trauma due to chewing of betel nut, tobacco and chemical burns from slaked lime result in microhaemorrhage. The factor responsible for coagulum in saliva precipitates the increased laying down of fibroblast[72]. Increase in immunoglobulin levels is typically associated with three main chronic disease classes: those affecting the liver, collagen and chronic infections. The severity of OSMF was directly proportional to the estimated elevated levels of the major immunoglobulins IgG and IgA[73].

Anti hypertensives in OSMF
Mechanism of action

Anti hypertensive drugs has potent rheologic modifying effects. Anti hypertensives and its metabolites blocks red cell aggregation, lower blood viscosity, inhibits microvascular constriction, and stimulates fibrinolysis. It also has significant anti-inflammatory, antifibrotic and immunomodulatory effects[74].

Effect on blood viscosity and flow

- Increased red cell deformability and aggregation
- Decreased circulating plasma fibrinogen
- Decreased vasoconstriction. Immunologic effects
- Increased leukocyte deformability
- Decreased leukocyte adhesion and aggregation
- Decreased neutrophil superoxide release and degranulation
- Decreased neutrophil priming by platelet activating factor
- Increased leukocyte chemotaxis
- Decreased monocyte TNF-α production
- Decreased leukocyte response IL-1 production
- Decreased natural killer cell activity Effect on coagulation and fibrosis
- Decreased platelet adhesion and aggregation
- Increased tissue plasminogen activator and plasmin Increased antithrombin III
- Decreased α2- Antiplasmin and α1 - Antitrypsin Effect on wound healing and connective tissue
- Increased fibroblast collagenases
- Decreased fibroblast collagen and fibronectin
- Decreased fibroblast glycosaminoglycans
- Decreased fibroblast response to TNF-α Anti hypertensive improves membrane deformability by increasing the amount of membrane ATP.

It also alters red blood cell membrane protein phosphorylation patterns, increase protein kinase activity and decrease Ca2+ dependent K+ efflux[75]. The mechanism of action of Anti hypertensives in increasing polymorphonuclear cell chemotaxis is multifactorial. Anti hypertensives causes a dose dependent increase in cyclic adenosine monophosphate (cAMP) in polymorphonuclear cells. Cytoskeletal interactions are important in neutrophil adhesion, chemotaxis, phagocytosis and superoxide production. Anti hypertensives may act as an adenosine analogue, modulating cytoskeletal interactions. Anti hypertensive inhibition of lymphocyte activation also involves a cAMP dependent pathway[76].

The effect of Anti hypertensives on decreased platelet aggregation can be explained on the basis of blocking of phosphodiesterase conversion of cAMP to AMP. Anti hypertensives stimulates vascular endothelium to release prostacyclin , which further inhibits platelet adhesion and aggregation.116 TNF-α has been implicated in disseminated intravascular coagulation by stimulating endothelial production of procoagulant tissue factor and decreasing endothelial thrombomodulin resulting in decreased protein C activation[77]. Some of the

beneficial effects observed with Anti hypertensive therapy for hypercoaguable states may be related to its anti-TNFα effects. The results of experimental studies have shown that fibroblasts cultured in the presence of Anti hypertensive produced twice as much collagenase activity and decreased amounts of collagen, glycosaminoglycans and fibronectin. Interleukin-1 induced fibroblast proliferation is also inhibited by Anti hypertensives[78].

Pharmacokinetics

Anti hypertensives is administered through oral and intravenous routes. The drug is almost completely absorbed after oral administration. It undergoes a first-pass metabolism and the various metabolites appear in plasma very soon after absorption. Intestinal absorption is rapid, with peak plasma concentrations obtained at 3.2 hours. The drug is metabolized by red blood cells and the liver, with an elimination half-life of 3.4 hours. There is extensive enterohepatic circulation. More than 90% of absorbed Anti hypertensives is excreted in urine in the form of six metabolic products. Anti hypertensive and a seventh metabolite are not excreted in the urine of humans which have more pronounced physiologic effects than the primary drug[79].

Dosage

The recommended adult dosage of oral Anti hypertensives is 400mg thrice daily with meals. Doses as high as 2200mg daily have been well tolerated in patients with severe peripheral vascular disease. Duration of 3 to 12 months may be required for noticeable improvement in fibrotic skin disorders or other fibrosis[80] .
Intravenous Anti hypertensive is also available. Slow intravenous infusion beginning with 100mg/day is recommended with a daily increase in increments of 50 mg. Although the maximum recommended adult dose is 300mg/day, doses as high as 600g twice a day have been used successfully to treat gangrenous arterial occlusive disease[81].

Preparations commonly available

Anti hypertensives being a FDA approved drug and is currently used for various disorders in the medical field without significant complications.
Vasoocclusive disorders:

- Peripheral vascular disease
- Cerebral vascular disease
- Diabetic vascular disease
- Polycythemia vera
- Ischemic heart disease
- Chronic renal insufficiency Hypercoagulable states
- Post operative thrombotic complications
- Transient ischemic attacks ADVERSE EFFECTS [82]

Most side effects caused by Anti hypertensives involve the gastrointestinal tract and central nervous system. Nausea, vomiting, indigestion, gastric irritation, headache, dizziness are the commonly reported side effects.

Drug interactions

Patient on oral anticoagulant are at higher risk of prothrombin time elevations when combining with Anti hypertensive. Hence patients on warfarin should have more frequent monitoring of prothrombin time. Patients with other risk factors like hemorrhage (e.g.,recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Combination of Anti hypertensive and theophylline should be avoided which leads to increased serum theophylline levels and toxicity in some individuals[83]. Anti hypertensive has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decrease in blood pressure has been observed in some patients treated with Anti hypertensive, periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of antihypertensive agents should be reduced.

Contraindication

Anti hypertensives should not be used in patients with recent cerebral or retinal hemorrhage or in patients who have previously exhibited intolerance to the drug or other methylxanthines such as caffeine, theophylline and theobromine.

Anti hypertensives and OSMF

Anti hypertensives with potent hemorrheologic properties has been proved to be effective in treating intermittent claudication[84]. It was therefore convicted that it might also be effective in treating OSMF which having mucosal ischemia and epithelial atrophy. The submucosal fibrosis, which is the hallmark of this disorder, is considered to be the result of a defective inflammatory reparative response resulting in fibrotic healing[85]. The anti-inflammatory and immunomodulatory actions of Anti hypertensives seems to have definite therapeutic implication in the management of OSMF. As OSMF is a chronic inflammatory disease, control of the inflammation or the factors influencing the inflammatory changes should form the basis of definitive management.

Anti hypertensives has the ability to decrease the production of tumour necrosis factor alpha (TNF-α), an important mediator of the inflammatory process[86]. Primary immunologic abnormalities have also been reported in OSMF which probably mediate local tissue damage. The immune-modulating actions of Anti hypertensive include decreased leukocyte adhesion, aggregation and degranulation, decreased superoxide release and decreased natural killer cell activity[87]. OSMF is considered to be a collagen metabolic disorder with abnormal accumulation of collagen in subepithelial layers. An increased production and a reduced degradation of the type I collagen have been observed in OSMF. Collagenases are the only proteinases which specifically cleave triple helical collagen at neutral pH.

A reduced content of functional collagenase observed in OSMF might be one of the mechanisms responsible for this collagen accumulation. Fibroblasts cultured in the presence of Anti hypertensive produce twice as much collagenase activity

and decreased amount of collagen, glycosaminoglycans and fibronectins[88]. Cytokines play an important role in regulating fibroblast function, such as proliferation, migration and matrix synthesis, hence it is likely to play a key role in regulating the initiation and progression of any fibrotic disease. Both interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α) stimulate fibroblast proliferation in vitro and intradermal injections of TNF-α stimulate the accumulation of fibroblasts and collagen.

Similarly, both IL-6 and IL-8 have been implicated in the development of fibrosis. Studies conducted in OSMF `patients have shown increased levels of proinflammatory cytokines: IL-1, IL-6, IL-8 and TNF-α and reduced anti-fibrotic cytokine interferon gamma (IFN-γ) which may be central to the pathogenesis of OSMF. Interleukin -1 induced fibroblast proliferation was inhibited by Anti hypertensive. In addition, Anti hypertensives blocked the TNF-α induced synthesis of fibroblast collagen, glycosaminoglycans and collagenolytic activity[89]. A randomized clinical trial was conducted to determine the effects of Anti hypertensives on the clinical and pathological course of OSMF. The results showed highly significant improvement in mouth opening (p=0.000), tongue protrusion (p=0.002), relief from perioral and buccal mucosal fibrotic bands (p=0.000), burning sensation of mouth (p=0.0005), tinnitus (p=0.00004), difficulty in swallowing (p=0.00007) and speech (p=0.000) in all the test subjects. Adverse effects reported were mild gastritis and gastric irritation, peripheral flushing that could be managed easily. The study concluded that Anti hypertensives is an effective adjunct therapy in the routine management of OSMF [43].

Conclusion

'The future directions in the management of OSMF should thus include development of treatment regimens that combine different drugs or uses sequential therapy. Though the evidence showed significant improvement on using Anti hypertensives in OSMF, additional studies are required to further establish the role of Anti hypertensive in observed therapeutic effects. Quality randomized, controlled trials and increasing the global awareness of the disease for greater inflow of research data and research on possible treatment approaches is the need of the hour. Lastly, OSMF is a preventable disease; simple public health awareness of the harmful effects of chewing areca and other products could go a long way in combating this debilitating disease.

References

1. Schwartz J. Atrophia Idiopathica Mucosae Oris. In: Demonstrated at the 11th Int Dent Congress;1952.
2. Joshi SG. Fibrosis of the palate and pillars. Indian J Otolaryngol 1953;4(1).
3. Paymaster JC. Cancer of the buccal mucosa.A clinical study of 650 cases in Indian patients. Cancer 1956;9(3):431-435.
4. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg. Oral Med. Oral Pathol. 1966;22(6):764-79.
5. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK. Prevalence of oral submucous fibrosis among 50,915 Indian villagers. Br. J. Cancer 1968;22(4):646-54.

6. Pindborg JJ. Oral submucous fibrosis: A review. Ann. Acad. Med. Singapore 1989;18(5):603-607.
7. Murti PR, Bhonsle RB, Gupta PC, Daftary DK, Pindborg JJ, Mehta FS. Etiology of oral submucous fibrosis with special reference to the role of areca nut chewing. J. Oral Pathol. Med. 1995;24(4):145-52.
8. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. Community Dent. Oral Epidemiol. 1985;13(6):340-1.
9. Tai YS, Liu BY, Wang JT, Sun A, Kwan HW, Chiang CP. Oral administration of milk from cows immunized with human intestinal bacteria leads to significant improvements of symptoms and signs in patients with oral submucous fibrosis. J. Oral Pathol. Med. 2001;30(10):618-25.
10. Krishnamoorthy B, Khan M. Management of oral submucous fibrosis by two different drug regimens: A comparative study. Dent. Res. J. (Isfahan). 2013;10(4):527-32.
11. Canniff JP, Harvey W, Harris M. Oral submucous fibrosis: its pathogenesis and management. Br. Dent. J. 1986;160(12):429-34.
12. Zhang M, Xu Y-J, Mengi SA, Arneja AS, Dhalla NS. Therapeutic potentials of pentoxifylline for treatment of cardiovascular diseases. Exp. Clin. Cardiol. 2004;9(2):103-11.
13. Ariyawardana A, Athukorala ADS, Arulanandam A. Effect of betel chewing, tobacco smoking and alcohol consumption on oral submucous fibrosis: a casecontrol study in Sri Lanka. J. Oral Pathol. Med. 2006;35(4):197-201.
14. Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis--a collagen metabolic disorder. J. Oral Pathol. Med. 2005;34(6):321-8.
15. N Dyavanagoudar S. Oral Submucous Fibrosis: Review on Etiopathogenesis. J. Cancer Sci. Ther. 2009;01(02):072-077.
16. Wanninayake Mudiyanselage Tilakaratne RPE. Oral Submucous Fibrosis: Review on Mechanisms of Pathogenesis and Malignant Transformation. J. Carcinog. Mutagen. 2013.
17. Yadav J. Role of Copper in Oral Submucous Fibrosis: A Cytological Correlation. Indian J. Dent. Sci. 2011;3(5):3-6.
18. Yang S-F, Hsieh Y-S, Tsai C-H, Chen Y-J, Chang Y-C. Increased plasminogen activator inhibitor-1/tissue type plasminogen activator ratio in oral submucous fibrosis. Oral Dis. 2007;13(2):234-8.
19. Tsai CC, Ma RH, Shieh TY. Deficiency in collagen and fibronectin phagocytosis by human buccal mucosa fibroblasts in vitro as a possible mechanism for oral submucous fibrosis. J. Oral Pathol. Med. 1999;28(2):59-63.
20. Rajendran R, Paul S, Mathews PP, Raghul J, Mohanty M. Characterisation and quantification of mucosal vasculature in oral submucous fibrosis. Indian J. Dent. Res. 16(3):83-91.
21. Rajendran R, Sunil, Twinkle SP, Anikumar T V, Annie J. Cell death does not herald epithelial involution (“atrophy”) in oral sub mucous fibrosis: a TEM study. Indian J. Dent. Res. 15(1):13-9.
22. Thangjam GS, Agarwal P, Khan I, et al. Transglutaminase-2 regulation by arecoline in gingival fibroblasts. J. Dent. Res. 2009;88(2):170-5.
23. Tsai C-H, Yang S-F, Lee S-S, Chang Y-C. Augmented heme oxygenase-1 expression in areca quid chewing-associated oral submucous fibrosis. Oral Dis. 2009;15(4):281-6.

24. Chatuvedi VN, Sharma AK, Chakrabarati S. Salivary coagulopathy and humoral response in oral submucous fibrosis (OSMF). J. Indian Dent. Assoc. 1991;62(3):51-3, 59.
25. Gupta P, R Naik S, Nc S, Durgvanshi A, Agarwal N. Salivary IgA Levels in Patients with Oral Submucous Fibrosis: A Study. Kailasam S, ed. J. Indian Acad. Oral Med. Radiol. 2011;23(4):536-538.
26. Samlaska CP, Winfield EA. Pentoxifylline. J. Am. Acad. Dermatol. 1994;30(4):603-621.
27. Seidler NW, Swislocki NI. The effects of pentoxifylline on the plasma membrane Ca2+ ATPase in age-separated rat and human erythrocytes. J. Clin. Pharmacol. 1992;32(4):332-37.
28. Currie MS, Rao KM, Padmanabhan J, Jones A, Crawford J, Cohen HJ. Stimulus-specific effects of pentoxifylline on neutrophil CR3 expression, degranulation, and superoxide production. J. Leukoc. Biol. 1990;47(3):244-50.
29. Wakefield PE, James WD, Samlaska CP, Meltzer MS. Tumor necrosis factor. J. Am. Acad. Dermatol. 1991;24(5 Pt 1):675-85.
30. Berman B, Duncan MR. Pentoxifylline inhibits normal human dermal fibroblast in vitro proliferation, collagen, glycosaminoglycan, and fibronectin production, and increases collagenase activity. J. Invest. Dermatol. 1989;92(4):605-10.
31. Srinivasu P, Rao BR, Rao YM, Rambhau D. Biopharmaceutics: Drug Metabolism and Pharmacokinetics: Circadian Variations in the Pharmacokinetics of Pentoxifylline in Man. J. Pharm. Pharmacol. 1998;50(1):71-74.
32. Antignani PL, Todini AR, Saliceti F, Pacino G, Bartolo M. Results of clinical, laboratory and haemorheological investigations of the use of pentoxifylline in high doses. Pharmatherapeutica 1987;5(1):50-6.
33. Perego MA, Sergio G, Artale F, Giunti P, Danese C. Haemorrheological improvement by pentoxifylline in patients with peripheral arterial occlusive disease. Curr. Med. Res. Opin. 1986;10(2):135-8.
34. Aviado DM, Porter JM. Pentoxifylline: A New Drug for the Treatment of Intermittent Claudication; Mechanism of Action, Pharmacokinetics, Clinical Efficacy and Adverse Effects. Pharmacother. J. Hum. Pharmacol. Drug Ther. 1984;4(6):297-306.
35. Ellison MJ, Horner RD, Willis SE, Cummings DM. Influence of pentoxifylline on steady-state theophylline serum concentrations from sustained-release formulations. Pharmacotherapy 1990;10(6):383-6.
36. Dettori AG, Pini M, Moratti A, et al. Acenocoumarol and pentoxifylline in intermittent claudication. A controlled clinical study. The APIC Study Group. Angiology 1989;40(4 Pt 1):237-48.
37. Rajendran R, Vijayakumar T, Vasudevan DM. An alternative pathogenetic pathway for oral submucous fibrosis (OSMF). Med. Hypotheses 1989;30(1):35- 7.
38. Zabel P, Schade FU, Schlaak M. Inhibition of endogenous TNF formation by pentoxifylline. Immunobiology 1993;187(3-5):447-63.
39. Kreth S, Ledderose C, Luchting B, Weis F, Thiel M. Immunomodulatory properties of pentoxifylline are mediated via adenosine-dependent pathways. Shock 2010;34(1):10-6.

40. Shieh TY, Yang JF. Collagenase activity in oral submucous fibrosis. Proc. Natl. Sci. Counc. Repub. China. B. 1992;16(2):106-10.
41. Haque MF, Harris M, Meghji S, Barrett AW. Immunolocalization of cytokines and growth factors in oral submucous fibrosis. Cytokine 1998;10(9):713-9.
42. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. Indian J. Dent. Res. 17(4):190-8.