

## REVIEW ARTICLE

# ETIOPATHOGENESIS OF ORAL SUBMUCOUS FIBROSIS - REVIEW OF LITERATURE

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### ABSTRACT:

The areca nut, popularly known as “betel nut” is almost symbolic of the culture of some Oriental nations and is one of the oldest known masticatories among Asians. Areca nut is consumed in various forms such as betel quid (areca nut + slaked lime + betel leaf) with or without tobacco, pan masala (Powdered areca nut with additives, flavoring agents and tobacco) and raw areca nut (seeval flakes and kotta pakku granules). There has been an increase in the use of areca nut, particularly pan masala in younger age groups in India, leading to increased incidence of OSMF. Many patients with OSMF have other habits concurrently, which may also play a role in the initiation and the progress of this pre-malignant condition.

Key Words: Areca Nut, Oral submucous fibrosis, Betel Quid, HLA

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### INTRODUCTION

Oral Submucous Fibrosis is a Chronic and high risk potentially malignant disorder. The definition of OSMF presently known today was proposed by Pindborg and Sirsat in the year 1966. They 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”<sup>1</sup> The world health organisation defines for an oral precancerous condition – “a generalized pathological state of the oral mucosa associated with a significantly increased risk of cancer”. The precancerous nature was first mentioned by Paymaster in 1956, who observed the development

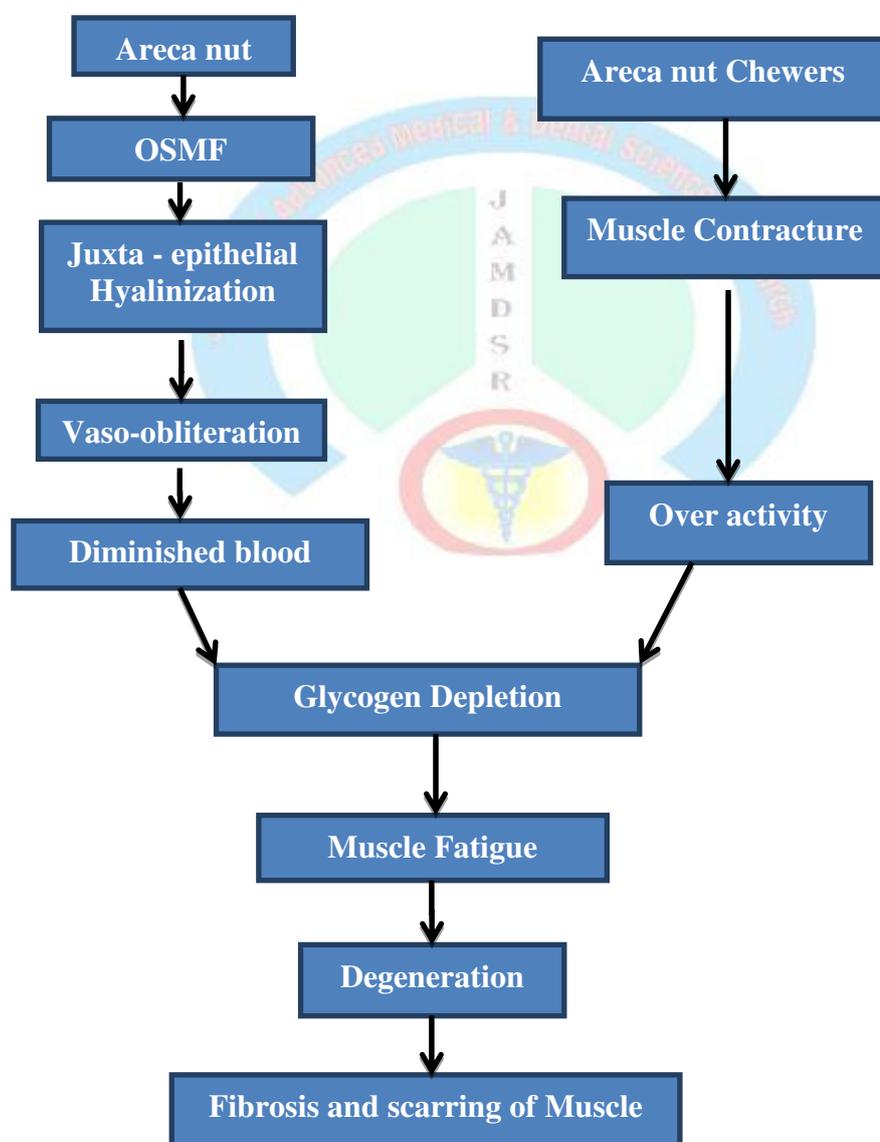
of slow growing squamous cell carcinoma in one third of his submucous fibrosis patients. Oral Submucous Fibrosis (OSMF) at present is a matter of great concern because it is a disabling disease of mouth and at its worst can give rise to oral cancer. Although 33 years have passed since its first description it still remains an incurable disease and which is progressive in nature even after cessation of the habits.<sup>2</sup>

### INITIAL EVENTS OF THE DISEASE

In most areas betel quid consist of a mixture of the areca nut, slaked lime, catechu and several condiment according to taste, wrapped in a betel leaf. Areca nut is the endosperm of the fruit of the areca catechu tree. Arecoline is the most abundant alkaloid. These alkaloids undergo nitrosation and give rise to N - nitrosamine, which might have a cytotoxic effect on cells. Arecoline has been demonstrated to promote collagen synthesis.<sup>3</sup>

Betel quid (BQ) is placed in the buccal vestibule for about 15 min to an hour and repeated for 5 to 6 times a day. There is constant contact between the mixture and oral mucosa. These alkaloids and flavonoids from the betel quid are absorbed and undergo metabolism. These constituents and their metabolites are a source of constant irritation of the mucosa. In addition, the coarse fibers of the areca nut also cause mechanical irritation to the oral mucosa. The micro trauma produced by the friction of the coarse fibers of the areca nut also facilitates the diffusion of betel nut alkaloids and flavonoids into sub epithelial connective tissue, resulting in a juxtaepithelial cell infiltration. Over a period of time, due to persistent habit, chronic inflammation sets in the site. Initial irritation leads to further atrophy and ulceration of mucosa.<sup>4</sup>

Inflammation is characterised by the presence of activated T cells, macrophages etc. there is an elaboration of various chemical mediators of inflammation, especially prostaglandins (PGs) play an essential role. PGs secretion by oral keratinocytes in response to Areca nut extract (ANE) has been shown aberrant and persistent tissue inflammation is crucial for the occurrence of cancer and tissue fibrosis. Thus, it can be considered that induction of the oral mucosal inflammation by BQ ingredient to be critical event in the pathogenesis of OSF. Cytokines like interleukin 6, tumor necrosis factor (TNF), interferon  $\alpha$  and growth factors like TGF- $\beta$  are synthesized at the site of inflammation.



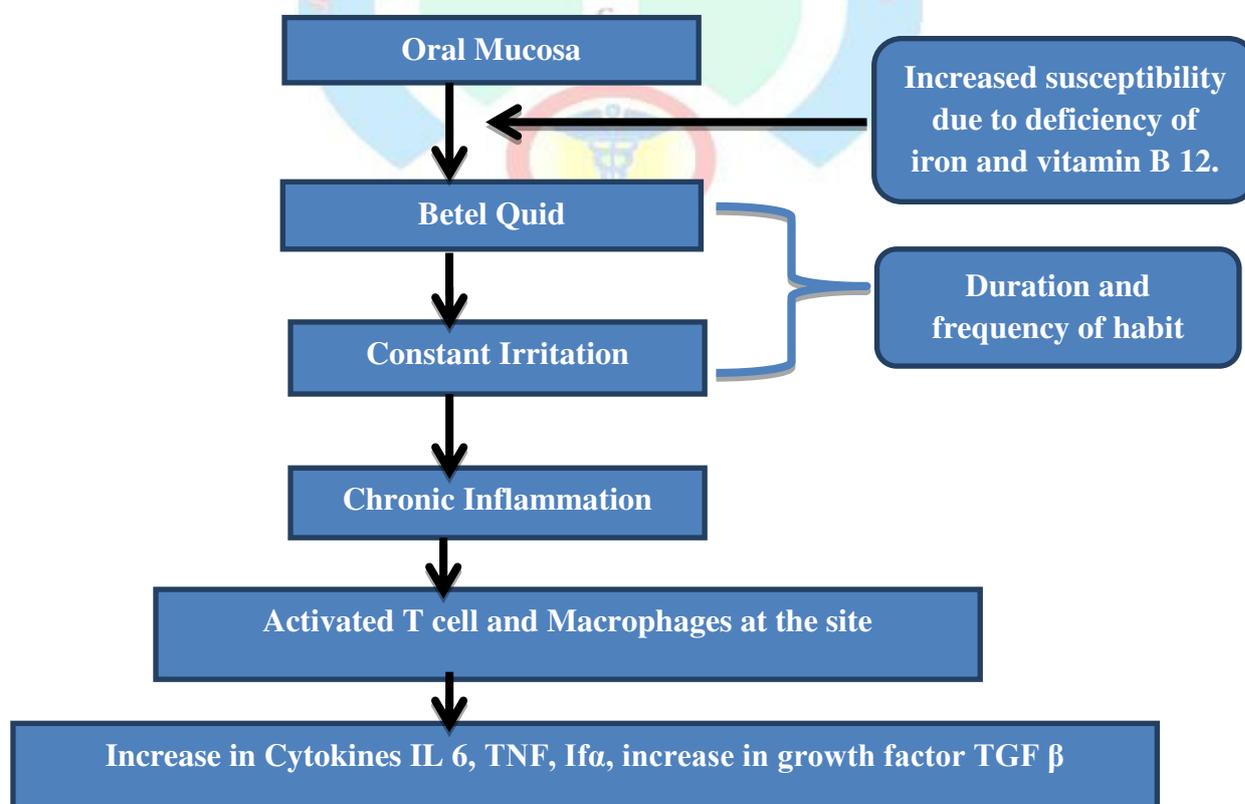
**Illustration 1:** Role of areca nut in pathogenesis of OSMF (muscle degeneration) as proposed by J. N. Khanna, N. N. Andrade<sup>5</sup>

Chewing of areca nut or its products is practised as chewing supari (areca nut alone), non-proprietary betel quid, mawa or proprietary forms collectively called as pan masala. Areca nut chewing is wide spread in India. Arecanut is the fruit of areca catechu plant containing chemical irritants like arecoline, flavonoids catechin and tannins. Arecoline has powerful parasympathetic properties producing euphoric and it counteracts fatigue. It has psychotropic and antihelminthic activity.

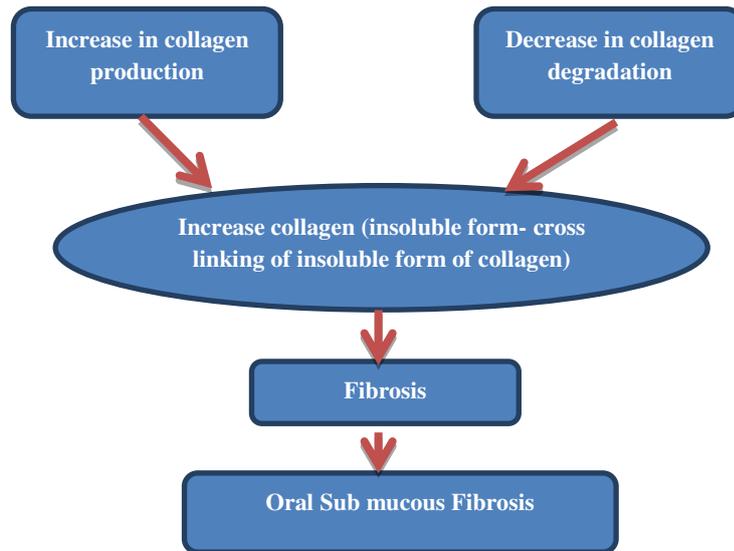
The *betel quid* is a mixture of areca nut (Areca catechu), catechu (Acacia catechu) and slaked lime (calcium oxide and calcium hydroxide) wrapped in a betel leaf (Piper betel). Condiments, sweetening agents and spices may be added according to individual preferences. In India, most habitual chewers of betel quid add tobacco.<sup>6</sup>

*Pan masala* is basically a preparation of areca nut, catechu, cardamom, lime and a number of natural and artificial perfuming and flavouring materials. Gutkha is a variant of pan masala, in which in addition to above ingredients flavoured tobacco is added. Both products are often sweetened to enhance the taste.<sup>6</sup>

*Mawa* is a preparation containing thin shavings of areca nut (5-6g) with the addition of some tobacco (about 0.3g) and few drops of watery slaked lime. The contents, kept on a piece of cellophane paper, are tied with a thread into a ball and the packet is rubbed vigorously on the palm to homogenise the contents. It is then opened and a portion, or the whole of it, is placed in the mouth.<sup>7</sup> In several reports comprising a total of 405 cases, the habit of areca nut chewing by itself, or in combination with betel leaf, lime and tobacco were present in 77% of the patients. The role of the constituents of areca nut in the pathogenesis of OSMF has been studied in detail over last two decades. It is apparent that fibrosis and hyalinization of sub-epithelial tissues account for most of the clinical features encountered in this condition. It is logical to hypothesize that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in the development of the disease. There are numerous biological pathways involved in the above processes and, it is likely that the normal regulatory mechanisms are either down regulated or up regulated at different stages of the disease.<sup>8</sup>



**Illustration 2:** Initial Event of Disease Process

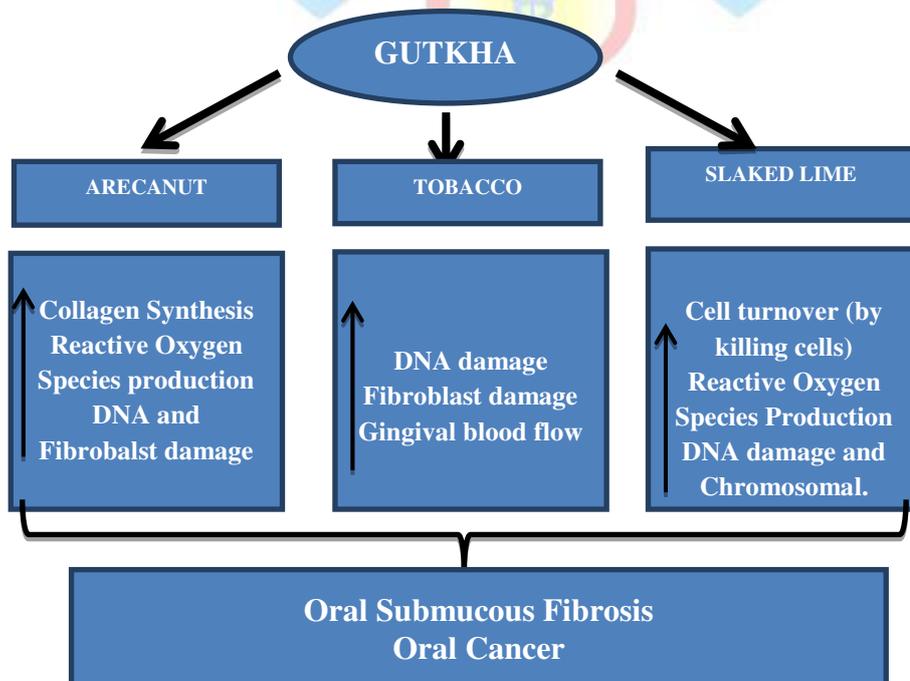


**Illustration 3:** Overall Effect of Activated TGF Beta Pathway

There is an increase in collagen production and cross linking (insoluble form) along with the decrease in the collagen degradation. This produces increased collagen deposition in the subepithelial connective tissue layer of the oral mucosa leading to OSMF.<sup>9</sup> The major areca nut alkaloids are arecoline, arecadine, arecolidine, guyaoline and guacine. The important flavonoid components in areca nut are tannins and catechins. These alkaloids undergo nitrosation and give rise to N-nitrosamine which might have cytotoxic effect on cells. The alkaloids from the quid are absorbed into the mucosa and undergoes

metabolism. Microtrauma produced by the friction of coarse fibers of areca nut also facilitates diffusion of the alkaloids into the subepithelial connective tissue resulting in juxtaepithelial inflammatory cell infiltration.

Gutka users consume more dry weight of tobacco, areca nut, and slaked lime, which causes nicotine to act synergistically on the cytotoxicity induced by arecoline (a major areca nut alkaloid), thereby increasing the vulnerability of buccal mucosal fibroblasts to damage and enhanced collagen production (up to 170%) that has been diagrammatically represented.



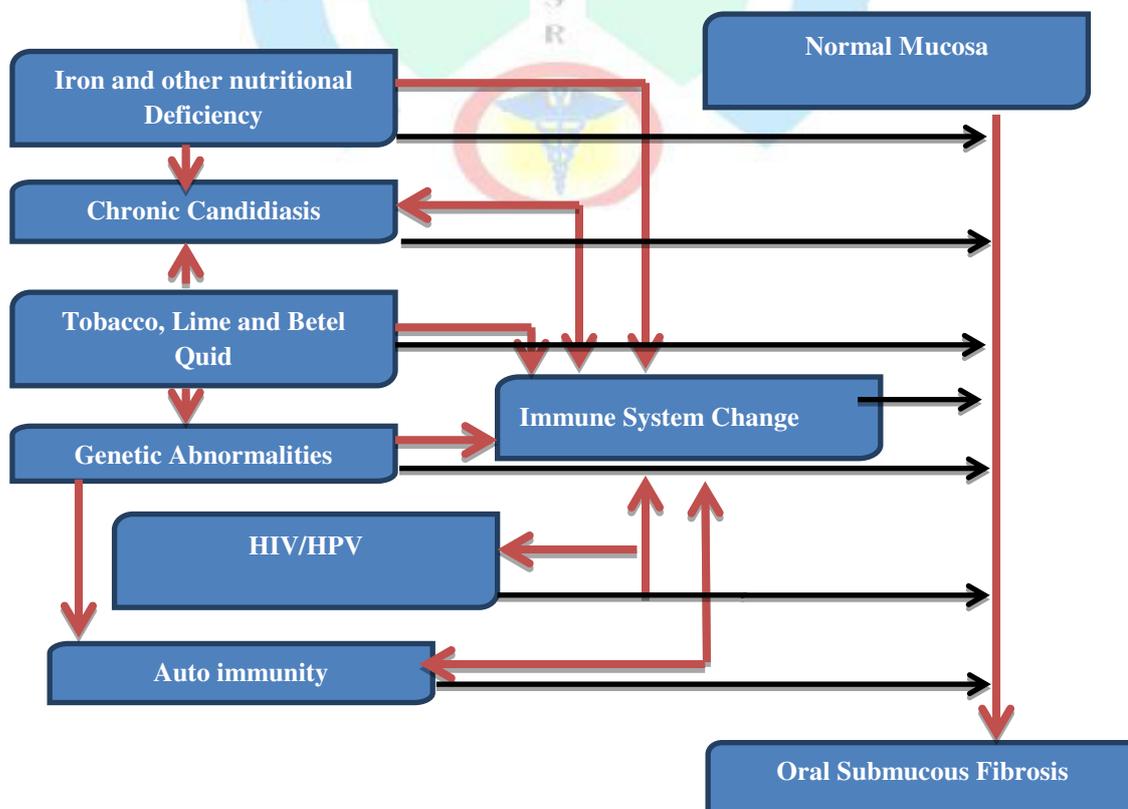
**Illustration 4:** Role of gutkha in OSMF.

### AUTOIMMUNITY

Autoimmunity as an aetiological factor for OSF has been examined. The reasons for investigating an autoimmune basis, included, slight female predilection and occurrence in the middle age reported in some studies. The presence of circulating immune complexes, their immunoglobulin contents and the detection of various auto antibodies in patient's sera. The presence of various autoantibodies at varying titres was reported in several studies suggesting the possibility of an autoimmune basis to the disease. The first report on this concept came in 1986 showing 65% of the sample being positive for at least one of the auto-antibodies tested. The antibodies which showed increased frequencies were, 38% anti gastric-parietal cell (GPCA), 23% anti thyroid microsomal, 8% anti-nuclear (ANA), 4% anti-reticulin and 4% anti smooth muscle (SMA) antibodies. In another study, it was revealed that ANA (23.9%), SMA (23.9%) and GPCA (14.7%) were positive in OSF patients compared with healthy control subjects. Increased levels of immune complexes and raised serum levels of IgG, IgA and IgM when compared with control groups have also been reported few studies

reported on HLA typing in OSF patients. The frequencies of HLA A10, DR3 and DR7 proved to be significantly different compared with an ethnically, regionally and age-matched control group. Further, haplotypic pairs A10/DR3, A10/B8 and B8/DR3 showed an increased frequency in OSF patients compared to controls, although the differences were not statistically significant.<sup>10</sup> Another study using polymerase chain reaction (PCR) has shown a significant increase in frequencies of HLA A24, DRB 1-11 and DRB3-0202/3. A recent study has revealed higher haplotype frequencies in pairs HLA B51/Cw7 and B62/Cw7 in OSF patients. Two new HLA DRB1 alleles were identified by sequencing-based typing and named as HLA DRB1-0903 and DRB1-1145. The association of HLA and OSF does not appear consistently as one study showed that there was no demonstrable specific pattern of HLA antigen frequencies in chewers with or without the disease. Although the data on various HLA types, raised autoantibodies and the detection of immune complexes tend to indicate an autoimmune basis for the disease, substantial number of cases and matched controls may be required to verify these findings.<sup>10</sup>

**Illustration 5:** A Multifactorial model for the pathogenesis of OSMF



*Brown arrows show effects mediated by various factors through the immune system, whereas black arrows show possible direct effects of the factors on oral mucosa.*

## CONCLUSION

In summary, the available literature indicates that the main aetiological factors for OSF are the constituents of areca nut, mainly arecoline, whilst tannin may have a synergistic role. These chemicals appear to interfere with the molecular processes of deposition and/or degradation of extracellular matrix molecules such as collagen, causing imbalance in the normal process. Although the above mechanisms may explain the induction, maintenance and progression of fibrosis in OSF, further research is required in order to identify the mechanism leading to carcinogenesis in this fibrotic oral mucosa. Although the involvement of HLA and genetic predisposition has been reported, specific haplotypes have not been determined. The individual mechanisms operating at various stages of the disease—initial, intermediate and advanced—need further study in order to propose appropriate therapeutic intervention

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