

## Oral Submucous Fibrosis: An Update on Etiopathogenesis

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### Abstract

The theories related to development of oral submucous fibrosis (OSMF) has been multifactorial. Many etiological factors include the consumption of areca nut (supari), betel leaves (paan), tobacco and intake of spicy food which are commonly found in asian foods. Systemic causes like nutritional deficiency, genetic predisposition, autoimmunity, heat shock proteins have also been proposed as causative factors for OSMF. Albeit the extensive documented aetiological factors, the precise etiology is not yet known and no conclusive evidence has been linked to the development and progression of Oral Submucous Fibrosis. The present review aims to decipher the various etiological agents and decoding their role in pathogenesis and progression of Oral Submucous Fibrosis.

**Keywords:** Oral Submucous Fibrosis; Areca Nut; Pathogenesis; Review

### Introduction

Oral Submucous Fibrosis is a chronic, progressive, potentially malignant condition of the oral cavity that predominantly affects people of South-East Asian origin [1]. It is characterized by a juxta-epithelial inflammatory reaction followed by fibroelastic change in the lamina propria and epithelial atrophy which leads to stiffness of the oral mucosa, trismus and inability to eat. It affects most parts of the oral cavity and may extend over time to include the pharynx and the upper third of esophagus [2].

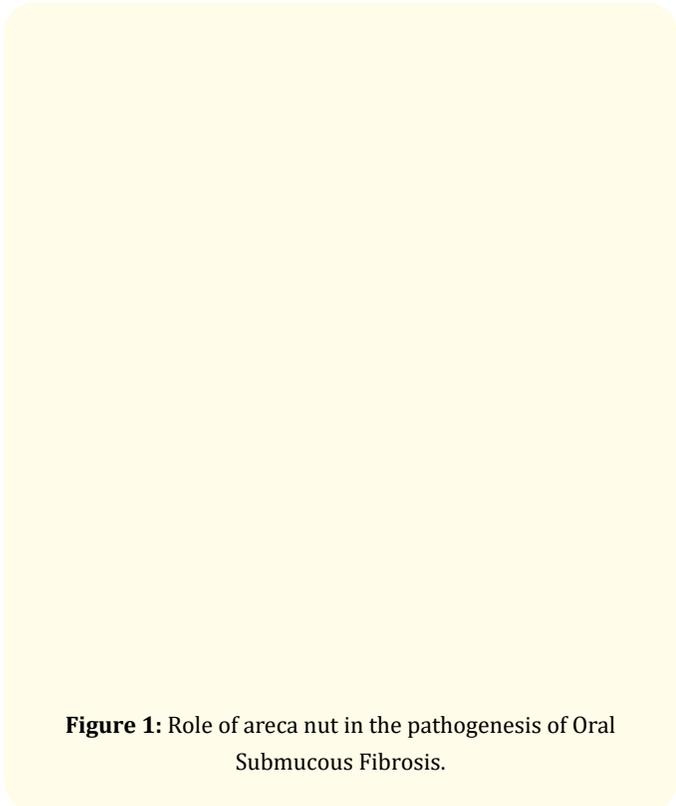
Various etiological factors such as areca nut, capsaicin in chillies, micronutrient deficiency and autoimmune nature of the disease has also been proposed [3]. The present review article aims to understand the detailed etiopathogenesis of oral submucous fibrosis.

### Etiopathogenesis

The most important etiological factor in OSMF is the use of areca nut. Areca nut contains arecoline, arecadine, guvacoline and guvacine which are responsible for fibroblast proliferation. With the addition of slaked lime ( $\text{Ca}(\text{OH})_2$ ), arecoline gets hydrolyzed to arecadine amplifying fibroblastic proliferation and increasing collagen formation [3].

Arecoline causes increased collagen synthesis by OSMF fibroblasts as compared to normal fibroblasts. This leads to clonal selection of a cell population in altered tissues under the influence of IL-1 which are released by inflammatory cells [5]. The presence of flavanoids such as tannins and catechins stabilise the structure of non soluble collagen (Type 3 collagen to highly resistant Type 1 collagen) and retards collagenase activity [5,6]. Arecoline pro-

motes Cystatin C leading to inhibition of collagen proteinases causing stabilization of collagen fibrils [7,8] (Figure 1).

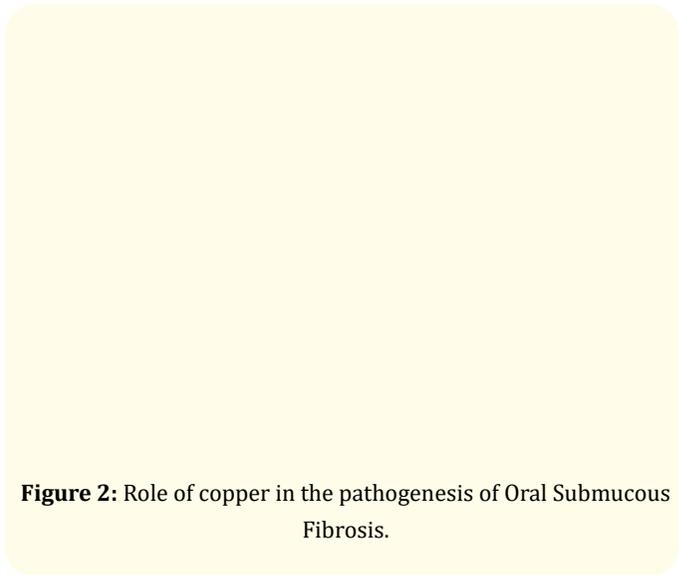


**Figure 1:** Role of areca nut in the pathogenesis of Oral Submucous Fibrosis.

**Role of copper**

Betel nut is usually grown at 15.5-38°C and is usually planted at pre monsoon period of May-June. The warm, moist and damp environment during this period predisposes various diseases. To avoid the onset of disease, a spray of 1% Bordeaux mixture in 10L water is used as a prophylactic spray before the monsoons. Bordeaux mixture is a fungicide which is prepared by adding milk of lime to a solution of copper sulphate to withstand heavy rainfall [9]. The high concentration of copper in areca nut is due to spraying of Bordeaux mixture that acts as a preservative [9].

On a molecular level, a significant amount of copper leads to up regulation of lysyl oxidase causing inhibition of collagenase degradation by activating tissue inhibitor of matrix metalloproteinase gene and plasminogen inhibitor activator gene leading to increase in production of insoluble collagen [10,11] (Figure 2).

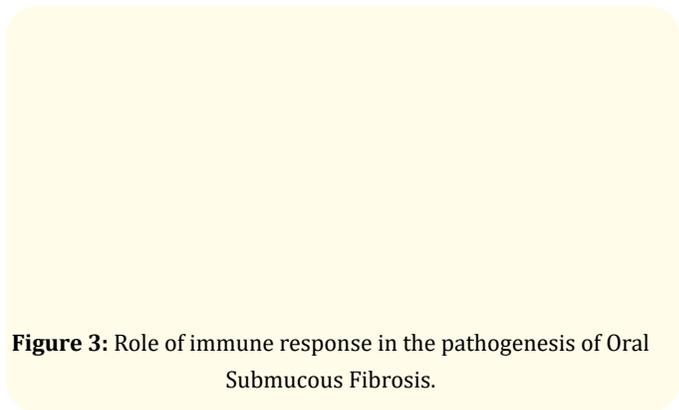


**Figure 2:** Role of copper in the pathogenesis of Oral Submucous Fibrosis.

**Role of immunity**

The normal collagen degradation is by phagocytosis which is inversely dose dependent to arecoline, safrole and nicotine in saliva. In OSMF, decrease in T cell activity leads to cell mediated immunity and causes impaired phagocytic activity [12]. Increased reactive oxygen species are formed by auto-oxidation in saliva or via intracellular metabolic activation [13].

Areca nut leads to upregulation of proinflammatory cytokines i.e. IL-6 and IL-8, TNF-α, TGF-β, platelet-derived growth factor(PDGF), basic fibroblast growth factors and decreased expression of antifibrotic cytokine IF-γ leading to increased fibrosis. This leads to altered immune response with increased Antigen Presenting Cells and lymphocytes and increase in permeability of arecoline and arecadine into the oral mucosa [14-16] (Figure 3).



**Figure 3:** Role of immune response in the pathogenesis of Oral Submucous Fibrosis.

An imbalance between the tissue inhibitors of matrix proteinases (TIMP) and matrix metalloproteinase's (MMP's) leads to increased deposition of Extracellular Matrix [17].

### Genetic susceptibility

A strong genetic susceptibility leading to dysregulation of collagen metabolism causing highly resistant collagen and genes such as COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 are also linked to the progression of the disease [18].

### Autoimmunity

A role of autoimmunity has also been seen as an etiological factor in the development and progression of the disease. Balram, *et al.* suggested that there is an increase in IgG, IgA and IgM and raised serum levels in patients with Oral Submucous Fibrosis [19,20].

### Heat shock proteins

47kDa Heat shock proteins are involved in the synthesis, processing and assembly of various collagen and is shown to cause accumulation of collagen in the mucosal connective tissue leading to accelerated fibroblastic activity [21,22].

### Nutritional deficiencies

Deficiency of iron, vitamin and protein has been linked with the progression of OSMF [23]. Hydroxyproline is present in collagen as hydroxylated form (4 hydroxyl proline) with the use of iron and ascorbic acid. Deficiency of iron leads to decrease in vascularity due to reduction in cytochrome oxidase leading to atrophy of epithelium, causing burning sensation and ulcerations. A vicious cycle forms due to inability to consume food due to burning leading to anaemia [24,25].

### Conclusion

Regardless of the extensive studies that have been done on the role of various etiological agents and their etiopathogenesis on the development of Oral Submucous Fibrosis, it is still understood in a passable way. The present review aims to highlight and explain the various aetiologies and their pathogenesis in the progression of Oral Submucous Fibrosis to ameliorate the diagnosis and treatment of the affected patients.

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