Review Article

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ROLE OF MATCHA GREEN TEA IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A REVIEW

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ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic premalignant condition of the mucosa of the oral cavity characterised by a severe burning sensation and a gradual decrease in mouth opening due to underlying fibrosis. Therapeutic medications available have been useful, but none have shown promising results except for their strong antioxidant potential. This antioxidant activity is incorporated abundantly in the naturally occurring ayurvedic formulation, matcha green tea (MGT). This article aims to provide information about molecular pathways involved in the etiopathogenesis of OSMF and a hypothesis on how these pathways can be affected by matcha green tea, thus the usefulness of MGT in the management of OSMF.

Keywords: Oral Submucous Fibrosis, Collagen, Matcha Green Tea, EGCG, Antioxidants, Areca nut Toxicity.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic premalignant condition of the oral cavity affecting a large population worldwide. In most of the regions where OSMF is endemic, males are predominantly affected, but the distribution does vary geographically. The prevalence of OSMF in India has been estimated to range from 0.2-2.3% in males and 1.2-4.6% in females[1]. In 1966, Pindborg defined OSMF as "an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. It is associated with a juxta-epithelial inflammatory reaction followed by fibroelastic changes in the lamina propria layer, along with epithelial atrophy, which leads to rigidity of the oral mucosa, trismus, and difficulty in mouth opening"[2]. Other terms used to describe this condition are juxta-epithelial fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, submucous fibrosis of the palate and pillars, sclerosing stomatitis, and diffuse OSMF[2]. The clinical picture can vary from a mild burning sensation to severe fibrosis causing no mouth opening. Many therapies have been tried till date for the treatment of OSMF, ranging from various medicinal herbs and antioxidants to the application of injections of pharmacological steroids. Recent systematic reviews explain that no single regime has proved to be entirely satisfactory[3,4]. Therefore, for such a chronic condition, newer modalities need to be introduced, with their applications being studied.

The role of antioxidants has been shown to play a promising role in OSMF treatment. One such herb with brilliant antioxidant potential is matcha green tea (MGT). MGT's antioxidant role has been studied and found to be beneficial in carcinogenic conditions like carcinoma of the lung and hepatic system. Understanding the etiopathogenesis of OSMF at the molecular level and the target areas where the MGT can exert its action will help justify the role of the MGT in OSMF. Thus, this review article aims to provide brief information about the probable role of Matcha green tea in the management of OSMF.

Etiopathogenesis

OSMF was first described by Schwartz in 1952, where it was classified as an idiopathic disorder by the term atrophia idiopathica (tropica) mucosae oris[6]. Since then, many hypotheses have been proposed that OSMF is multifactorial in origin, with etiological factors being areca nuts, capsaicin in chilies, and micronutrient deficiencies of iron, zinc, and essential vitamins. The autoimmune etiological basis of disease, with the demonstration of various autoantibodies with a strong association with specific human leukocyte antigens, has also been suggested[7].

Illustration of etiopathogenesis

Areca nut (betel nut) chewing is one of the most common causes of OMSF, which contains alkaloids such as arecoline, arecaidine, guvacine, and guvacoline (0.15%–0.67%). These alkaloids are responsible for the production of free radicals. There are many enzymatic sources for the formation of reactive oxygen species (ROS), including cytochrome P450 (CYP) enzymes, that contribute to cellular oxidation-reduction (redox) balance. This redox balance plays critical roles in normal cellular processes, including immune function and cell signaling[8,9]. Disruption of the

normal redox balance results in oxidative stress, and it is involved in several disease processes, including carcinogenesis and aging[9,10]. CYP enzymes can increase ROS and alter the redox balance, creating oxidative stress through their catalytic cycle and leading to damage to the affected endothelial cells[11]. This damage leads to epithelial changes and the development of symptoms of OSMF, mainly a burning sensation in the oral cavity (Figure 1).

Arecaidine is an active metabolite in fibroblast stimulation and proliferation, thereby inducing collagen synthesis. With the addition of slaked lime Ca $[OH]_2$ to areca nut, it causes the hydrolysis of arecoline to arecaidine, making this agent available in the oral environment.

1. Nitric oxide synthase (iNOS), b-FGF, TGF-β, PDGF, and HIF-1α are among the expressed angiogenesis-associated molecules in OSMF that help in the maintenance of connective tissue vascularity. Fibrosis of the underlying mucosa and arecoline toxicity induce hypoxic injury to the cells. In response to hypoxia, body cells try to overcome the hypoxic condition by stimulating angiogenesis [12,13]. In severe fibrosis, mucosal vascularity decreases, which is being proved by conventional histology and morphological analysis data[13] (Figure 1).

2. Damage to the mucosa of the mouth results in inflammatory changes that trigger the production of cytokines. One important cytokine implicated in the pathogenesis of OSMF is transforming growth factor-β (TGF-β)[4]. Arecoline also increases the levels of profibrotic and proinflammatory cytokines, including TNF-α, PDGF, b-FGF, KGF-1, IL-1, IL-6, and IL-8. It suppresses IFN-γ, which encourages the production of collagen[15,16]. Fibrosis is the consequence of changes in cytokines and growth factors that lead to fibroblast proliferation and collagen synthesis close to the site of injury. The primary causal event for the increased collagen formation and fibrosis has been hypothesised to be activation of transforming growth factor beta (TGF) signaling. TGF-beta is said to play a part in OSMF in some research[17] (Figure 1). The idea states that components of areca nuts induce TGF-β signalling in epithelial cells, which triggers the classical downstream SMAD signalling pathway and impacts neighbouring fibroblasts, ultimately leading to fibrosis through epithelial-mesenchymal interaction.

3. Tannin present in areca nuts reduces collagen degradation by inhibiting collagenases. OSMF is induced as a combined effect of tannin and arecoline by the mechanisms of reducing degradation and increasing production of collagen, respectively[6]. The abnormal crosslinking is caused by polyphenolic components, mainly the tannin of arecanut, via upregulation of 12-o-tetradecanoylphorbol-13 acetate-mediated oxidative stress, a pathway involved in the metabolism of polyphenols (Figure 1).

4. The copper content in the betelnut is responsible for the production of lysyl oxidase, an enzyme causing disruption in collagen metabolism, increased production of reactive oxygen species, and thus cytotoxicity. The copper content of areca nuts has a strong cytotoxic property. Increased oxidation of copper (II) in the presence of arecoline leads to the cleavage of DNA in a superoxide-dependent manner. This induced DNA cleavage by arecoline, and copper (II) is also supported by their complex formation[18] (Figure 1). Cytotoxicity induced by arecoline, and copper also follows an apoptotic pattern of cell death that is dependent on ROS generation.

Thus, multiple etiological factors are involved at the molecular level, which contribute to the etiopathogenesis of OSMF.

Matcha Green Tea

Japanese green tea (*Camellia sinensis*), specifically the Tencha kind, is known as matcha. The global popularity of this popular beverage has increased. The unique farming approach makes it very rich in antioxidant chemicals. The tea bushes are traditionally covered with bamboo mats for most of the growth period to protect the leaves from too much direct sunlight. Higher levels of amino acids and bioactive substances, such as chlorophyll and theanine, can be produced by plants during this process. These substances give matcha its distinctive, non-bitter flavour and distinctive, vivid colour[19].

Constituents of Matcha Green Tea (MGT)

Catechins: Green tea leaves contain four main catechins, which are polyphenols, namely epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG), of which EGCG is the most active and abundant. They have a greater capacity for scavenging free radicals than vitamin C on its own[17]. Catechin content in green teas is much higher than in black teas, amounting to 5.46–7.44 mg/g, compared with 0–3.47 mg/g in black tea[11]. Matcha may therefore be described as a major source of antioxidants among other tea varieties.

Phenolic Acids: Phenolic acids are secondary plant metabolites characterised by high antioxidant and anti-inflammatory potential[20]. In-depth research of matcha tea samples indicated the following levels of phenolic acids, which varied depending on several factors: Gallic acid has a molecular weight of 423 g/g, p-hydroxybenzoic acid has 243 g/g, chlorogenic acid has 4800 g/g, caffeic acid has 223 g/g, ferulic acid has 289 g/g, and ellagic acid has 371 g/g[21].

Rutin: Rutin is a polyphenolic compound. Its antioxidant and anti-inflammatory action offer potential for preventing conditions related to injury from free-radical or inflammatory origin[22]. Contrasting the level of rutin found in matcha (1968.8 mg/L) with that in buckwheat (62.30 mg/100 g), the latter is recognised as one of the richest sources of rutin in the human diet, and thus matcha tea may be a better source of the compound than other foodstuffs [22,23].

MGT contains additional antioxidant and anti-inflammatory effects with the addition of quercetin, vitamin C, chlorophyll, and theanine, all of which are beneficial to health[16].

Probable Role of MGT for OSMF

The probable pathways and targets interfered by green tea -
1.Alkaloids
2.Vascularity
3.Growth factors
4.Collagen crosslinking
5.Cytotoxicity

Illustration of probable pathways affected by Matcha Green Tea in OSMF

1.**Alkaloids**: Alkaloids in arecanut, mainly arecoline and arecaidine, contribute to the pathophysiological changes in OSMF. The pathway involves the formation of free radicals. EGCG disrupts ROS generation by decreasing the activity of CYP and thus preventing the formation of free radicals and progressing OSMF[23] (Figure 2).

2.**Vascularity**: In the vascular system, ECGC stimulates NO production with resulting vasodilation and microvascular recruitment and inhibits vasoconstriction by opposing ET-1 release and inhibiting serotonin-mediated vasoconstriction[24] (Figure 2). Thus, contributing to increasing vascular supply and reducing the atrophy of the cells.

3.**Growth factors**: It has been found in lung cancer cells that EGCG inhibits Transforming Growth Factor-β-Mediated

Epithelial-to-Mesenchymal Transition via the inhibition of Smad2 and Erk1/2 signalling pathways[25] (Figure 2). A similar way of inhibiting can be one of the pathways affecting growth factors.

4. **Collagen crosslinking**: EGCG, the major polyphenolic component of MGT, affects the collagen metabolism directly or indirectly. The abnormal crosslinking is prevented by directly affecting the polyphenolic component of areca nut via downregulation of 12-o-tetradecanoylphorbol-13 acetate-mediated oxidative stress, a pathway involved in the metabolism of polyphenols, thus preventing the conversion of immature collagen to fibroblasts[26] (Figure 2). The indirect pathway is the maintenance of balance between tissue inhibitors of matrix metalloproteinases (TIMP) and matrix metalloproteinases (MMP).

5.**Cytotoxicity**: This complex can be prevented by the metal-chelating property of green tea, which causes a disturbance of copper activity[27] (Figure 2). The chelating property towards heavy metals has proved to be useful in the management of heavy metal-induced oxidative stress[27].

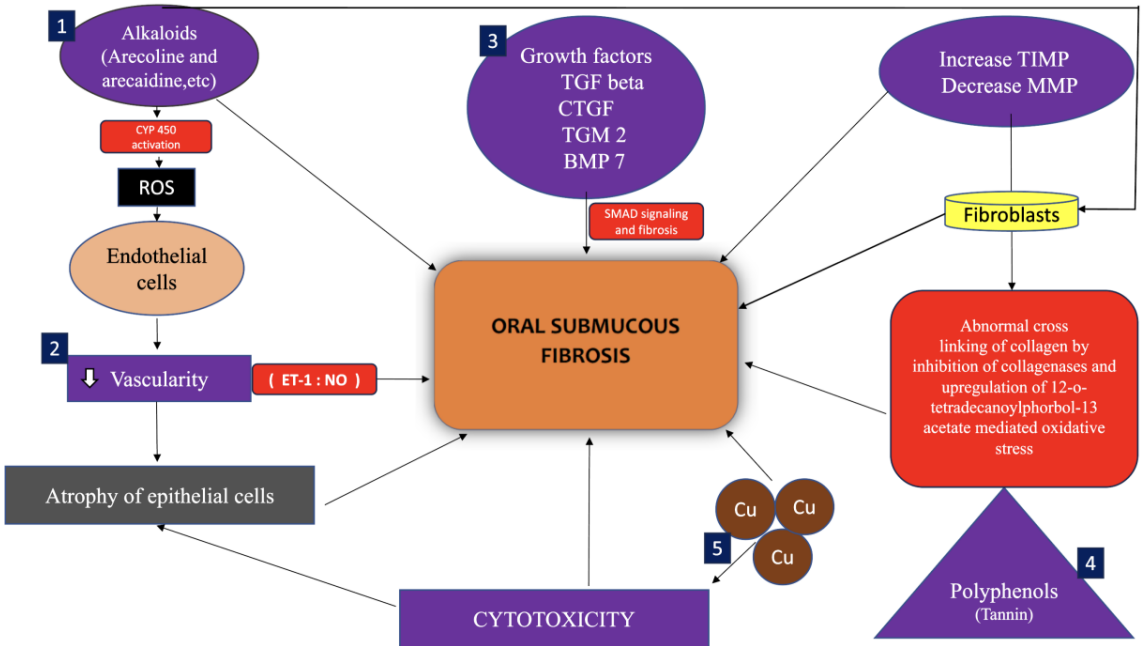

Figure 1: Etiopathogenesis of OSMF at molecular level.

(CYP 459- Cytochrome P450; ROS- reactive oxygen species; ET1- Endothelin, NO- Nitric oxide; (TGF)Transforming growth factor-β, CTGF- connective tissue growth factor, TGM-Transglutaminase 2; BMP- Bone morphogenetic protein; TIMP- Tissue Inhibitor of Metalloprotease, MMP- Matrix Metalloprotease, Cu-copper)

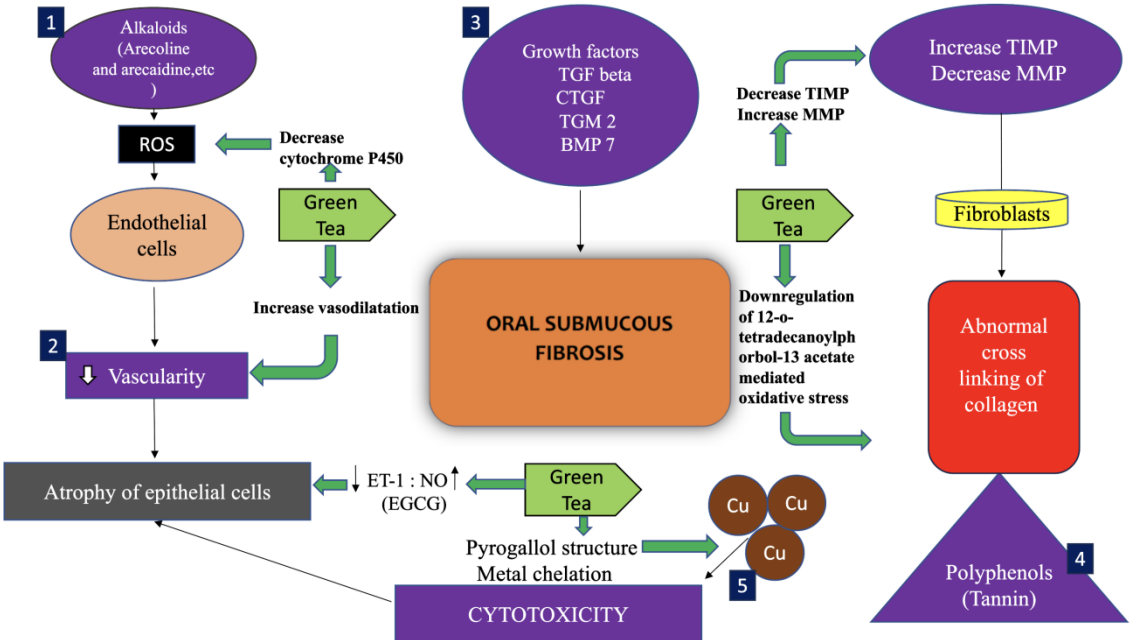

Figure 2: Illustration of pathways affected by Matcha Green Tea

(CYP 459- Cytochrome P450; ROS- reactive oxygen species; ET1- Endothelin, NO- Nitric oxide; (TGF)Transforming growth factor-β, CTGF- connective tissue growth factor, TGM-Transglutaminase 2; BMP- Bone morphogenetic protein; TIMP- Tissue Inhibitor of Metalloprotease, MMP- Matrix Metalloprotease, Cu-copper)

CONCLUSION

High concentrations of compounds with antioxidant and anti-inflammatory properties can be found in MGT. Because of its high polyphenolic content, it offers promising prospective health advantages. The data gathered from the literature suggests its possible beneficial effect in treating OSMF and preventing malignant transformation. Further, research is required to rule out other targets affected by MGT in the pathogenesis of OSMF, and clinical trials should be undertaken to rule out the best results in terms of efficacy.

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