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Original Article

ACHIEVABLE THERAPEUTIC EFFECTS OF MYRISTICA FRAGRANS (NUTMEG) ON PERIODONTITIS A SHORT REVIEW

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ABSTRACT

Myristica fragrans, commonly known as nutmeg has been used as a spice and flavouring agent in the food industry and domestic use since ages. It has also shown to have many medicinal properties due to the complex structural molecules present in it. Its role however in periodontal diseases has not been reported to the best of our knowledge. Periodontitis is an inflammatory disease affecting periodontium - the supporting structures of the teeth. It is caused by alterations in the oral microbial flora to pathogenic microorganisms followed by a cascade of events that cause inflammation, oxidation and collagenolysis leading to the destruction of periodontium. This review aims to relate the possible role of Myristica fragrans in the adjunctive treatment of periodontitis.

Keywords: *Myristica fragrans*, Nutmeg, Herbal remedies for gum diseases, Periodontitis.

INTRODUCTION

Periodontitis is an inflammation of periodontium - the supporting tissues of the teeth [1]. It is caused by infection with various putative periodontal pathogens, which may damage host periodontal tissue itself or may initiate immunological cascades, resulting in periodontal attachment loss [2]. The goal of periodontal therapy is to prevent, arrest, control or eliminate periodontitis, thereby to restore the lost form and function of the periodontium, as well as to maintain the oral aesthetics [3]. Various therapeutic attempts have been made for the treatment of periodontitis through systemic and locally delivered drugs with or without surgical therapy. Periodontitis is a complex interplay of various microcellular and macromolecular phenomena, starting from microbial accumulation and invasion of the periodontium to the host responses, which occur by the release of pro-inflammatory cytokines, prostanoids, Matrix-Metaloproteinases and reactive oxygen species. This review article mainly focuses on the possible anti-bacterial, anti-inflammatory, anti-collagenolytic and anti-oxidant effects of nutmeg on the gingiva and the periodontium. *Myristica fragrans* commonly known as nutmeg belongs to the kingdom: Plantae as Angiosperms, order: Magnoliales, family: Myristicaceae and genus: Myrstica. It is most commonly grown in the Banda Island in Moluccas of Indonesia, Penang island of

Fig. 1: Generalised chronic periodontitis.

MYRISTICA FRAGRANS

Malaysia, West Indies and Kerala state of India. The tree is about 25 feet high which does not bloom till it is nine years old, when it fruits; it continues to do so without attention. *Myristica fragrans* has four parts - The skin, the fruit, the seed and the mace. Fruit is a pendulous, succulent pericarp, the mace arillus covering the hard endocarp, and a wrinkled kernel with ruminated endosperm. When the arillus is fresh it is a brilliant scarlet, when dry it is more of a horny, brittle texture, and a yellowish brown colour. The seed of nutmeg is firm, fleshy, whitish, traversed by reddish brown veins, abounding in oil. Skin, pulp, mace and seed have been widely used in traditional Ayurvedic, Chinese and Thai medicine [4].

Fig. 2: Nutmeg fruit (top), dried mace (bottom left), nutmeg seed (bottom right)

The major constituents in the essential oil of nutmeg contain myristicin, elemicin, safrole and sabenene which comprise 80% of the oils [5]. Gas chromatographic analysis of nutmeg by Gopalakrishnan in 1992 showed that α-pinene, β-pinene and sabinene constituted 77.38% and 60.76% in nutmeg and mace oil respectively [6]. Other constituents present in lesser quantities are limonene (4%), γ-terpinene (3.9% in nutmeg oil and 6.6% in mace

oil), terpinolene (3.3% in mace oil), terpinene-4-ol (7.2% in nutmeg oil and 23.6% in mace oil), methyl euginol (3.7% in mace oil) [7].

Anti-microbial effect

The beginning of periodontal diseases occurs by accumulation of microorganisms in the form of an adherent plaque. The enamel is coated with a thin conditioning film called as pellicle which is formed by the deposition of hydrophobic macromolecules of saliva. The pellicle provides room for the attachment of the bacteria. Gram positive bacteria begin to accumulate into a mass and are called early colonizers. *Actinomyces viscosus* and *Porphyromonas gingivalis* adhere through fimbriae on the bacterial surface to proline rich proteins found on the saliva coated tooth surfaces [8,9]. Adherence of *A. Viscosus* occurs through surface fimbriae to a polysaccharide receptor on the cells of *Streptococcus sanguis* [10]. *Porphyromonas gingivalis*, a gram negative, black pigmented anaerobe has been strongly implicated in the etiology of periodontal disease [11]. An arginine specific cystein protease Arg-gingipain (gingipain R, EC3.4.22.37) is one of the major proteases produced by *P. Gingivalis* [12,13]. Chikara Shinohara et al determined that malabaricone C isolated from nutmeg irreversibly inhibited Arg-gingipain by 50% at a concentration of 0.7 µg/ml and selectively suppressed *Porphyromonas gingivalis* growth [14]. An in vitro study by Yanti et al determined that at 24 hours of biofilm growth, *S. mutans*, *A. viscosus* and *S. sanguis* biofilms were reduced by up to 30%, 30% and 38% respectively after treatment with micro g/mL macelignan isolated from nutmeg for 5 min [15]. Zaleha Shafiei et al showed a significant decrease in the bacterial concentration of *Aggregatobacter actinimycetemcomitans* and *Porphyromonas gingivalis* with the ethyl acetate and ethanol extracts of flesh, seed and mace of *Myristica fragrans* as determined by minimum bacterial concentration and minimum inhibitory concentration [16]. Hence, *Myristica fragrans* can potentially be used as a natural anti-microbial agent in oral care products and thereby mitigates systemic toxicity and bacterial resistance otherwise caused by standard synthetic antibacterial drugs.

Anti-oxidant effect

Periodontitis has a bacterial etiology that causes destruction of the connective tissue and the bone. As a result of stimulation by bacterial antigen PMN produces free radicals via respiratory burst as a part of the host response to infection [17]. These endogenously generated free radical cause damage by a variety of different mechanisms which include DNA damage, lipid peroxidation, protein damage, oxidation of enzymes (e.g. anti-protease) and stimulation of pro-inflammatory cytokines release [17]. Reactive oxygen species (ROS) are not true free radicals but they are capable of producing a number of free radical moeties in the intra- and extra- cellular environment, viz. hydrogen peroxide, hypochlorous acid, ozone, singlet oxygen.

It has been reported that the total phenolic content and anti-oxidant potential of a product has a significant and positive correlation [18]. Nutmeg is rich in phenolic constituents, and determined by the FRAP (ferric reducing antioxidant power) and TEAC (trolox equivalnt antioxidant capacity), it demonstrated good anti-oxidant capacity with the highest level found in the seed and inconsistently in the skin, pulp [19]. Anti-oxidant property of nutmeg is contributed by various phytochemicals, mainly vitamins, carotenoids, terpenoids, alkaloids, flavonoids, lignans, simple phenols and phenolic acids [19]. According to Shan et al., the high anti-oxidant activity in nutmeg seed was contributed by caffic acid and catechin [20]. Water extract of *Myristica fragrans* scavanged free radicals better than BHA (butylated hydroxyanisole) but worse than BHT (butylated hydroxytoluene) taken as standards [21]. DPPH radical scavenging activity, chelation activity on Fe^{2+} and β-Carotene bleaching activity of various parts of nutmeg have also been reported [22]. Nutmeg can thus be used as a potential anti-oxidant agent in periodontitis as an adjunct to the routine treatment protocols. Oral administration of aqueous extract of nutmeg inhibited isoprotenol induced changes in the plasma levels of hepatic markers, myocardial levels of anti-oxidant enzymes and peroxidation levels of lipids in rats [23].

It has been reported that upon excessive drying, anti-oxidant activity decreases significantly which could be attributed to the interaction of oxidised phenolics or free phenols with the cellular polyaccharides upon drying; this reinforces the significance of using fresh spices [24].

Anti-inflammatory effect

Inflammation, which is the host response to tissue injury or insult, plays a central role in the pathogenesis of periodontal diseases. Neutrophils act as the first line of defence followed by the monocytes/ macrophages, T cells and B cells. Once they are activated, they produce inflammatory mediators such as anaphylotoxins of the complement cascade, kinins of the coagulation system, leukotrienes, prostaglandins and neuropeptides. Various pro-inflammatory cytokines have been implicated in the destruction of periodontium. Cytokines responsible for early responses are IL-1α, IL-1β, IL-6 and TNF-α [25]. Other pro-inflammatory mediators include leukemia inhibiting factor (LIF), IFN-γ, oncostatin M (OCM), ciliary neurotrophic factor (CNTF), transforming growth factor beta (TGF-β), IL-11, IL-12, IL-17, IL-18, IL-8 and a variety of other chemokines that attract inflammatory cells [26-31]. In the inflammatory process there is also the expression of cellular adhesion molecules, such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) [32].

The essential oil of nutmeg contains limonene, β-pinene, α-pinene and sabinene which are known 5-lipoxygenase inhibitors [33]. Limonene also is a COX-2 selective inhibitor having significant inhibitory effects on PGE_2 production [34]. Terpene-4-ol which is 7.2% in seed oil and 23.6% in mace oil suppresses the production of TNF-α and IL-1β, IL-8, IL-10 and PGE_2 [7,35]. α-pinene was able to reduce pro-inflammatory IL-6 production in mouse colon but does not suppress IL-1β [36]. Sabinene, euginol, α-pinene inhibits TNF-α production [32]. Sabinene also inhibits IL-1β and IL-6 [33]. A study by Morita et al, among 21 spices, only myristicin - the major component of nutmeg oil - presented a potent hepatoprotective activity due to the inhibition of TNF-α release from macrophages [37].

Hence, as *Myristica fragrans* is known to show anti-inflammatory property, it could be used in patients with periodontitis as a supportive therapy.

Anti- collagenolytic activity

The principle structural component of periodontal connective tissues is collagen which is an important group of multifunctional proteins of the extracellular matrix that participate in many biologic events. Although, degradation and resynthesis of collagen and other matrix elements are the key components of normal tissue remodelling including that of the periodontium, yet undeterred degradation of collagen and extracellular matrix would contribute greatly to the pathogenesis during the course of inflammatory diseases such as periodontal diseases. Collagenases appear to be key initiators of connective tissue breakdown and are augmented by matrix metalloproteinases (MMPs), interstitial collagenases, type IV collagenases, gelatinases etc. generated by the host.

It has been suggested that PMNs provide the major source of collagenase that mediates tissue breakdown during inflammatory periodontal disease whereas fibroblasts contribute the collagenase required for connective tissue remodelling in normal gingiva [38].

Tetracyclines possess the ability to inhibit pathologic collagenolysis by blocking mammalian collagenases and other matrix degrading metalloproteinases by binding to the matrix degrading metal ions in the enzyme, possibly to Ca^{2+} but more likely to Zn^{2+}[39].

The MMPs of significance in periodontal disease are MMP-1 (fibroblast collagenase), MMP-8 (neutrophill collagenase), MMP-9 (from gellatinase granules) and MMP-13.

A study by Lee et al indicates that macelignan isolated from Myristica fragrans regulates the expression of MMP-1 and type I procollagen in UV-irradiated human skin fibroblasts [40]. Macelignan has also shown to inhibit MMP-9 expression [41].

Myristica fragrans can thus be used as an anti-collagenolytic agent, although further studies need to be carried out to evaluate the expression of MMPs in periodontitis.

Adverse effects and Toxicity

In low doses, nutmeg produces no noticeable physiological or neurological response, but in large doses, raw nutmeg has psychoactive effects. In its freshly ground form (from whole nutmegs), nutmeg contains myristicin, a monoamine oxidase inhibitor and psychoactive substance [42]. Myristicin poisoning can induce convulsions, palpitations, nausea, eventual dehydration, and generalized body pain [43].

In human beings 6-7 mg/kg body weight of nutmeg is enough to cause psycho pharmacological effects. Ingestion of 5 gram of nutmeg corresponding to 1-2 mg myristicin/ kg body weight has been shown to cause intoxication [44].

Nutmeg was once considered an abortifacient, but may be safe for culinary use during pregnancy. However, it inhibits prostaglandin production and contains hallucinogens that may affect the foetus if consumed in large quantities [45].

Nutmeg has also shown to possess aphrodisiac property on administration of 50% ethanolic extracts of nutmeg on male mice [46].

CONCLUSION

Nutmeg possesses medicinal properties that are anti-bacterial, anti-inflammatory, anti-oxidant and anti-collaginolytic in effect. These are the properties that are required for a successful treatment of periodontitis. Nutmeg, in proper doses therefore, can be used as an adjunctive treatment of periodontitis. Further studies are however required to prove its clinical efficacy for the treatment of periodontitis.

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Conflict of Interest

The authors do not have any conflict of interests regarding this article.

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