# Potential of clove of *Syzygium aromaticum* in development of a therapeutic agent for periodontal disease. A review

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## SUMMARY

**Introduction:** Clove (*Syzygium aromaticum*) is a plant-derived spice that has been traditionally used as a natural medicine for the treatment for various ailments including dental diseases.

**Aim and objective:** To present a comprehensive report on the properties of clove based on an analysis of contemporary scientific and professional literature in order to explore the prospects for its application in the treatment of plaque-induced periodontal diseases.

**Methods:** An online search was performed in PubMed and Google Scholar using a combination of key words which included clove buds, clove essential oil, eugenol, *Eugenia caryophyllata*, spices, medicinal plant, chemical composition, biological effect, therapeutic use, anti-bacterial, anti-fungal, anti-viral, anti-oxidant, anti-inflammatory, anaesthetic, periodontal, dental, and periodontitis.

**Results:** *In vitro* studies have shown *Syzygium aromaticum* to have bacteriostatic, bactericidal, anti-viral, anti-mycotic, anti-oxidant, anti-carcinogenic, anaesthetic and analgesic properties. Clove oil has a specific anti- inflammatory property as it inhibits the cyclo-oxygenase-2 and lipo-oxygenase enzymes.

**Conclusion:** Clove and its derivatives have a definite potential to be used as specific anti-plaque and anti-inflammatory agents for the treatment of periodontal disease. Future research should concentrate on designing new formulations based on clove derivatives in the form of local drug delivery system or topical agents for the treatment of periodontal diseases.


**Keywords:** *Syzygium aromaticum*; periodontitis; biofilm; non-surgical periodontal therapy


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## ACRONYMS

| | |
|---|---|
| **BHT:** | butylated hydroxyl toluene |
| **DPPH:** | diphenyl-p-picryl hydrazyl |
| **FRAP:** | ferric reducing/ antioxidant power |
| **LPO:** | LOX-catalysed lipid peroxidation |
| **MIC:** | minimum inhibitory concentration |
| **ROS:** | reactive oxygen species |

## INTRODUCTION

Periodontitis is a multifactorial inflammatory disease process that leads to the destruction of the tissues supporting the teeth.[1] The presence of bacterial plaque is the main etiologic factor involved in the initiation and progression of periodontitis and is related to gingival crevice colonization by microorganisms such as *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, and Treponema denticola*.[1,2] These bacteria elicit an immune response that results in periodontal breakdown, causing destruction of soft tissues and bone. The primary goal of periodontal therapy is to remove periodontal pathogens by providing patients with adequate oral hygiene methods combined with professional mechanical plaque control.[3] However, this conventional treatment strategy is not always successful and the addition of chemical agents as an adjunct has been suggested to enhance efficacy in achieving better oral health.[4] Another line of treatment involves modulating the host responses.[5] Chemotherapeutic agents have been used commonly as adjuncts but increasing incidence of failure and the development of resistance to conventional antibiotics has led to the screening of several medicinal plants for their potential antimicrobial activity and host modulating effects.[6]

Down the ages natural products such as essential oils and other extracts of plants have evoked interest in their possible application in the treatment of oral diseases.[7-9] Natural plant products represent a significant source of substances for managing plaque-related diseases such as gingivitis and periodontitis.[8,9] The World Health Organization observed that the use of traditional medicine for pri-

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mary healthcare is more popular in many populations than hospital-based conventional care.[10] Many spices possess medicinal properties and their use in traditional systems of medicine has been on record for a long time.[11]

Clove is a spice obtained from the dried flower bud of the clove tree, *Eugenia caryophyllata* Thunb. (syn. *Syzygium aromaticum*, *Eugenia aromaticum*, Family: *Myrtaceae*).[11] Clove has a nail-like appearance and is known by different names in different languages, such as Dutch (nagel), Spanish (clavo) and Portugese (cravo). They vary in length from about ½ to ¾ inch and contain 14-20% essential oil.[11] Clove oil is extracted from the buds, leaves or stems of the tree *Syzygium aromaticum* by steam or water distillation. Traditionally clove leaf oil has been used to treat burns and cuts and even in dental care for alleviating tooth ache and infection.[12] Clove has been shown to be effective against bacteria associated with dental caries and periodontal disease as well as against a large number of other bacteria.[13] In addition, studies have reported anti-fungal, anti-carcinogenic, anti-allergic and anti-mutagenic activity of *Syzygium aromaticum*.[12,14] Eugenol, the primary component of clove oil, displays antioxidant and anti- inflammatory properties.[11,15] The aim of this review is to explore the pharmacological effects of clove and its active components in order to identify the potential for the development of a therapeutic agent in treating periodontal disease.

## SEARCH STRATEGY

MEDLINE/PubMed (National Library of Medicine, Bethesda, Maryland) and Google-Scholar was searched for appropriate articles using the following keywords in various combinations: ''clove'', ''*Syzygium aromaticum*'', ''eugenol'', ''clove essential oil'', ''*Eugenia caryophyllata*'', ''spices'', ''medicinal plant'', ''herbal medicine'' "chemical composition", "biological effect", "therapeutic use", "anti-oxidant", "anti-inflammatory", "anti-bacterial", "anti-viral", "anti-mycotic". "periodontal", "periodontitis" and "dental". All articles on human, animal, *in vitro* and *in vivo* studies and reviews published in English were selected. Preference was given to articles that described the composition, pharmacological effects and toxicity of clove. Titles and abstracts of articles that satisfied the eligibility criteria were screened and checked for agreement. The full text of the articles judged by title and abstract to be relevant were read and independently assessed by two reviewers (SJP and SN).

## HISTORY OF *SYZYGIUM AROMATICUM*

The West Indies, Madagascar, Tanzania and Zanzibar are major producers of clove. However, Asian countries such as Indonesia, India, Malaysia and Sri Lanka produce clove in greater quantities.[16] Clove has been used as a spice and fragrance for more than 2,000 years in China. Since ancient times clove has been used to treat medical conditions like dyspepsia, acute or chronic gastritis and diarrhoea.[11,12,14] Clove oil was used medicinally in France for the first time(1640), as a remedy for treating toothache and was documented in 'Practice of Physic'.[17] Kim *et al*.[18] used it for the treatment of asthma and various allergic disorders by oral administration. In the food industry clove oil or its extract has found use as a flavouring agent in whisky, ice cream, baked goods, candy and mouthwashes.[12,19] Clove has been used in clinical dentistry in root canal therapy, surgical dressings, pulp capping agents, cavity liners and in temporary fillings.[13, 20]

## COMPONENTS OF CLOVE

Three essential oils are available from clove spices: clove bud oil, clove stem oil and clove leaf oil. Each has a different chemical composition and flavour. The major components of clove oil are eugenol, β-caryophyllene, eugenol acetate and in lesser amounts, benzyl alcohol, chavicol, acetyl salicylate and humulenes.[14, 21] All the active agents which may be extracted are described in Table 1.

Chaieb, Hajlaoui, Zmantar *et al*.[14] isolated clove essential oil by hydro-distillation using gas chromatography- mass spectrometry (GC-MS) analysis. The chemical analysis resulted in the identification of 36 components, with a high concentration of eugenol (88.58%), eugenol acetate (5.62%), β-caryophyllene (1.39%), 2-heptanone (0.93%), ethyl hexanoate (0.66%), humulenol (0.27%), α-humulene (0.19%), calacorene (0.11%) and calamenene (0.10%). Eugenol (4-allyl-1-hydroxy-2-methoxybenzene), a phenolic non-nutrient compound, is one of the major components with a molecular weight of 164.20. β-caryophyllene, the other major constituent of clove oil has a molecular weight of 204.35. Similar results were also observed by Lee and Shibamato.[20] The reported proportions of each constituent vary widely. Prashar, Locke and Evans *et al*.[22] found the content of eugenol to be 78%, with 13% β-caryophyllene, whereas Pawar and Thaker[23] found that the content of eugenol was 47.64%, with the concentration of benzyl alcohol at 34.10%. Alma, Ertas, Nitz *et al*.[21]

**Table 1:** Composition and percentage of clove essential oil obtained with GS-MS analysis.

| Sno | Compound | Percentage |
|---|---|---|
| 1. | 2-Heptanone | 0.93232 |
| 2. | Ethyl hexanoate | 0.66098 |
| 3. | β-Caryophyllene | 1.38830 |
| 4. | α-Humulene | 0.19985 |
| 5. | Calamenene | 0.10538 |
| 6. | Calacorene | 0.11437 |
| 7. | Eugenol | 88.58535 |
| 8. | Eugenyl acetate | 5.62086 |
| 9. | Humulenol | 0.27527 |
| 10. | α-pinene | 0.04 |
| 11. | p-cymene | 0.01 |
| 12. | limonene | 0.01 |
| 13. | 2-Heptyl cetate | 0.04 |
| 14. | (E)-β-Ocimene | 0.33 |
| 15. | 2-Nonaone | 0.02 |
| 16. | Lanalool | 0.01 |
| 17. | Methyl salicylate | 0.07 |
| 18. | p-Allyl phenol | 0.19 |
| 19. | A-Copaene | 0.10 |
| 20. | Δ-Cadinene | 0.04 |
| 21. | Caryophyllene oxide | 0.02 |

found the composition to include eugenol (87%), eugenol acetate (8.01%) and β-caryophyllene (3.56%).

## PHARMACOLOGICAL EFFECTS OF CLOVE

### Antibacterial activity

Natural remedies have been used for a long time for the treatment of various bacterial infections. In the recent practice of medicine, the misuse of antibiotics has led to the development of bacterial resistance. Therefore there is a need for identifying novel antibacterial agents against which there is minimal or no bacterial resistance. Studies on clove oil or its extract may contribute to the development of novel antimicrobial agents to offset the effects of resistance to antibiotics. Essential oils have anti-quorum sensing activity which might be important in reducing the virulence and pathogenicity of drug-resistant bacteria.[24,25] (Quorum sensing is a means of bacterial intercellular communication. Anti-quorum sensing interrupts that process). A combination therapy of clove with antibiotics could be another method of overcoming bacterial resistance.

Several studies have shown the effectiveness of clove against numerous strains of bacteria.[26-35] Clove oil and eucalyptus oil exhibited antibacterial properties against the most common oral pathogen *S. Mutans*.[27-29] Cai and Wu[13] showed preferential growth-inhibition activity of a crude extract of clove against the gram-negative oral pathogens: *Porphyromonas gingivalis, Streptococcus mutans, Actinomyces viscosus and Prevotella intermedia*. Several other studies have confirmed the *in vitro* antibacterial activity of clove against gram negative bacteria like *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Campylobacter jejuni*, and *Salmonella enteritidis*, and gram-positive bacteria like *Bacillus subtilis* and *Staphylococcus aureus*.[30-35] Duraipandiyan, Ayyanar and Ignacimuthu.[36] observed antibacterial activity against *Bacillus subtilis*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Escherichia coli*, *Ervinia sp*, and *Proteus vulgaris*. Clove oil exhibited antibacterial activity against five strains of *S. epidermidis* (reference strains CIP106510, E13, S27, S23 and S38) which is mainly attributed to the presence of eugenol,[12] extracts of which have shown antibacterial activity against *Salmonella typhi*.[37] Clove oils protects against bacterial colonization of the lungs, seen *in vitro* and in mice infected with *Klebsiella pneumoniae*.[38, 39] Mytle, Anderson, Doyle, *et al*.[40] reported that the growth rates of *Listeria monocytogenes* strains were significantly reduced by treatment with 1% and 2% clove oil. Furthermore Ogunwande, Olawore, Ekundayo *et al*.[41] found that the essential oil of the fruit exhibited antibacterial activity against *Staphylococcus aureus*, while the leaf oil inhibited the growth of Bacillus cereus, with an MIC of 39mg/mL. Hospital-acquired infections are important due to presence of methicillin-resistant *Staphylococcus aureus* (MRSA) and its ability to cause severe soft tissue, bone or implant infections.[42] Clove proved to be beneficial against Staphylococcus strains including MRSA and Streptococcus strains.[43,44] The antibacterial property of clove is due to the damaging effect it has on the bacterial cell membrane.[37]

Several authors have investigated the synergistic interaction of clove oil molecule together with a conventional antibiotic.[45-47] Time - kill studies have been used to evaluate the effect of interaction between eugenol together with ampicillin and with gentamicin. The hydrophilic antibiotics such as vancomycin and β-lactam antibiotics have a marginal activity on gram negative bacteria but exhibit enhanced antibacterial activity when pre-treated with eugenol.[12,46] This synergistic effect could be explained by the fact that eugenol is able to damage the membrane of bacteria allowing increased penetration of vancomycin and β-lactam antibiotics and therefore effecting a greater antimicrobial effect.[46] In a recent study Moon, Kim and Cha[45] assessed the inhibitory effects of a combination of eugenol and antibiotics on cariogenic and periodonto-pathogenic bacteria. Although eugenol is effective against both gram-positive and gram-negative microorganisms, contrasting results were found in other studies.[48,49] Clove was found to be less effective when compared with cinnamon oil.[49]

No clinical studies were identified which had evaluated the effect of eugenol or any of clove extracts on periodonto-pathogenic microorganism.

### Anti- Inflammatory activity

Bacteria are responsible for the initiation of periodontal disease, but it is the host immune-inflammatory response which is responsible for the progression of the disease and destruction of the periodontal attachment. One of the pathways is through the synthesis and release of prostaglandin and other arachidonic acid metabolites locally within the periodontal tissue. Tissue damage leads to the production of free arachidonic acid, which is further metabolized via either the cycloxygenase (COX) pathway to the prostaglandin ($PGE_2$), prostacyclin and thrombaxane or the lipoxygenase (LOX) pathway to the leukotrienes. Therefore it is recognised that potential COX and leukotrienes inhibitors be considered as anti-inflammatory agents.

Few authors have investigated eugenol and acetyl eugenol for potential anti-inflammatory action on COX-2 and LOX enzymes.[50,51] Eugenol appeared to directly inhibit COX-2 enzyme activity, possibly through complete inhibition of $PGE_2$, suppression of the nuclear factor kappa B (NF-κB) pathway and inhibition of interleukin (IL) - 6 production.[52] Bachlega, de Sousa, Bastos *et al*.[53] demonstrated immune-modulatory and anti-inflammatory effects of clove, as it inhibited production of IL-1β, IL-6 and IL-10. Likewise, Thompson and Eling[54] demonstrated that eugenol inhibited prostaglandin H synthase activity. Similarly Raghavendra, Diwakr, Lokesh *et al*.[55] observed in human polymorphonuclear leucocytes that eugenol effectively inhibited the LOX enzyme in a non-competitive nature. Naidu[56] demonstrated concentration-dependent inhibition of LOX-catalysed lipid peroxidation (LPO) by eugenol. Though no clinical studies have been done, Koh, Murakami, Tanaka *et al*.[57] found that eugenol exhibits potent anti-inflammatory effects on cultured human gingival fibroblasts.

### Antioxidant property

The reactive oxygen species (ROS) produced by our body are responsible for tissue damage and cell death and can inhibit normal function of cellular lipids, proteins, DNA and RNA. This can lead to many chronic diseases such as heart disease, cancer and even periodontitis.58 Clove has been identified as a potent anti-oxidant. Antioxidant activity of clove might be due to the higher concentration of phenolic compounds such as eugenol (71.56%), eugenol acetate

(8.99 %) and thymol.[59,60] The antioxidant activity of clove extract was comparable to that of the natural antioxidant, α-tocopherol (vitamin E) and butylated hydroxyl toluene (BHT).[20,61,62] *Syzygium aromaticum* derivatives can prevent injury by ROS by scavenging free radicals, by chelation of transition metal ions, by inhibition of oxidant enzymes or by regeneration of α-tocopherol from α-tocopheroxyl radical.[12,14,59,60]

**Table 2:** Pharmacological effects of clove for dental application.

| Activity studied | Effect | Reference |
|---|---|---|
| Antibacterial | • Effective against gram positive and gram negative bacteria. | 13, 26-29 |
| Anti-inflammatory | • Cytokine inhibition<br>• Suppression of the NF-κB pathway | 50-53 |
| Antioxidant | • Suppresses LPO<br>• Reactive oxygen scavenging activity<br>• DPPH scavenging activity<br>• Hydroxyl radical scavenging activity | 59-62 |
| Antifungal | • Effective against *Candida albicans* | 68-70, 77, 79 |
| Antiviral | • Effective against HSV 1 and HSV 2 | 80, 81 |
| Analgesics | • Anti-nociceptive effect | 83-85 |
| Anaesthetic | • Local anaesthesia | 86-88 |

The anti-oxidant capacity of clove was present when measured by the metal chelating activity, by bleomycin dependant DNA oxidation, by diphenyl-p-picryl hydrazyl (DPPH) radical scavenging activity and by the ferric reducing antioxidant power (FRAP).[59,60] *Syzygium aromaticum* showed the highest antioxidant activity among 19 different extracts from Thai medicinal plants.[63] Cloves showed the highest DPPH radical scavenging activity (90%), highest FRAP values, high metal chelation ability and DNA oxidation among different spices.[59,60] Clove also showed increased ability to inhibit metal-ion induced LPO.[59,60] Some of the earlier *in vitro* studies have demonstrated that flavonoids can scavenge $O_2$, OH and peroxyl radicals, and inhibit LPO in different systems.64-66 High DPPH scavenging activity as well as $O_2$ radical scavenging activity and metal chelating activity may be responsible for the marked antioxidant action of cloves. Thus the antioxidant properties of spices may be attributed to various mechanisms, which include prevention of chain initiation, chelation of transition metal ion catalysts, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging activity.[59]

The effect of eugenol is concentration dependant. At low concentrations it has anti-oxidant and anti-inflammatory effects, whereas at high concentrations it acts as a pro-oxidant, leading to tissue damage resulting from the enhanced generation of free radicals.[12,60] Clove exhibited a higher bleomycin-dependent DNA oxidation activity indicating a pro-oxidant effect.[60] Clove oil thus shows a powerful antioxidant activity, and can be used as an easily accessible source of natural antioxidants in pharmaceutical applications. No direct studies on periodontal cells or markers have been done to elucidate the effect of clove extracts as an anti-oxidant.

## Antifungal activity

Clove possesses fungicidal characteristics *in vitro* and *in vivo* due to its phenolic components, carvacrol and eugenol.[67,68] The potential drawback in the treatment of fungal diseases is the possibility of the development of antimicrobial resistance. Combination therapy with clove could form an alternative treatment method especially in treating fluconazole-resistant or multi-drug resistant fungal diseases. Studies have shown synergistic interaction with the use of eugenol and/or methyl-eugenol or either in combination with fluconazole or amphotericin B.[69]

Antifungal activity has been seen against *Candida albicans* and *Trichophyton mentagrophytes*,[70,71] *Onychomycosis*,[72] *Saccharomyces cerevisiae*,[73] *E. Caryophyllata*[74] and *Aspergillus niger*.[75] The antifungal activity is due to considerable reduction in the quantity of ergosterol, a specific fungal cell membrane component.[76] Eugenol displayed *in vitro* activity against *C. albicans* cells within biofilms.[77] Garg and Singh[78] conducted an experiment using eugenol-loaded lipid nanoparticles in immunosuppressed rats and showed significant improvements in the eugenol-treated site. Similarly eugenol exhibited the minimum inhibitory concentration (MIC) ranging from 0.06 to 0.25% (v/v) and minimum concentration of drug that inhibited 50% of the isolates (defined as MIC50) ranging from 0.06 to 0.12% (v/v) when tested against 38 strains of Candida species from denture wearers and 10 collection strains.[79]

## Antiviral activity

Viruses are highly sensitive to the components of essential oils. The antiviral activity of eugenol has been tested against the herpes simplex-1 (HSV-1) and HSV-2 viruses.[80,81] Hussein, Miyashiro, Nakamura et.al[82] found that *Syzygium aromaticum* extract was highly active at inhibiting replication of the hepatitis C virus. Synergistic interaction between acyclovir and eugenol combination has been seen.

## Analgesic activity

For many ages eugenol has been used as a natural remedy for relieving tooth pain. Similarly this technique in modern dental practice has been adopted by many clinicians, in which eugenol can act as an analgesic agent. Eugenol exhibited an analgesic effect in different experimental pain models in mice.[83,84] Kurian and co-workers[84] studied the anti-nociceptive ability of eugenol (100mg/kg) in several mouse models and found that the effect was more pronounced in the inflammatory phase than the neurogenic phase. Eugenol can, however, alleviate neuropathic pain.[84] Guenette, Beaudry, Marier *et al*.[85] in their study in male Sprague-Dawley rats, showed that eugenol, at a dose of 40mg/kg, was capable of prolonging reaction time to thermal stimuli. All these results suggested the possible use of eugenol as an analgesic agent.

## Anaesthetic activity

Eugenol is cheap and is an easily available topical anaesthetic. It is relatively user-friendly and can be used effectively in lower concentrations than other local anaesthetics.[86] It is rapidly metabolized and excreted, thus requiring no withdrawal period.[87] Eugenol shows good anaesthetic effects on inflamed pulpal tissues.[88]

## OTHER ACTIVITY OF *SYZYGIUM AROMATICUM*

### Anti-tumour activity

Clove essential oil has been reported to show anti-carcinogenic and anti-mutagenic potential.[12] To overcome the toxic effects of synthetic drugs, clove essential oil can be used to inhibit, delay, block, or reverse the initiation of and promotional events associated with carcinogenesis. Sesquiterpenes found in *Syzygium aromaticum* were investigated as potential anticarcinogenic agents.[11] Volatile oils display cytotoxic action towards the human tumour cell lines PC-3 and Hep G2 50.[14] A derivative of eugenol, dihydro-eugenol, has been shown to induce apoptosis of human cancer cells.[14] Studies have demonstrated that eugenol provides protection from chemically induced skin cancer.[89]

### Cardiovascular activity

The consumption of polyphenol-rich foods like clove can lower the risks for cardiovascular disease, arterial sclerosis and other disease related to oxidative stress.[90-92] Eugenol produces dose-dependent, reversible vasodilator responses, negative inotropic effects in heart muscle, hypotensive effects and smooth muscle relaxant effect.[93-95]

## POTENTIAL OF CLOVE (*SYZYGIUM AROMATICUM*) FOR TREATMENT OF PERIODONTAL DISEASE

Periodontal disease initiation and progression occurs as a consequence of the host response to microorganisms present in dental biofilm.[1,2] The pathogens stimulate the host response resulting in the release of harmful by-products such as cytokines and prostaglandins by leukocytes, fibroblasts or other host tissue-derived cells and enzymes. These break down extracellular matrix components, such as collagen, as well as host cell membranes, consequently leading to periodontal attachment loss and bone resorption.[2]

Host modulation therapeutic strategies are aimed at inhibition of the progression of inflammatory bone loss associated with periodontitis.[5] Although a range of biological and pharmacological activities of clove have been reported, there has been a lack of research into its therapeutic potential for destructive periodontal disease. Table 2 describes the therapeutic use of clove for dental application.

Clove exhibited antibacterial activity against gram-negative anaerobic periodontal pathogens, including *Porphyromonas gingivalis* and *Prevotella intermedia*.[13] Clove may reduce periodontal inflammation by modulation of the signalling pathway (NF-κB) and suppression of IL-6, COX-2 and TNF-α.[52-55] Besides its anti-inflammatory properties, clove also has antioxidant property.[59,60,62] It has an important property for reducing the oxidative stress which is often seen in periodontal disease. It promotes DPPH scavenging activity, hydroxyl radical scavenging and inhibits lipid peroxidation.[59-62] It exhibits antifungal activity against *Candida albicans*[68-70,77] and antiviral activity against Herpes Simplex virus (HSV) 1 and 2.[80,81] Analgesic[83-85] and anaesthetic properties[87] of clove could be a natural way of performing painless dental and oral procedures. Additionally, Karmarkar, Choudhury, Das *et al.*[96] observed that dried clove buds rich in eugenol and eugenol derivative were effective in preventing bone loss and this property would be beneficial for treating periodontal disease.

All these studies demonstrated that therapy with clove and its active components like eugenol can be beneficial for the treatment of periodontal disease as a natural anti-plaque or anti-gingivitis agent. Research has been particularly lacking in the areas of periodontal disease control. Clove can be effectively incorporated in therapeutic agents formulated against periodontal diseases in the form of mouthwashes, tooth pastes, topical agents and local drug delivery devices.

## CYTOTOXICITY OF CLOVE

Clove oil and its components are generally recognized as 'safe', but the *in vitro* study by Prashar *et al.*[22] demonstrated cytotoxic properties of both the oil and eugenol towards human fibroblasts and endothelial cells. The cytotoxicity may be a function of more than one component. Clove oil was found to be highly cytotoxic at concentrations as low as 0.03% (v/v) with up to 78% of this effect attributable to eugenol and phenolic terpene.[22] The second component β-caryophyllene did not contribute towards cytotoxicity. Localised irritation of the skin, ulcer formation, allergic contact dermatitis, tissue necrosis, reduced healing and in rare cases even anaphylactic-like shock are some the observed reactions when using dental products containing eugenol.[97] Hartnoll, Moore and Douek[17] reported severe side effects after clove oil ingestion such as hepatotoxicity, generalized seizures and disseminated intravascular coagulopathy. Further research is still required to clearly define the cytotoxic effects of clove.

## CONCLUSION

Clove has many properties which have been identified in both basic and specific disease- targeted research that could be of benefit in the treatment of periodontal disease. Yet the review shows glaring gaps in research which is specific to inflammatory periodontal disease. Eugenol, an important constituent of clove, has important anti-microbial and anti-inflammatory properties which could be harnessed and designed for the control and cure of periodontal disease. The fast developing fields of pharmaceutical and nano-technology are bound to impact on the designing of eugenol/clove extract formulations. There are opportunities wherein specific cell or tissue- targeting technology could effectively deliver the natural remedies in appropriate quantities and form. This will also negate the few cytotoxic properties of these compounds. Concerted effort is needed, as revealed by this review, to initiate investigations which could bring the findings hidden on the research benches to effective clinical use. Interdisciplinary research especially between pharmacy and clinical periodontics is seriously advocated. This paper suggests that there will be merit in the return to natural medicine for the treatment of periodontal diseases.

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