

# The Invaluable Role of Phytotherapeutic Agents in the Adjunctive Treatment of Periodontal Disease

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## ABSTRACT

Periodontal disease involves the tissues that support and surround the teeth. It is initiated by the microbial biofilms on tooth surfaces. A complex interplay between these microbial communities and the host tissue ensues resulting in tissue damage which is clinically recognized as periodontitis. Mechanical removal of these microbial deposits by scaling and root planing brings about significant improvements in clinical parameters. Antimicrobial agents have been advantageous when used as adjuncts to mechanical therapy. However, their use has also been associated with undesirable effects and increased cost of treatment. Phytotherapeutic agents may prove to be a promising alternative to these when used as an adjunct to scaling and root planing due to their manifold benefits. This review discusses the possible mechanisms by which phototherapeutic agents such as curcumin, triphala, neem, *Aloe vera*, green tea, tulsi, pomegranate, garlic, ginger, clove and cinnamon could exert a favorable effect on the periodontium when used as adjuncts in the treatment of periodontal disease.

**Key words:** Phytotherapeutic agents, periodontitis, curcumin, triphala, neem, *Aloe vera*, green tea, tulsi, pomegranate, garlic, ginger, clove, cinnamon.

## INTRODUCTION

Human beings have been plagued by gingival and periodontal disease since ancient times as established by paleopathologic studies. Various treatments were attempted, much of which included the use of phytotherapeutics. As the quest to understand and more effectively treat periodontal disease continues, there has been renewed interest in evaluating the effects of phytotherapeutic agents on the periodontium. Phytotherapy is defined as the study of the use of extracts of natural origin as medicines or health promoting agents.<sup>1</sup>

In the non-surgical treatment of periodontal disease, scaling and root planing (SRP) itself results in significant reductions in pocket probing depth (PD) and gains in clinical attachment levels (CAL). Gains of 1.5 mm or more are typically found, making

SRP the standard in the non-surgical treatment of periodontitis.<sup>2</sup>

Research has suggested that adjuncts to scaling and root planing may further improve treatment outcomes. The adjuncts commonly used include locally delivered antimicrobial agents such as minocycline, tetracycline, metronidazole, chlorhexidine, and others.<sup>2</sup> However; these agents may be associated with undesirable effects such as altered taste, staining of teeth, allergic potential, antibiotic resistance and increased costs.

Phytotherapeutic agents may prove to be a readily available, highly beneficial, cost effective alternative that can be used as an adjunct to periodontal treatment. These natural products have good patient acceptance as well as tolerance. Their usage is not associated with antibiotic resistance. The costs of these agents are relatively low,

thus making it an affordable alternative which will be beneficial especially to lower-income communities. This review discusses the possible mechanisms by which phytotherapeutic agents could function in the adjunctive treatment of periodontal disease.

### **Turmeric (Curcumin)**

Turmeric, *Curcuma longa*, often referred to as “the golden spice of India”, is a rhizomatous, perennial, herbaceous plant belonging to the ginger family, *Zingiberaceae*. Its rhizomes, fresh or dried,<sup>3</sup> have been used for their potent anti-inflammatory,<sup>4-6</sup> antioxidant,<sup>7,8</sup> antibacterial,<sup>9,10</sup> antifungal,<sup>8</sup> and wound healing properties<sup>11</sup> in addition to many others.

Turmeric contains a variety of phytochemicals.<sup>12,13</sup> However, its therapeutic effects can be attributed mainly to curcumin. Turmeric comprises of 2-5% of curcumin. It is what imparts the yellow colour to turmeric.<sup>12,13</sup>

Nuclear factor-kappa B (NF- $\kappa$ B) is an inducible transcription factor and a key signaling molecule involved in inflammatory responses. Its activation has been reported in several chronic inflammatory diseases such as inflammatory bowel disease, pancreatitis, gastritis and rheumatoid arthritis.<sup>13</sup> Activation of NF- $\kappa$ B is also associated with chronic periodontitis. Inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) or lipopolysaccharide (LPS) from periodontal pathogens, stimulate cells, resulting in the activation of NF- $\kappa$ B.<sup>14</sup>

Curcumin suppresses the activation of NF- $\kappa$ B,<sup>4</sup> thus playing a role in managing inflammation in chronic periodontitis. By inhibiting NF- $\kappa$ B, curcumin also downregulates the expression of cell adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1) and E selectin. These molecules are induced by inflammatory cytokines. Curcumin also has a repressive effect on such inflammatory cytokines namely IL-1 $\beta$ , IL-2, IL-5, IL-6,

IL-8, IL-12, IL-18, and TNF- $\beta$  which play an important role in the periodontal disease process.<sup>13</sup>

Cyclooxygenase-2 (COX-2) is an enzyme responsible for the production of prostaglandins (PGs) that are linked to inflammatory conditions including periodontitis. Curcumin decreases COX-2 expression resulting in reduced PGE<sub>2</sub> synthesis, which would otherwise negatively influence bone resorption.<sup>5</sup>

Inducible nitric oxide synthase (iNOS) is expressed in inflammatory and epithelial cells in periodontitis. Inflammatory cytokines like TNF- $\alpha$ , IL-1 $\beta$  and LPS from periodontal pathogens increase the expression of iNOS thus producing large concentrations of nitric oxide (NO) which has a detrimental effect on soft and hard tissues via a cytotoxic action.<sup>15</sup> Curcumin has been found to inhibit the upregulation of iNOS while also aiding in its degradation.<sup>7</sup> Curcumin also prevents the expression of activator protein 1 (AP-1),<sup>4</sup> a transcription factor, thereby inhibiting the expression of inflammatory cytokines, iNOS and matrix metalloproteinases (MMPs).<sup>16</sup>

Curcumin has potent antioxidant properties by scavenging superoxide anions (O<sub>2</sub><sup>-</sup>), hydroxyl radicals (OH), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), singlet oxygen and NO. The expression of cytoprotective superoxide dismutase (SOD), catalase, glutathione reductase and peroxidase is upregulated by curcumin.<sup>13</sup>

Curcumin has bacteriostatic to bactericidal antimicrobial properties against *Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Lactobacillus casei*, *Actinomyces viscosus*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Treponema denticola*.<sup>9, 17</sup> It also has antifungal properties against *Candida albicans* and *Paracoccidioides brasiliensis*.<sup>8</sup>

With the exception of *Aggregatibacter actinomycetemcomitans*, curcumin showed dose-dependent inhibition of periopathogenic bacteria *P. gingivalis*, *P.*

*intermedia*, *F. nucleatum*, and *T. denticola*. The minimum inhibitory concentration (MIC) for these organisms was within a range of 5 to 15 µg/ml of curcumin. There was no significant effect of curcumin against *A. actinomycetemcomitans* even at a concentration of 100 µg/ml.<sup>9</sup> The antibacterial actions of curcumin may be attributed to inhibition of cell division and an increase in the cell membrane permeability.<sup>13</sup>

*P. gingivalis* has a very influential role to play in the pathogenesis of periodontitis due to its virulence factors such as proteases (arg-gingipain and lys-gingipain) and fimbriae. At 20 µg/ml, curcumin inhibited arg and lys-gingipain activity by 80% and 45-55% respectively.<sup>9</sup>

Curcumin also inhibited *P. gingivalis* homotypic biofilm formation, in a dose-dependent manner, with more than 80% inhibition at 20 µg/ml. Biofilm formation with *P. gingivalis* and *Streptococcus gordonii*, an early colonizer of the dental biofilm, showed 90% inhibition at a concentration of 20 µg/ml. Curcumin may adhere to *P. gingivalis*' fimbriae, thereby preventing it from binding with streptococcal GADPH (glyceraldehyde-3-phosphate dehydrogenase). It was also suggested that curcumin may alter auto-aggregation and interaction of fimbriae with salivary proteins.<sup>9</sup> Curcumin also inhibited *S. mutans* sortase A, which is involved in anchoring *S. mutans*' surface proteins in host cells and biofilms.<sup>18</sup> This suggests that curcumin may have a role to play in the suppression of early stage dental biofilm formation. Additionally, mature multispecies biofilms, when treated by curcumin over 24 hours, exhibited reduced metabolic activity and altered extracellular matrix.<sup>19</sup>

Curcumin demonstrated synergistic antifungal and antioxidant activity with ascorbic acid against *Candida albicans*. While curcumin alone was effective against *C. albicans*, its MIC decreased 5 to 10 fold when used along with ascorbic acid. The antioxidant activity of the mixture was also

found to be greater than that of each compound alone.<sup>8</sup>

Curcumin is reportedly safe and well tolerated. No adverse effects were elicited when curcumin was administered in doses as high as 8000 mg/day, orally, for 3 months.<sup>20</sup> However, curcumin, being hydrophobic, is poorly absorbed when administered orally and undergoes extensive first-pass metabolism, with only traces of curcumin observed in blood serum. Thus it may be a worthy candidate for topical applications due to greater curcumin availability at the diseased site.<sup>11</sup>

When 1% curcumin solution was used as a subgingival irrigant, mild to moderate beneficiary effects were seen.<sup>21</sup> Curcumin based collagen sponge, with 50 mg/cm<sup>2</sup> of curcumin, when placed in periodontal pockets produced significant improvements in periodontal parameters. This formulation was said to undergo resorption in 8 to 12 weeks by enzymatic degradation.<sup>22</sup> A decoction of 20% curcumin that was used as a mouthwash, twice daily, for 21 days, was found to be comparable to chlorhexidine when used as an anti-inflammatory agent.<sup>6</sup> 1% curcumin gel, locally delivered as an adjunct to SRP, improved clinical parameters significantly and also effectively reduced periodontal pathogens *P. gingivalis*, *P. intermedia*, *F. nucleatum* and *Capnocytophaga* at test sites.<sup>10</sup>

### Triphala

Triphala meaning "three fruits" is a herbal formula consisting of equal parts of powdered dried fruit of *Emblica officinalis* (Indian gooseberry, also called Amalaki), *Terminalia chebula* (Haritaki) and *Terminalia bellerica* (Bibhitaki). *E. officinalis* is a rich source of vitamin C, carotene, nicotinic acid, riboflavin, and tannins. *T. chebula* contains tannins, anthraquinones and polyphenolic compounds. *T. bellerica* contains tannic acid and glycosides.<sup>23</sup> The components of phenolic nature contribute to the pharmacologic activity of triphala.<sup>24</sup> In

addition to numerous other beneficial properties, triphala has antimicrobial,<sup>24</sup> antioxidant,<sup>24</sup> anticollagenase<sup>25</sup> and wound healing<sup>26</sup> properties.

Triphala was found to have antibacterial action against *Streptococcus mutans*, *Staphylococcus aureus*, *Streptococcus sanguinis*, *Streptococcus salivarius* and *Lactobacillus*.<sup>24,26-28</sup> Epigallocatechin gallate (EGCG), one of the condensed tannins, present in triphala plays a major role in the antimicrobial action of triphala.<sup>26</sup> Triphala exhibited MIC and minimal bactericidal concentration (MBC) to *S. mutans* at a concentration of 50 µg/ml.<sup>24</sup> Antibacterial action was observed with both aqueous and ethanolic extracts, with increasing activity as the concentration increased. A stock solution of 1000 mg/ml which was serially diluted showed maximum effectiveness at 50% concentration.<sup>27</sup>

Triphala was found to be effective against both Methicillin Sensitive *Staphylococcus Aureus* (MSSA) and Methicillin Resistant *Staphylococcus Aureus* (MRSA) at a MIC of 7.81 mg/ml. This suggests that its antimicrobial activity is not affected by methicillin resistant mechanisms and may be through mechanisms other than that of methicillin.<sup>26</sup>

Triphala also showed prominent antiplaque action.<sup>24,28</sup> Its antiplaque efficacy, when used as a 0.6% mouthwash, was found to be similar to that of 0.1% chlorhexidine mouthwash, without the disadvantage of staining of teeth.<sup>29</sup> This antiplaque and antimicrobial effect has been proposed to be due to its tannin content. Tannic acids may be adsorbed onto the tooth hydroxyapatite or salivary mucins. Tannins may also bind to the anionic groups on bacterial cell surfaces, causing protein denaturation leading to bacterial cell death.<sup>24</sup>

The substantivity of triphala was investigated with a 10% decoction used as a mouthwash. Subjects rinsed with 50 ml of the decoction for 4 minutes. Samples collected every 2 hours indicated that

triphala had antibacterial activity for the first 3-4 hours only. Based on this evidence, the investigators suggested that using triphala mouthwash three times a day may boost its activity.<sup>30</sup>

Triphala has strong antioxidant activity. The most active antioxidant action is provided by *T. belerica* followed by *E. officinalis* and *T. chebula*. Their contents of phenolic nature scavenge free radicals, thus offering protection to cells from damage caused by these radicals. Triphala extract showed maximum free radical scavenging activity of 99.71% at a concentration of 250 µg.<sup>24</sup>

Triphala also exerts an inhibitory effect on MMPs. Collagenases are responsible for the destruction of connective tissue in periodontal disease. MMPs extracted from gingival tissue samples from patients with chronic periodontitis and treated with 1500 µg/ml of triphala demonstrated reduced MMP-9 activity of 76.7% compared to 58.7% reduction seen when treated with 300 µg/ml doxycycline.<sup>25</sup>

Enhanced proliferation of fibroblasts and collagen synthesis, maturation and crosslinking were observed in triphala treated wounds. There was an increase in type III collagen. This was attributed to the vitamin C content in triphala. Vitamin C is a co-factor in the hydroxylation of proline and lysine, a step necessary in collagen formation. Procollagen molecules that are under-hydroxylated in the absence of vitamin C are less stable and more sensitive to pepsin digestion.<sup>26</sup>

## Neem

*Azadirachta indica* is the botanical name for Neem. It is also commonly referred to as "Indian Lilac" or "Margosa". The neem tree has also been known as the "Village Pharmacy". Its flowers, fruit, seeds, leaves, bark and roots have proven to be useful due to their anti-inflammatory,<sup>31</sup> antioxidant,<sup>32</sup> antimicrobial,<sup>32</sup> and other functions.<sup>33</sup> Neem contains nimbidin, sodium nimbidate, nimbolide, nimbin, gedunin, azadirachtin, gallic acid,

epicatechin, catechin, triterpenes, quercetin flavonoids and polysaccharides which are the major contents responsible for its beneficial properties.<sup>34,31</sup>

Neem leaf extract exerts its anti-inflammatory effect by acting at different levels of the NF- $\kappa$ B pathway. At a dose of 240 $\mu$ g/ml, neem leaf extract inhibited 80% of TNF- $\alpha$  activation, thus inhibiting TNF- $\alpha$  triggered induction of NF- $\kappa$ B. Additionally after TNF- $\alpha$  induced activation of NF- $\kappa$ B, neem leaf extract further halted the binding of NF- $\kappa$ B to DNA, which is required for the proper functioning of NF- $\kappa$ B.<sup>31</sup>

Neem was found to have a dose-dependent, bacteriostatic action against *Porphyromonas gingivalis*. 5  $\mu$ M GAE (Gallic Acid Equivalents) of neem extract induced 50% growth inhibition, which was significantly higher at 10 and 20  $\mu$ M GAE. However, neem did not affect *Fusobacterium nucleatum* or the coaggregation of *P. gingivalis* and *F. nucleatum*. It was postulated that this effect was probably due to different cell surfaces in different bacterial species, possibly implying specificity of neem extract to *P. gingivalis*.<sup>32</sup>

Neem leaves are a rich source of polyphenol agents having antioxidant effects. These polyphenols avidly bind to microbial and mammalian cell surfaces, bestowing them with powerful antioxidant properties. These microorganisms, killed or alive, then provide long lasting antioxidant activity while serving as a carrier of the polyphenols. This binding of neem polyphenols to cell surfaces may be amplified by red blood corpuscles (RBCs) and salivary cationic lysozymes. Extravasated RBCs, from inflamed periodontal tissues, and salivary lysozymes function as adhesives. They are inevitably available in the oral cavity, thus substantially supplementing the antioxidant function of the bacteria-neem complex. Neutrophils may also release further cationic substances which would increase the antioxidant and anti-inflammatory effects of neem. This impressive antioxidant

activity may come as a mixed blessing. Inflammatory tissue damage due to reactive species on one hand is reduced. However catalase negative periopathogenic bacteria may be shielded against oxidants induced by inflammation or cariogenic streptococci.<sup>32</sup>

Neem twigs have been used as chewsticks referred to as “dantun”. When used properly it has the beneficial effect of mechanically disrupting plaque and increasing salivation. Some of the benefits of the chewstick can also be attributed to its antibacterial and antioxidant activity as discussed above.<sup>32</sup> Additionally the tannins in neem stick extract have been found to have bacterial aggregating properties by binding to surface associated bacterial proteins, resulting in their precipitation. This decreases the bacteria available for binding to tooth surfaces, thereby leading to reductions in the plaque mass while also facilitating their removal. These tannins also caused reductions in glucosyltransferase activity, which would affect total plaque formation.<sup>35</sup>

Clinical studies demonstrated no statistically significant differences in clinical parameters between neem leaf based mouthrinse and chlorhexidine. The mouthrinse contained 25% neem leaf extract along with saccharin and peppermint oil to mask the bitter taste of neem. Subjects rinsed with 15 ml of this solution for 30 seconds, twice a day, for 7 days. Mild burning sensation and altered taste was reported, although mild and transient.<sup>36</sup>

### ***Aloe vera***

*Aloe*, also known as the “lily of the desert”, has over 500 species of flowering succulent plants. The *Aloe* species known for its wide medicinal use is *Aloe barbadensis miller*, also commonly referred to as *Aloe vera*. The name is derived from the Arabic word “Alloeh” which means “shining bitter substance” and the Latin word “vera” meaning “true”.<sup>37</sup>

The leaf consists of a central mucilaginous part surrounded by protective peripheral bundle sheath cells. Between

these two layers lies a middle layer of latex containing the yellow, bitter sap which is rich in anthraquinones and glycosides, often used as a laxative. The parenchymal inner portion of the leaf produces a clear, tasteless and thin jelly known as *Aloe* gel. This gel is made up of glucomannans, amino acids, lipids, sterols, vitamins and 99% water.<sup>37</sup> This gel has had useful applications in the treatment of burns, bruises, insect bites, skin infections, hair loss, hemorrhoids, gastrointestinal pain and sinusitis.<sup>38</sup> *Aloe vera*'s anti-inflammatory,<sup>39, 40</sup> antioxidant,<sup>41</sup> and wound healing actions<sup>42</sup> make it potentially useful in the treatment of periodontal disease.

*Aloe vera* extract was found to inhibit inflammation to a degree that is similar to that produced by well-known anti-inflammatory drugs indomethacin and dexamethasone. Its anti-inflammatory action is produced by preventing PGE<sub>2</sub> production by an inhibitory action on the arachidonic acid pathway via cyclooxygenase inhibition.<sup>39</sup> *Aloe* extract was also found to have bradykininase activity.<sup>40</sup>

*Aloe vera* has antioxidant activity.<sup>41</sup> Hence the inactivation of protease inhibitors by reactive oxygen species is reduced. These protease inhibitors have an inhibitory effect on MMPs, thus counteracting oxidative as well as proteolytic mediated injury to tissues at the site of inflammation. This anticollagenase activity is affirmed by an increase in collagen content detected during wound healing.<sup>43</sup> Wounds treated with *Aloe vera* demonstrated increase in the granulation tissue ground substance, higher protein and DNA content, increased collagen synthesis per cell and crosslinking of proteins, and increased wound contraction resulting in accelerated wound healing.<sup>42</sup>

When *Aloe vera* gel was placed within periodontal pockets, significant improvements were seen in clinical parameters.<sup>44, 45</sup> A significant increase in SOD activity and total antioxidant activity was also observed 2 months after

periodontal pockets were treated with 80% *Aloe vera* gel.<sup>41</sup>

*Aloe vera* mouthwash reduced gingival inflammation in participants who rinsed twice daily for 90 days, with 15 ml of solution for one minute. While no adverse effects on the oral mucosa were observed, the mouthrinse was reportedly unpalatable by a few patients.<sup>46</sup> In another study, 99% *Aloe vera* juice mouthwash was compared to chlorhexidine. Volunteers rinsed with 10 ml twice daily, for 30 days. *Aloe vera* demonstrated antiplaque and antigingivitis activity that was similar to chlorhexidine.<sup>47</sup>

*Aloe vera* inner gel has been evaluated to be generally safe and nontoxic. However, the anthraquinones in *Aloe vera* whole leaf extract and latex have potential cytotoxic, mutagenic and carcinogenic properties. While hypersensitive reactions to *Aloe vera* gel has been reported, no carcinogenicity or severe adverse effects appear to be associated with the use of *Aloe vera* gel.<sup>48</sup>

### Green tea

Green tea is a well-known beverage made from the leaves and buds of the plant *Camellia sinensis*. Green tea leaves are not subject to the withering and oxidation processes used to make other teas so as to preserve its polyphenols and volatile organic compounds. These polyphenols are the active compounds in green tea. They include catechin, epicatechin, epicatechin gallate, epigallocatechin, gallic acid, epigallocatechin gallate and epigallocatechin gallate (EGCG). Green tea also contains caffeine, carotenoids, tocopherols, ascorbic acid, and minerals such as zinc, magnesium, selenium and chromium.<sup>49, 50.</sup>

Green tea has potent antioxidant properties due to its active polyphenol content. Green tea's potential anti-inflammatory action is by preventing the activation of NF- $\kappa$ B and reducing LPS induced TNF- $\alpha$  production.<sup>49</sup>

Green tea has been found to inhibit the growth of *Prevotella intermedia*, *Prevotella nigrescens* and *Porphyromonas*

*gingivalis* at MIC of 1 mg/ml.<sup>51</sup> Periopathogenic microorganism *P. gingivalis* is known to adhere to oral epithelial cells. This adherence is facilitated by the fimbriae of *P. gingivalis*. Adherence of the bacteria to epithelial cells is followed by bacterial growth, colonization and production of virulence factors which ultimately leads to tissue destruction. EGCG, epicatechin gallate and gallic acid inhibits the adherence of *P. gingivalis* to epithelial cells. It has been postulated that tea polyphenols bind to the fimbria of *P. gingivalis*, thus preventing their adherence to epithelial cells.<sup>52</sup> Green tea polyphenols also have been found to reduce the production of cytotoxic metabolites by *P. gingivalis* such as butyric acid, propionic acid and phenylacetic acid.<sup>53</sup>

MMPs produced by periopathogenic bacteria breaks down collagen of the periodontal extracellular matrix and facilitates the progression of periodontal disease. The catechin EGCG decreases MMP activity by inhibiting gene expression of MMP-2 and MMP-9 by suppressing extracellular signal regulated kinase 1 and 2 (ERK 1/2) phosphorylation. It also downregulates MMPs by inhibiting mitogen activated protein kinase (MAPK).<sup>54</sup>

A characteristic feature of periodontal disease is alveolar bone loss. This destruction is carried out by multinucleated osteoclast cells. EGCG could potentially inhibit bone resorption by reducing the number of osteoclast like cells and also by inducing osteoclastic cell death. It causes a dose dependent decrease in the number of osteoclast cells, while simultaneously having no effect on the osteoblasts cultured with it. The osteoclast cell death can be attributed to increased caspase activity, in a dose dependent manner, resulting in nuclear disintegration. Caspases are protease enzymes which play important roles in programmed cell death. EGCG also caused a reduction in size of resorption pits on dentine slices. The number of resorption pits, however, remained unchanged. This is because while

resorption pits may form as early as 2 hours, it takes approximately 4 hours for EGCG stimulation to upregulate lethal caspase activity.<sup>55</sup>

Green tea catechin impregnated strips that were placed in deep periodontal pockets after scaling resulted in reductions in pocket depths and in proportions of *P. gingivalis* and *Prevotella* species. Peptidase activity in gingival crevicular fluid also reduced.<sup>51</sup> A meta-analysis on green tea based mouthwash compared to chlorhexidine suggested that it can be considered an alternative to chlorhexidine, with no significant evidence of adverse effects.<sup>56</sup>

### Tulsi

“The Queen of Plants”, *Ocimum sanctum*, commonly known as “Holy Basil”, is known for its medicinal value in the treatment of several diseases, where various part of the plant have been used. It has antibacterial, anti-inflammatory and antioxidant properties which can be harnessed in the treatment of periodontal disease. The biologic activity of tulsi leaf extract can be attributed to its essential oils such as eugenol, caryophyllene, germacrene-A, clemene and caryophyllene oxide and phytochemicals such as ursolic acid, rosmarinic acid and oleanolic acid.<sup>57</sup>

The ursolic acid content of tulsi may be one of the major contributors of its anti-inflammatory activity. Activation of NF- $\kappa$ B by TNF- $\alpha$ , H<sub>2</sub>O<sub>2</sub> and cigarette smoke was found to be inhibited by ursolic acid. Ursolic acid prevented I $\kappa$ B $\alpha$  (inhibitor of nuclear factor kappa-B- $\alpha$ ) degradation, I $\kappa$ B $\alpha$  phosphorylation, IKK (I $\kappa$ B kinase) activation, phosphorylation of p65, nuclear translocation of p65 and NF- $\kappa$ B dependent reporter gene expression. This NF- $\kappa$ B inhibition further suppressed expression of COX-2 and MMP-9.<sup>58</sup>

When tulsi leaf extract was administered for 4 weeks, in 300 mg capsules, it set in motion an efficacious immune response when challenged by LPS. There was an increase in IL-4 levels and an

even greater increase in interferon- $\gamma$  (INF- $\gamma$ ). Significant increases in T helper cells and natural killer cells were also detected.<sup>59</sup>

The anti-inflammatory effect of 2% *O. sanctum* gel, when used in the experimental model, peaked at 24 hours, and was present even after 48 hours, which prompted the investigators to administer the gel every alternate day to treat experimental periodontitis.<sup>60</sup>

Tulsi leaf extract demonstrated antimicrobial activity against *Streptococcus mutans* and *Staphylococcus aureus* at a MIC of 125  $\mu$ g and 250  $\mu$ g and MBC of 250  $\mu$ g and 500  $\mu$ g respectively.<sup>61</sup> At 5% and 10% concentrations, tulsi leaf extract also had antibacterial action against *Aggregatibacter actinomycetemcomitans* similar to that of doxycycline.<sup>62</sup> When 10 different concentrations (1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% and 10%) of tulsi leaf extract were compared, tulsi exhibited maximum efficacy against *A. actinomycetemcomitans* at a concentration of 6%. This antimicrobial action was attributed to the membrane damaging effects of phenolic components which stimulate leakage of potassium from the microbial cell.<sup>57</sup>

Tulsi extract has been found to be an active biosynthesizer of silver nanoparticles when allowed to react with a silver nitrate solution. Silver ions were bioreduced into silver nanoparticles as early as 8 minutes, suggesting rapid biosynthesis of these ecofriendly, stable nanoparticles.<sup>63</sup> These nanoparticles have antimicrobial activity and potential future use in periodontal treatment as silver has a strong activity against periopathogenic microorganisms such as *Porphyromonas gingivalis*, *Prevotella denticola*, *Prevotella intermedia*, *A. Actinomycetemcomitans*, *Tannerella forsythia*, *Eikenella corrodens*, *Fusobacterium nucleatum* and *Campylobacter rectus*. This antimicrobial activity is probably due to the ability of silver to bind to sulfhydryls.<sup>64</sup>

Clinically, SRP and subgingival irrigation with 4% tulsi extract was equally effective in reducing plaque, gingivitis,

pockets and loss of attachment levels as 0.2% chlorhexidine over 4 weeks.<sup>65</sup> Similarly a mouthwash of 4% tulsi leaf extract showed reductions in plaque and gingivitis, which was comparable to chlorhexidine, when 10 ml was used twice daily for 30 days.<sup>66</sup> 4% tulsi extract mouth rinse when used twice daily for 1 minute, for 7 days was as effective as Listerine and chlorhexidine in reducing salivary *S. mutans* counts.<sup>67</sup> No adverse effects of tulsi were reported in these studies,<sup>65-67</sup> except a bitter taste of tulsi mouth rinse.<sup>67</sup>

### Pomegranate

Pomegranate, botanically known as *Punica granatum*, derives its name from Medieval Latin “pomum” meaning apple and “granatum” meaning seeded. It has a wide range of medicinal properties. The pericarp, seeds, and juice of the fruit, its flowers, leaves, twigs, stem and roots have been used in traditional medicine. The seed oil is rich in punicic acid (95%), and contains other components such as ellagic acid, fatty acids and sterols. The pericarp contains phenolic punicalagins, gallic and other fatty acids, catechin, EGCG, quercetin, rutin and other flavones and anthocyanidines. The leaves comprise of tannins and flavones. The flowers contain gallic acid, ursolic acid, triterpenoids such as maslinic acid and asiatic acid. Roots and bark contain tannins and piperidine alkaloids.<sup>68,69</sup>

Punicic acid, a fatty acid unique to pomegranate seed oil,<sup>70</sup> has excellent anti-inflammatory action due to its ability to inhibit PG production and suppress cyclooxygenase and lipoxygenase enzymes in vitro.<sup>70</sup> Cyclooxygenase enzymes play an important role in converting arachidonic acid to PGs, whereas lipoxygenase catalyzes the conversion of arachidonic acid to leukotrienes.

Pomegranate extract was also found to inhibit IL-1 $\beta$  induced breakdown of proteoglycans and IL-1 $\beta$  induced MMP expression.<sup>71</sup> Pomegranate also inhibits NF- $\kappa$ B activity, extracellular signal-regulated



kinase (ERK-1/ERK-2) activation and nitric oxide and PGE2 synthesis. NF- $\kappa$ B inhibition is through a mechanism independent of I $\kappa$ B phosphorylation.<sup>72</sup>

Pomegranate fermented juice extract and cold pressed seed oil extract was found to have antioxidant activity superior to that of red wine and comparable to that of green tea.<sup>70</sup> The flavonoids in pomegranate increase total plasma antioxidant capacity by scavenging free radicals, reducing macrophage oxidative stress and cellular lipid peroxide. Pomegranate extract also boosts the free radical scavenging activity of hepatic enzymes catalase, SOD and peroxidase.<sup>68,69</sup>

Pomegranate extract has also been found to accelerate wound healing. The strong antioxidant activity of its tannins and flavonoids maintain low levels of oxidants during the healing process. Pomegranate extract also increased fibroblast proliferation, collagen regeneration, vascularization and epithelialization of wounds in experimental models.<sup>73</sup>

The antibacterial action of pomegranate is possibly due to the tannins which impede bacterial adherence onto tooth surfaces, increase bacterial lysis and form high molecular weight complexes with soluble proteins.<sup>74</sup> It has antibacterial efficacy against *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, *Eikenella corrodens*, *Streptococcus sanguinis*, *Streptococcus mutans* and others, thus it may have a potential part to play in preventing plaque formation.<sup>75, 76</sup> Pomegranate bark extract also inhibited quorum sensing, suggesting a possible future use in overcoming antibiotic resistance.<sup>77</sup>

Synergistic actions of pomegranate fruit extract with antibiotics chloramphenicol, gentamicin, ampicillin, tetracycline, and oxacillin against MRSA and MSSA was observed. The extract also enhanced the post-antibiotic effect of ampicillin from 3 to 7 hours. It could potentially inhibit the efflux pump or

improve the influx of the drug, suggesting future use of pomegranate extract with these antimicrobials.<sup>78</sup> Synergistic effects of pomegranate peel extract was also seen with probiotic *Lactobacillus rhamnosus*.<sup>79</sup> *L. rhamnosus*, as with other probiotics, has shown favorable results in the non-surgical treatment of periodontal disease.<sup>80</sup>

Clinical studies with a mouthwash made from the seeds of pomegranate that was used twice daily for 1 month, in patients with mild to moderate gingivitis after SRP, showed a significant reduction in plaque and bleeding indices.<sup>76</sup> Another mouthrinse of 100 mg pomegranate flavonoid, administered in 3 subdivided doses a day, for four weeks, significantly changed salivary measures. Reduced total protein (which could suggest a reduction in plaque forming bacteria), reduced aspartate aminotransferase activity (an indicator of cell injury), reduced alpha-glucosidase activity (a sucrose degrading enzyme), increased antioxidant enzyme ceruloplasmin activity and increased radical scavenging capacity was observed. The investigators suggested thus that pomegranate could reduce the risk of gingivitis.<sup>81</sup>

In the adjunctive treatment of chronic periodontitis, 10% pomegranate juice extract gel applied in pockets of 5-7 mm depth following SRP, showed significant reductions in bleeding, gingival and plaque indices after 15 days, as well as in microbiological growth. Histological observation revealed increased collagen fibers with mild perivascular infiltrates in test specimens compared to destruction of collagen fibers with dense infiltratory infiltrates in control sites.<sup>82</sup>

## Garlic

*Allium sativum* Linn, also known as garlic, is a perennial herb with compound underground bulbs which are of medicinal value.<sup>83</sup> Garlic bulbs in their whole form barely exhibit any odour. However, as soon as the bulbs are crushed or cut, its distinctive odour is perceived. This is due to the formation of allicin, by the action of the

enzyme alliinase on alliin. Allicin, a colourless, unstable oil, is the main active component of garlic. It shows antibacterial activity against Gram positive and Gram negative microorganisms in dilutions as low as 1:85,000 to 1:125,000. 1 mg allicin is comparable to 15 Oxford units of penicillin.<sup>84</sup>

Garlic has been found to be active against *Candida albicans* and oral Gram negative species such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Prevotella nigrescens*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Leptotrichia buccalis*. The MIC concentrations were 1.1 mg/ml (*P. nigrescens*, *F. nucleatum*), 4.4 mg/ml (*P. intermedia*, *P. gingivalis*), 17.8 mg/ml (*A. actinomycetemcomitans*) and 35.7 mg/ml (*L. buccalis*) of garlic. These doses corresponded to 0.4 µg/ml, 1.7 µg/ml, 6.87 µg/ml and 13.75 µg/ml of allicin. Gram positive organisms had higher MIC and MBC values. Time kill curves demonstrated that while no apparent killing of Gram positive *Streptococcus mutans* was observed until 4 hours, killing of Gram negative *P. gingivalis* began almost at once. It's possible that the access of allicin to periplasmic and cytoplasmic enzymes is influenced by the features of the bacterial cell envelope. *L. buccalis*, which has scale like folds on its external surface, thus had higher MIC and MBC values. In the case of Gram positive microorganisms, the cell's thick peptidoglycan layer may diminish access of allicin to periplasmic and cytoplasmic enzymes. Otherwise, allicin has the ability to easily penetrate cell membranes.<sup>85</sup> *P. gingivalis*' trypsin like and total protease activity, which is one of its virulence factors associated with periodontal disease, was also almost totally inhibited by garlic extract.<sup>85, 86</sup>

This antimicrobial action of garlic is due to the rapid reaction of allicin with essential, bacterial thiol-containing enzymes such as cysteine proteases, alcohol dehydrogenases and thioredoxin reductases.<sup>87, 88</sup> These enzymes are essential

for the proper functioning of bacteria. At low concentrations of allicin, inhibition of thiol proteases may hamper the microbes' virulence, while not being lethal to it. At higher concentrations, interactions with dehydrogenases and reductases could prove lethal for the microorganism.<sup>88</sup> This mode of action is unlike that of other antibiotics, making allicin very valuable, due to the inability of most bacteria to develop resistance to it. Bacterial resistance to beta-lactam antimicrobials may be a 1000-fold easier.<sup>88</sup>

Some potential hurdles to be dealt with in the therapeutic use of garlic are that allicin, being unstable, breaks down within 16 hours; the antimicrobial efficacy of garlic on oral biofilms is yet to be thoroughly proven as has been done on planktonic cells; the efficacy of allicin may be reduced at bleeding periodontal sites since allicin complexes with blood proteins; and glutathione, which is present in gingival crevicular fluid (although at diminished levels at diseased periodontal sites) counters the action of allicin on cysteine proteases of *P. gingivalis*.<sup>85</sup>

Clinically a reduction in gingival inflammation and gingival bleeding was observed when aged garlic extract was consumed daily for 4 months.<sup>89</sup> Another study revealed a significant reduction in *S. mutans* counts when 10 ml of 3% garlic extract mouthwash was used once daily for 7 days.<sup>90</sup> Rinsing with 10 ml of 2.5% garlic solution for 1 minute for 7 days also caused a reduction in *S. mutans* counts, with a residual effect seen in the two weeks after mouth rinsing was stopped. Adverse reports such as burning sensation, bad breath and unpleasant taste of the solution was reported.<sup>91</sup>

## Ginger

Ginger (*Zingiber officinale*) belongs to the Zingiberaceae family. Ginger's pungent compounds, mainly gingerols, in its rhizomes have beneficial health activities including antioxidant,<sup>92, 93</sup> anti-inflammatory,<sup>94</sup> antimicrobial<sup>95</sup> and

antifungal functions.<sup>96, 97</sup> Shogaols are dehydration products of gingerols, present in trace quantities in fresh ginger. However they are found in higher quantities in dried and thermally treated ginger.<sup>93, 96</sup> Shogaol appears to have very potent antioxidant and anti-inflammatory activity.<sup>92, 93</sup>

Nitric oxide produced by iNOS in response to stimuli from oxidants, proinflammatory cytokines, LPS, bacteria and viruses can be cytotoxic in itself. However, it also results in the formation of peroxynitrite by interacting with superoxide anions. Peroxynitrite is the most reactive nitrogen species (RNS). Gingerol was also found to protect tissues against peroxynitrite induced damage plausibly by scavenging peroxynitrite radicals and formation of a reaction product.<sup>92, 93, 98</sup> Ginger suppressed lipid peroxidation<sup>99</sup> and increased levels of antioxidant enzymes such as SOD, glutathione and catalase by increasing their gene expression. Ginger also attenuated the increase in IL-1 $\beta$  induced caspase.<sup>100</sup>

The anti-inflammatory effect of ginger is said to be due to its ability to inhibit PG and leukotriene biosynthesis, inhibit COX-1 and COX-2 expression and activation of TNF- $\alpha$  and other proinflammatory cytokines, reduced I $\kappa$ B $\alpha$  degradation and faulty NF- $\kappa$ B translocation of p65.<sup>97</sup>

The antioxidant and anti-inflammatory effects of ginger were observed in patients with diabetes mellitus and chronic periodontitis treated with non-surgical periodontal therapy. After 8 weeks of treatment with 2 g of ginger/day, significant improvements were seen in CAL and PD and in inflammatory markers IL-6, hs-C-reactive protein, and TNF- $\alpha$ . Antioxidant enzymes, protective against the effect of ROS, such as SOD and glutathione peroxidase were significantly increased.<sup>94</sup> Ginger also improved the glycemic control of patients with diabetes and chronic periodontitis.<sup>101</sup>

Ginger has also been useful in pain management after periodontal flap surgery. Patients received 500 mg of ginger extract

one hour before surgery and every 6 hours subsequently for 3 days. Other groups received 400 mg of Ibuprofen or cornstarch placebos at similar time intervals. Results indicated that ginger extract performed almost as well as Ibuprofen. Ibuprofen was better immediately after surgery and at 4 and 8 hours after surgery, whereas both had the same effect at 12, 24, and 48 hours.<sup>102</sup>

Gingerols were effective against black pigmented periodontal pathogens *Porphyromonas gingivalis*, *Porphyromonas endodontalis* and *Prevotella intermedia* in vitro, at a MIC range of 6-30  $\mu$ g/ml.<sup>95</sup> Further research on the effect of ginger in vivo on the periodontium is an area of potential research.

### Clove

Cloves are the aromatic, dried flower buds of the tree *Syzygium aromaticum*. Clove oil is extracted from the tree's stem, leaves or buds.<sup>103</sup> Clove and its oil are found to have antibacterial,<sup>104, 105</sup> antioxidant,<sup>106</sup> anti-inflammatory,<sup>107</sup> analgesic and local anesthetic<sup>108, 113</sup> properties amongst numerous others.

Eugenol, a major component in clove oil, is responsible for its therapeutic actions.<sup>103-105</sup> Treatment of Gram negative organisms *Escherichia coli*, *Klebsiella aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Salmonella typhimurium* with 1 and 10 mM of eugenol caused 50% and 80% cell membrane damage. A synergistic effect of eugenol with antimicrobials ampicillin, penicillin, oxacillin, erythromycin, norfloxacin, chloramphenicol, polymycin B, tetracycline, vancomycin and rifampicin against these organisms was also observed, possibly due to the increased penetration of the antibiotics after loss of bacterial cell membrane integrity, in addition to the usual action of the drug on its targets. The MIC of these antimicrobials reduced 5-1000 fold.<sup>104</sup> Clove oil also demonstrated synergy with ampicillin and gentamicin against cariogenic bacteria and periopathogenic microorganisms *Aggregatibacter*

*actinomycetemcomitans*, *Fusobacterium nucleatum*, *Prevotella intermedia* and *Porphyromonas gingivalis*, reducing their MIC > 4 fold. The MIC of clove oil alone against these organisms ranged from 0.1-0.8 mg/ml.<sup>105</sup>

The antioxidant activity of clove is due to its higher concentration of phenolic compounds like eugenol, eugenol acetate and thymol. Clove exhibited excellent radical scavenging capacity, metal chelating activity (which inhibited metal ion induced lipid peroxidation) and had high ferric reduction antioxidant power.<sup>106</sup>

Clove's anti-inflammatory action occurs due to eugenol's ability to suppress NF- $\kappa$ B thereby affecting PGs and other inflammatory mediators.<sup>107</sup> This anti-inflammatory action also partly contributes to the analgesic and antinociceptive action of clove.<sup>108</sup> Clove gel, made from finely ground clove powder and glycerin in the ratio of 2:3, was applied to the buccal mucosa of volunteers followed by a needle prick. 2 g of gel was applied for 4 minutes, then reapplied for 1 more minute. 4 participants (5.4%) developed small ulcers. Both clove and benzocaine significantly lowered pain scores with no significant differences between them.<sup>109</sup>

While the usage of clove is generally considered safe, cytotoxicity towards human fibroblasts and epithelial cells have been observed in vitro.<sup>110</sup> At lower concentrations, eugenol may function as a contact allergen resulting in a localized delayed hypersensitivity reaction. At high concentrations, eugenol, being cytotoxic, may produce necrosis and reduce healing. Very rarely, eugenol may even cause a generalized, anaphylactic like reaction.<sup>111</sup> All this suggests that while clove has excellent bioactive properties, further research is necessary so as to safely incorporate clove into therapeutics.

## Cinnamon

Cinnamon, an aromatic condiment, is obtained from the inner barks of trees of the *Cinnamomum* genus.<sup>112</sup> Its essential oil

contains large amounts of cinnamaldehyde and lesser quantities of eugenol, which are its most active components.<sup>113, 114</sup>

Cinnamaldehyde is an electronegative compound. Electronegative compounds impede biologic processes that involve electron transfers. They also react with nitrogen containing compounds such as nucleic acids and proteins, and thereby discourage the growth of microorganisms.<sup>115</sup> Cinnamon bark essential oil and cinnamaldehyde had a MIC of 6.25  $\mu$ g/ml and 2.5  $\mu$ g/ml against *Porphyromonas gingivalis*. Dose dependent, irreversible loss of bacterial cell membrane integrity with DNA, RNA and protein leakage was observed. Electron microscopy revealed irregular, deformed, shrivelled and distinctly wrinkled cells with sagging and small holes. Biofilm formation was inhibited, while cinnamon bark oil further inhibited established biofilm mass.<sup>114</sup>

When evaluated clinically, 20% cinnamon extract mouthwash was equally effective as 0.2% chlorhexidine mouthwash, when used twice daily for 30 days, as an antiplaque and antigingivitis agent. No adverse reactions were reported.<sup>116</sup> Type 2 diabetic and non-diabetic patients with chronic periodontitis who rinsed with 0.5% cinnamon mouthwash, twice daily for 3 weeks, had a significant reduction in *Candida albicans* counts from buccal mucosal scrapings.<sup>117</sup>

A systematic review on adverse effects of cinnamon revealed that while cinnamon may be well tolerated in controlled clinical settings, its therapeutic usage, which may call for larger doses for long durations may be associated with adverse effects. Although these are mostly minor and self-limiting, clinical monitoring should be done. Also due attention has to be paid to the species of cinnamon used, since different species have different levels of toxic ingredients.<sup>112</sup>

## CONCLUSION

The phytotherapeutic agents discussed here are just a small number of an

expansive, inexhaustible treasure trove available to us. The mechanisms discussed here are only those that could possibly have a direct effect on periodontal disease. Additionally, these agents have immeasurable beneficial effects on other systems of the body, thus may also indirectly, positively impact the periodontium. The clinical effectiveness of many phytotherapeutic agents is at present not sufficiently defined, thus warranting further investigation. Currently a majority of the data pertaining to their oral effects comes from studies done in vitro or on experimental models which may not translate into having the same effect in vivo. Further research is required to throw more light on their pharmacodynamics and pharmacokinetics, clarify their dose and dosage forms and elucidate their drug interactions and adverse effects.

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