Accepted Manuscript

Title: Is there a role for herbal medicine in the treatment and management of periodontal disease?

Authors: Julija Milovanova-Palmer, Barbara Pendry

PII: S2210-8033(18)30014-9
DOI: https://doi.org/10.1016/j.hermed.2018.02.004
Reference: HERMED 215

To appear in:

Received date: 9-6-2017
Revised date: 28-1-2018
Accepted date: 25-2-2018

Please cite this article as: Milovanova-Palmer, Julija, Pendry, Barbara, Is there a role for herbal medicine in the treatment and management of periodontal disease?.Journal of Herbal Medicine https://doi.org/10.1016/j.hermed.2018.02.004

Is there a role for herbal medicine in the treatment and management of periodontal disease?

Julija Milovanova-Palmer[1]

& Barbara Pendry*[1]

[1]Medicines Research Group, School of Health, Sport and Bioscience, University of East London, Water Lane, Stratford, London E15 4LZ, UK.

* Corresponding author:
E-mail addresses: juliamilova@gmail.com (J. Milovanova-Palmer), b.pendry@uel.ac.uk

(B Pendry).

Abstract

Periodontal disease is an inflammatory condition of the tissues of the periodontium that affects up to 90% of the world's population. Emerging antibiotic and antimicrobial resistance in oral biofilms has sparked off an increased interest in the potential of medicinal plants to treat periodontal pathologies. The last decade has seen a surge in numbers of *in vitro* and *in vivo* studies on herbs traditionally used for their anti-bacterial properties in ethno-pharmacological applications. This review paper assesses the current status and role of medicinal plants in the treatment and management of periodontal disease.

1. Introduction

Periodontal disease is widely recognised as a public health issue (Petersen, 2012). It is a leading cause of tooth loss (FDI World Dental Federation Report, 2014) and thus can seriously compromise quality of life (Batchelor, 2014; Sravani *et al.*, 2015). Periodontal disease has high prevalence. The milder form (gingivitis) affects up to 90% of the world's population (Philstrom *et al.,* 2005), whereas the severe form of the disease (chronic periodontitis) affects up to 20% of the world's population (FDI World Dental Federation Report, 2014). From the information of

the National Health Service of the United Kingdom, about 50% of the UK population suffers from some form of periodontal disease (National Health Service, 2015).

1.1. **Pathogenesis of periodontal disease**

Periodontal disease is a chronic inflammatory pathology that gradually destroys the structures of the periodontium: gingiva, alveolar bone, cementum and periodontal ligament (Jain *et al.*, 2008). Periodontal disease can manifest as gingivitis, reversible inflammation of the gums, or chronic periodontitis, inflammation of the subgingival areas with irreversible damage to the periodontium and formation of distinctive periodontal pockets (Nguyen *et al.*, 2015; Highfield, 2009).

The major cause of periodontal disease is the proliferation of pathogenic oral biofilms, which are robust layers of mucilage adhering to solid surfaces and containing communities of bacteria and other micro-organisms, resulting in dental plaque formation (Palombo, 2011). Different bacteria occur in supragingival (cariogenic) and subgingival (periodontopathogenic) dental plaques. Supragingival plaque is host to facultative anaerobic bacteria such as *Streptoccocus* spp. and *Actinomyces* spp., whereas subgingival plaque is host to Gram-negative anaerobic bacteria such as *Porphyromonas gingivalis*, *Actinobacillus*, *Prevotella intermedia*, *Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Capnocytophaga spp.* and *Veillonella spp*. (Lazar *et al.*, 2016). Chronic periodontitis is associated with proliferation of subgingival Gram-negative oral biofilms (Kouidhi *et al.*, 2015; Srinath *et al.*, 2014; Palombo, 2011; Batista *et al.*, 2014;). It thus can be deduced that gingivitis is associated with facultative anaerobic bacteria.

The progress of periodontal disease includes cyclical phases of exacerbation, remission and latency and is closely associated with the host immune-inflammatory response (Lazar *et al.*, 2016, Yarnell, 2009, p.286; Cochran, 2008; Preshaw, 2000). Bacteria in subgingival dental plaques cause excessive proliferation of pro-inflammatory mediators (cytokines, prostanoids and enzymes) which intensify the destruction of periodontium. (Preshaw, 2008).

1.2. **Risk factors**

There are factors that may increase the risk of development of periodontal disease. These include hormonal changes due to pregnancy and puberty (Highfield, 2009; Hoffman, 2003, p. 268), systemic diseases such as diabetes mellitus (Highfield, 2009; Izuora *et al.*, 2015), certain medications (Highfield, 2009), and such common behavioral risk factors as smoking, alcohol, poor diet, physical inactivity, and obesity (Genco and Genco, 2014). Furthermore, periodontal

disease has been associated with systemic pathologies including cardiovascular pathologies, (Aarabi *et al.*, 2015; Nguyen *et al.*, 2015), stroke (Genco and Genco, 2014), oral cancer (Javed and Warnakulasuriya, 2015), and rheumatoid arthritis (Kaur *et al.*, 2014).

1.3. **Problems with current periodontal disease management**

Surgical intervention to reduce periodontal pockets is expensive. For example, in the U.S. surgery costs US$4000-5000 and is not covered by health insurance. (Lazar *et al*., 2016).

The standard non-surgical treatment for periodontal disease is mechanical plaque removal (professional scaling, root planing and tooth brushing) alongside strict plaque control using antibacterial mouthwashes (e.g. chlorhexidine, which is considered the gold standard) and/or local and systemic application of antibiotics (tetracycline and metronidazole, the latter acting primarily on anaerobic bacteria) (Batista *et al.*, 2014; Kouidhi *et al.*, 2014; Karim *et al.*, 2014, Jain *et al.*, 2008) as well as systemic use of subantimicrobial dose doxycycline as a new adjunct host-modulatory therapy option (Preshaw, 2000; Shinwari *et al.*, 2014).

Non-surgical treatments have significant drawbacks. Mechanical plaque removal cannot reach all the areas where bacteria hide and can lead to re-colonization with pathogens (Batista *et al.*, 2014). Chlorhexidine, when used for longer than 15 days, exhibits several adverse effects in staining the teeth and tongue, increasing oral sensitivity and provoking allergic reactions (Balappanavar *et al.*, 2013; Batista *et al.*, 2014). Long term use of chlorhexidine was also found to increase accumulation of dental calculus (Schwach-Abdellaoui *et al.,* 2000).

A major issue with current periodontal disease management is the risk of development of antibiotic and antimicrobial resistance. Recent research suggests that long-term use of chlorhexidine products has a link to the development of multidrug resistance in dental plaque bacteria. Moreover, chlorhexidine appears to have the same mode of action in causing bacteria to develop anti-microbial resistance as four major groups of antibiotics ampicillin, kanamycin, gentamicin and tetracycline (Saleem *et al.*, 2016). This puts under long term threat the therapeutic value of the major pharmaceutical anti-plaque agent for gingivitis and periodontal disease.

Herbal medicine as an alternative solution for management of periodontal disease

A combination of antibiotic resistance risk and the drawbacks of existing treatment modalities create a need for alternative treatments that are safe and effective (Batista, 2014; Karim, 2014; Srinath, 2014; Palombo, 2011; Projan & Youngman, 2002). In the last decade, there has been

much *in vitro* and *in vivo* research into the efficacy of medicinal plants with known anti-inflammatory and antibacterial qualities to treat periodontal disease. This paper reviews the evidence in order to determine whether herbal medicine has a role in the treatment and management of periodontal disease.

2. Method

2.1 Herbal texts

A selection of contemporary western herbal texts was screened in order to identify traditionally used herbs for treatment and management of periodontal disease. The following search words were used: "gingivitis", "periodontal disease" and "gum disease". To be included, the texts had to be written by professional herbalists, pertain to Western Herbalism, have information on treatment of periodontal disease in its content, be easily accessible to professionals and public alike and date not earlier 1995. There were 18 texts that met the inclusion criteria which are listed here in date order: Alexander and Staub-Bruce, 2014; Pizzorno and Murray, 2013; Braun, 2010; McIntyre, 2010; Fisher, 2009; Yarnell, 2009; Wood, 2008 and 2009; Chevallier, 2007; Hoffman, 2003; Mills and Bone, 2003; Barnes *et al.*, 2002; Barker, 2001; Weiss, 2001; Blumental, 2000; Mindell, 2000; Tyler, 1999; Bartram, 1998; Robins, 1995.

2.2 Literature review

A systematic literature search was performed using four online databases: Science Direct, PubMed, Scopus and ResearchGate from October 2015 to May 2017. Wiley Online and Web of Science generated no additional research literature of interest to this study during preliminary assessment, so these sources were not included. Search terms applied were "periodontal disease OR gingivitis OR gum disease OR oral biofilm OR periodontal bacteria", and "herbal medicine OR phytotherapy OR herbs OR medicinal plants". The full text of each paper was obtained. Initially, an electronic search for *in vitro* papers generated 423 articles in total, and n=37 articles met all inclusion criteria, which were for *in vitro* studies on herbs showing activity against periodontal bacteria, published in English in peer-reviewed journals from 2007 onwards. An electronic search for randomised controlled trials initially generated 954 articles, and n=26 articles met all inclusion criteria, which were for clinical studies testing whole herb extracts on humans, published in English in peer-reviewed journals from 2007 onwards. Studies on animal cells or animals, studies on single herbal constituent extracts and articles on commercial products containing herbal extracts were excluded. It was beyond the scope of this review to cover the use of essential oils in the treatment of periodontal disease.

3. Results

3.1 Herbal texts

3.1.1 Medicinal Plants for treatment of gingivitis and periodontitis

In total, 64 medicinal plants were identified in the western herbal texts by 18 authors. Only 14 medicinal plants were mentioned by at least 3 different authors (Table 1). *Commiphora molmol* (n=12) was the most popular choice in the herbal texts. Thus, Wood (2008) and Hoffman (2003) considered *Commiphora molmol* to be a specific remedy for periodontal disease. *Salvia officinalis* (n=11) was the second most popular choice, followed by *Calendula officinalis* and *Matricaria recutita* (n=7). The other popular herbs appeared in the following sequence: *Echinacea purpurea* (n=6), *Hydrastis canadensis*, *Quercus spp*. and *Vaccinium myrtilis* (n=5); *Camellia sinensis* (n=4); *Achillea millefolium*, *Azadirachta indica*, *Centella asiatica*, *Mentha piperita*, *Myrica spp*., *Plantago spp*., *Symphytum spp*. and *Thymus vulgaris* (n=3).

It is difficult to ascertain whether this list is exhaustive since many authors gave marginal attention to periodontal disease, gum disease or gingivitis.

3.2 Literature Review

3.2.1 Significance of medicinal plant research *in vitro* against oral periodontal bacteria

Herbal extracts demonstrated inhibitory effects on supragingival and subgingival bacteria in 37 *in vitro* studies published since 2007 (see Table 2). These studies tested whole plant extracts of 52 different species. The highest numbers of *in vitro* studies were carried out on *Psidium guajava* (n=4), followed by *Camellia sinensis* (n=2), *Murraya koenigi* (n=2), *Punica granatum* (n=2) and *Salvadora persica* (n=2). The total number of *in vitro* studies in recent years has increased. Table 2 displays the results in order of lead author's name. Out of 37 studies, 20 investigated inhibition of *Streptococcus mutans* and 24 investigated inhibition of *Porphyromonas gingivalis*.

3.2.2 Significance of medicinal plants in clinical research: randomised controlled clinical trials

There were 26 randomised clinical trials since 2007 which fulfilled eligibility criteria. These clinical trials are summarized in Appendix 1 (available in supplementary data only), including detailed information on herbal extracts assessed, trial aim, type of preparation, trial duration, number of participants, inclusion/exclusion criteria, dosage and results.

Due to space limitations in the current review paper, only summary findings of the clinical trials are offered in the body of the text. The findings of the clinical trials are divided into categories based on the delivery mechanism of the herbal extracts: subgingival delivery, herbal mouthwashes, trans-mucosal delivery, chewing gum, oral gel. For more detail on each trial, please refer to the Appendix 1 (available in the supplementary data only).

3.2.3 Subgingival delivery of herbal extracts in chronic periodontitis

There were 4 clinical trials (see Appendix 1) which evaluated efficacy of medicinal plants in subgingival delivery mode for patients with chronic periodontitis.

Subgingival irrigation with *Azadirachta indica* (neem) extract significantly (P<0.05) reduced gingivitis, bleeding, and periodontal disease over a 30-day period in a group of 15 chronic periodontal disease sufferers (Bedi *et al.* 2011).

In another short-term study, Bhat *et al.* (2011) demonstrated that *Aloe vera* gel injected into periodontal pockets significantly (P<0.05) reduced periodontal pocket depth, gingivitis and bleeding.

Rassameemasmaung *et al.* (2008) found that when *Garcinia mangostana* gel was introduced to the subgingival space, the periodontal pocket depths were reduced but not to a significant level (P<0.05). Gingival inflammation and bleeding were reduced significantly (P<0.05) after 3 months.

Phogat *et al.* (2014) found that subgingivally-delivered polyherbal gel containing extracts of *Mimusops elengi* bark, *Acacia arabica* bark and *Punica granatum* was equally as effective as chlorhexidine gel (P<0.05).

3.3 Herbal Mouthwashes

3.3.1 Comparison of herbal mouthwashes to chlorhexidine

The effectiveness of herbal mouthwashes was compared to chlorhexidine, considered to be the gold standard commercial mouthwash, in 18 randomised clinical trials (see Appendix 1,

available in supplementary data only). Of these, 17 studies showed no significant difference in effectiveness (P<0.05) between chlorhexidine and the following herbal mouthwashes (in concentrations ranging from 0.2% to 0.12%): 0.5% *Camellia sinensis* and 2% *Azadirachta indica* (Balappanavar *et al.*, 2013)*; Camellia sinensis* (Kaur *et al.*, 2014); *Azadirachta indica* (Sharma *et al*., 2014); *Punica granatum* and *Matricaria recutita* (Batista *et al.*, 2014); *Aloe vera* 100% gel mouthwash (Chandrahas *et al.*, 2012), *Aloe vera* mouthwash (Karim *et al.*, 2014; Gupta *et al.*, 2014; Vangipuram *et al.*, 2016); *Ocimum sanctum* (Gupta *et al.*, 2014); a polyherbal mouthwash of *Zingiber officinale*, *Rosmarinus officinalis* and 5% *Calendula officinalis* (Mahyari *et al.*, 2016); a polyherbal mouthwash containing *Salix alba*, *Malva sylvestris* and *Althaea officinalis* alongside scaling and root planing (Radvar *et al.* 2016); *Cinnamomum verum* (Gupta and Jain, 2015); *Terminalia chebula* (Gupta *et al.*, 2015); *Curcuma longa* (Waghmare *et al.*, 2011); a polyherbal mouthwash of *Salvadora persica* and *Camellia sinensis* (Abdulbaqi *et al.*, 2016), a polyherbal mouthwash triphala of *Emblica officinalis*, *Terminalia chebula* and *Terminalia bellirica* (Naiktari *et al.*, 2014); a polyherbal mouthwash of *Salix alba*, *Malva sylvestris* and *Althaea officinalis* (Radvar *et al.*, 2016). No side effects were observed from herbal mouthwashes.

In contrast, one study found that *Aloe vera* mouthwash was significantly less effective in reducing plaque than chlorhexidine (Yeturu *et al.*, 2016).

3.3.2 Comparison of herbal mouthwashes to placebo

Jenabian *et al.* (2012) tested 5ml of 5% *Camellia sinensis* mouthwash against a placebo in schoolchildren with gingivitis. Both groups carried out flossing and tooth brushing three times a day. Gingivitis reduction was highly effective with the mouthwash (P<0.001), but there was no statistically significant difference from gingivitis reduction outcomes of the placebo group (P>0.05). Aspalli *et al.* (2014) found that, following scaling, a polyherbal mouthwash containing *Salvadora persica*, *Terminallia bellerica*, *Piper bitel*, *Gandhapura taila*, Ela, Peppermint satva and Yavani satva significantly reduced gingivitis, plaque and bleeding (P<0.05).

3.4 Trans-mucosal herbal patch

A study on a transmucosal herbal patch containing extracts of *Centella asiatica*, *Echinacea purpurea* and *Sambucus nigra* on gingivitis patients showed high effectiveness (P=0.009) compared to a placebo controlled group, and no side effects (Grbic *et al.*, 2011).

3.5 Herbal chewing gum

A chewing gum randomised clinical trial conducted by Amoian *et al.* (2010) tested S*alvadora persica* extract in a chewing gum administered 4 times daily for at least 1 hour following tooth brushing to 72 high school students with gingivitis. There was a significant reduction in gingivitis (P<0.001) and bleeding (P<0.005), but no significant reduction in plaque (P<0.579).

3.6 Oral gel

Farjana (2014) evaluated efficacy of *Curcuma longa* gel for gingivitis treatment with significant reduction of bleeding on probing (P<0.579).

4 Discussion

Periodontal disease is a highly complex pathology that stems from the actions of pathogenic bacteria and the host immune-inflammatory response (Lazar *et al*., 2016). The standard periodontal treatment protocol focuses on the eradication of pathogenic biofilms through mechanical and antimicrobial means including systemic antibiotics and antimicrobial mouthwashes. However, periodontopathogenic bacteria have been developing resistance to antibiotics and most recently also to antibacterial mouthwashes such as chlorhexidine, the gold standard in periodontology (Saleem *et al.*, 2016). It is just a matter of time for these standard treatment modalities to become ineffective.

Future treatment strategies will need to provide several modes of anti-bacterial action at once, alongside down-modulation of the host inflammation response (Lazar *et al.*, 2016). Lazar refers to the benefits of the synergistic action of herbal medicines in finding new treatment modalities for periodontal disease. Synergy is the core concept of herbal medicine in which complex interactions take place between combinations of phytochemical constituents generating a synergistic effect where the whole effect is greater than the sum of the part effects (Heinrich *et al.*, 2012). For example, the flavonoid quercetin is an active constituent of *Calendula officinalis* that exhibits strong antioxidant activity. A whole plant extract of *Calendula officinalis* showed stronger inhibition of pro-inflammatory MMP-2 enzymes and gingival fibroblast-mediated collagen degradation than quercetin alone (Saini *et al*., 2012).

Petrovic *et al.* (2015) considers “the biggest problem” in validating herbal treatments for periodontal disease is the lack of understanding of mechanisms of action of multiple compounds working in synergy. However, lack of understanding of the synergistic model does not indicate its lack of effectiveness.

Further benefits of herbal medicine are the low research cost, low consumer cost and few or no side effects (Lazar *et al.*, 2016; Batista, 2014; Pizzorno and Murray 2013, p. 257).

4.1 Difference in treatment protocols – holistic treatment protocol

Until recently, the standard treatment protocol for periodontal disease was confined to a single-pointed focus on eradication of pathogenic biofilms by mechanical or antimicrobial means. Host inflammatory mediators are now believed to be the main cause of disease progression (Lazar *et al.*, 2016). Host modulation therapy, a relatively new concept in periodontics, has now been offered as an adjunct therapy with the only licenced systemic medication in the form of a sub-antimicrobial dose of doxycycline (Shinwari *et al.*, 2014).

In comparison, herbal medicine's treatment protocol is holistic at its core, and would include a choice of herbs with vulnerary (wound healing), anti-inflammatory, anti-bacterial, anti-haemorrhagic, membrane and collagen integrity improving, analgesic and immunomodulatory actions (Table 3).

4.2 Pros and cons of the evidence

Successful use of herbal medicine to treat chronic periodontal disease or gingivitis was evident in 85% of the 26 clinical trials that met the inclusion criteria. Gingivitis treatment was successful in 15 trials (58%) using herbal extracts from *Aloe vera* (n=4), *Azadirachta indica* (n=2), *Camellia sinensis* (n=3), *Centella asiatica* (n=2), *Curcuma longa, Echinacea purpurea*, *Garcinia mangostana, Matricaria recutita, Punica granatum* (n=2), *Salvadora persica* (n=3), *Calendula officinalis*, *Rosmarinus officinalis*, *Sambucus nigra, Terminalia chebula, Ocimum sanctum* and *Zingiber officinale* delivered through varying therapeutic modalities. Chronic periodontitis treatment was successful in 6 trials (23%) using herbal extracts from *Althaea officinalis*, *Azadirachta indica*, *Malva sylvestris*, *Matricaria recutita*, *Punica granatum*, triphala (*Emblica officinalis, Terminalia chebula* and *Terminalia bellirica*), *Salix alba* and gels containing *Aloe vera* and *Garcinia mangostana* extracts (see Appendix 1).

Many studies (n=18, 69%) compared the efficacy of herbal extracts to chlorhexidine mouthwash. Of these, 17 studies showed herbal extracts to be equally effective to chlorhexidine in reducing disease indicators. These 17 studies examined extracts from 12 plants, including *Aloe vera, Althaea officinalis*, *Azadirachta indica, Calendula officinalis, Camellia sinensis, Malva sylvestris*, *Matricaria recutita, Ocimum sanctum, Punica granatum*, *Rosmarinus officinalis,*

Salix alba and *Zingiber officinale*. In contrast to chlorhexidine, however, herbal extracts showed no side effects.

Several studies (n=4) compared herbal extracts to a placebo, together with mechanical debridement, but without including a chlorhexidine control group. Statistically significant reductions in gingivitis disease indicators were achieved for *Centella asiatica*, *Echinacea purpurea*, *Sambucus nigra*, *Camellia sinensis* and *Salvadora persica* via delivery systems such as a trans-mucosal herbal patch (Grbic *et al.*, 2011) and chewing gum (Amoian *et al.*, 2010).

Chronic periodontitis was treated by subgingival delivery of *Azadirachta indica*, *Aloe vera*, *Centella asitatica, Punicum granatum* and *Garcinia mangostana* as herbal extracts, gels and biodegradable strips (Bedi *et al.*, 2011; Bhat *et al.*, 2011). There was significant reduction of periodontal pocket depth, gingivitis and bleeding following the mechanical debridement therapy of scaling and root planing.

Some clinical studies showed a mixture of positive and negative results. *Salvadora persica* extracts significantly reduced gingivitis and bleeding but had no significant effect on plaque (Amoian *et al.* 2014). *Aloe vera* extracts reduced plaque and gingivitis but not by as much as chlorhexidine (Yeturu *et al.* 2016). Whilst *Asadirachta indica* extract showed equal efficacy to chlorhexidine in reducing plaque, it was not as good at reducing gingivitis, though still a significant improvement compared to controls (Sharma *et al.* 2014). One study found that *Curcuma longa* extract significantly reduced total bacterial numbers and gingivitis but was not as good as chlorhexidine at reducing plaque (Waghmare *et al.* 2011). Another study found that *Curcuma longa* extract significantly reduced plaque and gingivitis, and though chlorhexidine performed slightly better in this test, the difference was not significant (Gupta & Jain 2015).

4.3 Limitations of the current evidence

Despite a fairly convincing number of clinical trials (n=26) presented in the current review, the design of the studies has the following limitations: (a) most studies n=16 (62%) were small in size, conducted on ≤100 participants, whilst there were only a few larger studies n=10 (38%), conducted on ≥100 participants, and only n=3 on ≥200 particpants (11%); (b) the dose of herbal extracts administered was not specified in n=17 (65%), whilst none of the studies established the minimum effective dose level; (c) n=6 (23%) studies out of 26 did not indicate *P*-value creating ambiguity in the statistical significance of the research. Webb (2002, p.129) cited a systematic study by Mother *et al.* (1998) that found that "low quality trials were associated with a 39% increase in estimated treatment benefit compared to better conducted trials".

The inclusion criteria presented some limitations, e.g. English language research publications only meant that some potentially valuable evidence was not assessed.

Most clinical trials for periodontal disease were based in India (n=16, 62%), where herbal medicine is supported and promoted at a Governmental level. These tended to research medicinal plants pertinent to Ayurvedic *Materia Medica* that are not usually used in western herbal practice. Other countries where clinical trials were conducted were Iran (n=4), Thailand (n=2), Brazil (n=1), Malaysia (n=1), Thailand (n=1) and USA (n=1). This could be the reason why there were no clinical trials conducted on the two most popular herbs listed in the western herbal texts, *Commiphora molmol* and *Salvia officinalis*.

4.4 Other Factors

On a different note, it is also important to remember that the overall success of periodontal treatment depends, not only on medical intervention, but also on the absence of negative behavioural factors in treated individuals (Sravani, 2015) such as incorrect tooth brushing, smoking and poor diet. Somu *et al.* (2012) referred to research that many adults fail to brush teeth properly (Nogueira-Filho *et al.*, 2000). Genco and Genco (2014) discussed smoking cessation interventions that successfully reduced periodontal disease. Kondo *et al.* (2014) confirmed that a high-fibre, low-fat diet improved periodontal disease markers.

4.5 Recommendations

After evaluating the literature, this review proposes three recommendations to improve the quality of medicinal plant research for periodontal disease treatment: a) Clinical trials should be conducted with larger, more statistically-reliable populations; (b) Recommended therapeutic dosage and minimum dosage should be identified; (c) *P*-values showing statistical significance of all studies should be presented. These steps would greatly improve the quality of the clinical trials and boost their statistical significance and reliability. This would then increase the value of using the Cochrane GRADE system to assess the quality of evidence for the outcome that herbal treatments are effective for treating periodontal disease.

Most of the plants identified in the randomised controlled clinical trials were tested only once on rather small population numbers which reduced the statistical reliability of such studies and undermines the attractiveness of medicinal plants on a larger scale. Since several trials tested the same herbal species, there may be some opportunities for increasing population size through meta-analysis, combining several studies into one. However, the variability of the trial conditions may reduce the value of this route of investigation.

The two most popular herbs for treatment of periodontal disease in herbal texts and pharmacopoeias, *Commiphora molmol* and *Salvia officinalis*, were not tested in randomised clinical trials. These medicinal plants should be important candidates for future clinical trials.

5. Conclusion

Herbal medicine has great potential to treat periodontal disease, especially in the context of emerging global antimicrobial resistance to conventional drugs. Whole plant herbal extracts are less susceptible to antibiotic resistance due to complex pharmacological profiles and synergistic action. The herbal protocol is holistic in its nature and would allow several medicinal plants with antibacterial, anti-inflammatory and immunomodulatory actions to be combined. Herbal medicine appears most effective in treating gingivitis using herbal mouthwashes and managing chronic periodontitis via subgingival delivery of herbal gels, alongside scaling and root planing.

There is ample evidence *in vitro* that many whole plant extracts are effective against periodontopathogenic bacteria, with the most popularly-studied plants being *Psidium guava*, *Camellia sinensis*, *Punica granatum*, *Murraya koenigi* and *Salvadora persica*. However *in vivo*, 88% of clinical trials show significantly positive reduction in gingivitis and chronic periodontitis, and 82% demonstrated significant reductions in plaque, gingivitis and bleeding levels. The most popular plants for *in vivo* studies are *Aloe vera*, *Azadirachta indica* and *Camellia sinensis*. Herbal medicines have the key benefit of being safe and showing no side effects, unlike commercial mouthwashes.

In order for this positive evidence of efficacy to be translated into herbal medicine use by mainstream clinicians, clinical trial quality must be improved to increase confidence. This should be done through increased population sample sizes, more standardised calculation methodology for statistical significance and specifying the dosage of herbal extracts being tested. Future research should focus on the most successful plant candidates in order to increase the statistical significance of earlier findings. These should include medicinal plants with proven traditional evidence as listed in western herbal texts, such as *Commiphora molmol, Salvia officinalis, Calendula officinalis* and *Matricaria recutita*. These should also include herbs with the highest numbers of successful trials, including *Aloe vera, Camellia sinensis, Centella asiatica* and *Punica granatum*.

References

Alexander, M. and Straub-Bruce, L. (2014) *Dental herbalism – natural therapies for the mouth*. Rochester: Healing Arts Press.

Amoian, B., Moghadamnia, A. A., Barzi, S., Sheykholeslami, S., & Rangiani, A. (2010). *Salvadora persica* extract chewing gum and gingival health: Improvement of gingival and probe-bleeding index. *Complementary Therapies in Clinical Practice*, *16*(3), 121–123. https://doi.org/10.1016/j.ctcp.2009.11.002

Antonio, A. G., Iorio, N. L. Pierro, V.S., Candreva, M.S, Farah, A., dos Santos, K. R., *et al.* (2011). Inhibitory properties of *Coffea canephora* extract against oral bacteria and its effect on demineralisation of deciduous teeth. *Arch. Oral Biol.* 56, 556-564. doi: 10.1016/j.archoralbio.2010.12.001

Araghizadeh, A., Kohanteb, J., & Fani, M. M. (2013). Inhibitory activity of green tea (*Camellia sinensis*) extract on some clinically isolated cariogenic and periodontopathic bacteria. *Medical Principles and Practice*, *22*(4), 368–372. https://doi.org/10.1159/000348299

Aspalli, S., Shetty, V., Devarathnamma, M., Nagappa, G., Archana, D. & Parab, P. (2014). Evaluation of antiplaque and antigingivitis effect of herbal mouthwash in treatment of plaque induced gingivitis: a randomized, clinical trial. *Journal of Indian Society of Periodontology* 18(1), pp. 48-52, doi: 10.4103/0972-124X.128208.

Balappanavar, A., Sardana, V. & Singh, M. (2013) Comparison of the effectiveness of 0.5% tea, 2% neem and 0.2% chlorhexidine randomized control trial. *Indian Journal of Dental Research* 24(1), pp. 26-34.

Bardají, D. K. R., Reis, E. B., Medeiros, T. C. T., Lucarini, R., Crotti, A. E. M., & Martins, C. H. G. (2016). Antibacterial activity of commercially available plant-derived essential oils against oral pathogenic bacteria. *Natural Product Research*, *30*(10), 1178–1181. https://doi.org/10.1080/14786419.2015.1043630

Bardaji, D. K. R., Mangabeira da Silva, J. J., Bianchi, T. C., de Souza Eugenio, D., Francielli de Oliveira, P., Leandro, L. F., … Martins, C. H. G. (2016). *Copaifera reticulata* oleoresin: Chemical characterization and antibacterial properties against oral pathogens. *Anaerobe*, *40*(April), 18–27. https://doi.org/10.1016/j.anaerobe.2016.04.017

Barker, J. (2001) *The medicinal flora of Britain and northwest Europe*. West Wickham: Winter Press.

Bartram, T. (1998) *Bartram's encyclopaedia of herbal medicine*. London: Robinson Publishing Ltd.

Batchelor, P. (2014). Is periodontal disease a public health problem? *British Dental Journal*, *217*(8), 405–409. https://doi.org/10.1038/sj.bdj.2014.912

Batista, A. L. A., Lins, R. D. A. U., de Souza Coelho, R., do Nascimento Barbosa, D., Moura Belém, N., & Alves Celestino, F. J. (2014). Clinical efficacy analysis of the mouth rinsing with

pomegranate and chamomile plant extracts in the gingival bleeding reduction. *Complementary Therapies in Clinical Practice*, *20*(1), 93–98. https://doi.org/10.1016/j.ctcp.2013.08.002

Bedi, H., Chandrashekar, K. T., & Prakash, H. (2011). Effect of neem extract on periodontal status & AST levels in chronic periodontitis: a clinical & biochemical study. *Journal of Pierre Faucharad Academy (India Chapter)*, *25*(1), 55–61. https://doi.org/10.1016/S0970-2199(11)50002-5

Bhat G, Kudva P & Dodwad V. (2011) '*Aloe vera*: nature's soothing healer to periodontal disease', *Journal of Indian Society of Periodontology*, 15, pp. 205-209. http://www.jisponline.com/text.asp?2011/15/3/205/85661

Blumenthal, M *et al.* (2000). *Herbal Medicine – Explained Commission E Monographs.* Newton: Integrative Medicine Communications.

Braun, L. and Cohen, M. (2010*) Herbs and Natural Supplements. An Evidence Based Guide.* 3d Edition. Chatswood: Churchill Livingstone.

Cavalcanti, A., Da Silva, N., Alexandria, A. F., De Lima, A., Claudino, L., De Oliveira Carneiro, T., Valença, A. G. (2012). *In vitro* antimicrobial activity of mouth washes and herbal products against dental biofilm-forming bacteria. *Contemporary Clinical Dentistry*, *3*(3), 302. https://doi.org/10.4103/0976-237X.103623

Chandrahas, B., Jayakumar, A., Naveen, A., Butchibabu, K., Reddy, P., & Muralikrishna T. (2012) 'A randomized, double-blind clinical study to assess the antiplaque and antigingivitis efficacy of *Aloe vera* mouth rinse', *Journal of Indian Society of Periodontology*. 2012 Oct-Dec; 16(4): 543–548, doi: 10.4103/0972-124X.106905.

Cochran, D. (2008). Inflammation and Bone Loss in Periodontal Disease. *Journal of Periodontology*, 79(8 Suppl):1569-76. doi: 10.1902/jop.2008.080233 doi: 10.4103/0975-9476.96525

De Oliveira, J. R., De Castro, V. C., Vilela, P. das G. F., Camargo, S. E. A., Carvalho, C. A. T., Jorge, A. O. C., & de Oliveira, L. D. (2013). Cytotoxicity of Brazilian plant extracts against oral microorganisms of interest to dentistry. *BMC Complementary and Alternative Medicine*, *13*(1), 208. https://doi.org/10.1186/1472-6882-13-208

Fani, M., & Kohanteb, J. (2012). Inhibitory activity of *Aloe vera* gel on some clinically isolated cariogenic and periodontopathic bacteria. *Journal of Oral Science*, *54*(1), 15–21. https://doi.org/10.2334/josnusd.54.15

Farjana, H. N., Chandrasekaran, S. C., & Gita, B. (2014). Effect of oral curcuma gel in gingivitis management - a pilot study. *Journal of Clinical and Diagnostic Research*, *8*(12), ZC08-ZC10. https://doi.org/10.7860/JCDR/2014/8784.5235

FDI World Dental Federation. (2014). *Oral Health Worldwide*.

Fisher, C. (2009) *Materia medica of western herbs*. New Zealand: Vitex Medica.

Genco, R. J., & Genco, F. D. (2014). Common risk factors in the management of periodontal and associated systemic diseases: the dental setting and interprofessional collaboration. *Journal of Evidence-Based Dental Practice*, *14*(SUPPL.), 4–16. https://doi.org/10.1016/j.jebdp.2014.03.003

Granica, S., Kłębowska, A., Kosiński, M., Piwowarski, J. P., Dudek, M. K., Kaźmierski, S., & Kiss, A. K. (2016). Effects of *Geum urbanum* L. root extracts and its constituents on polymorphonuclear leucocytes functions. Significance in periodontal diseases. *Journal of Ethnopharmacology*, *188*, 1–12. https://doi.org/10.1016/j.jep.2016.04.030

Grbic, J., Wexler, I., Celenti, R., Altman, J., & Saffer, A. (2011). A phase II trial of a transmucosal herbal patch for the treatment of gingivitis. *Journal of American Dental Association*, *142*(10), 1168–1175.

Gunjal, S., Ankola, A., & Bhat, K. (2015). *In vitro* antibacterial activity of ethanolic extract of Morus alba leaf against periodontal pathogens. *Indian Journal of Dental Research*, *26*(5), 533. https://doi.org/10.4103/0970-9290.172082

Gupta, R. K., Gupta, D., Bhaskar, D. J., Yadav, A., Obaid, K., & Mishra, S. (2014). Preliminary antiplaque efficacy of *Aloe vera* mouthwash on 4 day plaque re-growth model: randomized control trial. *Ethiopian Journal of Health Sciences*, *24*(2), 139–144. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4006208&tool=pmcentrez&rendertype=abstract

Heinrich M, Barns J, Gibbons S, Williamson EM. *Fundamentals of Pharmacognosy and Phytotherapy*. 2nd ed. London: Churchill Livingstone Elsevier; 2012.

Highfield, J. (2009). Diagnosis and classification of periodontal disease. *Australian Dental Journal*, *54*(1 Suppl.), S11–S26. https://doi.org/10.1111/j.1834-7819.2009.01140.x

Hoffman, D. (2003) *Medical herbalism. The science and practice of herbal medicine.* Rochester: Healing Arts Press.

Izuora, K., Ezeanolue, E., Schlauch, K., Neubauer, M., Gewelber, C., Umpierrez, G. (2015) Impact of periodontal disease on outcomes in diabetes. *Contemporary Clinical Trials* 41: 93—99, http://dx.doi.org/10.1016/j.cct.2015.01.011

Jain, N., Jain, G. K., Javed, S., Iqbal, Z., Talegaonkar, S., Ahmad, F. J., & Khar, R. K. (2008). Recent approaches for the treatment of periodontitis. *Drug Discovery Today*, *13*(21–22), 932–943. https://doi.org/10.1016/j.drudis.2008.07.010

Javed F., Warnakulasuriya S. (2015).Is there a relationship between periodontal disease and oral cancer? A systematic review of currently available evidence. *Critical Review of Oncology/Hematology.* http://dx.doi.org/10/1016/j.critrevonc.2015.08.018

Jelvehgaran Esfahani, Z., Kadkhoda, Z., Eshraghi, S. S., & Salehi Surmaghi, M. H. (2014). Antibacterial effect of an herbal product persica on *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*: an in-vitro study. *Journal of Dentistry (Tehran, Iran)*,

11(4), 464–472. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4283749&tool=pmcentrez&rendertype=abstract

Jenabian, N., Moghadamnia, A. A., Karami, E., & Mir A, P. B. (2012). The effect of *Camellia sinensis* (green tea) mouthwash on plaque-induced gingivitis: a single-blinded randomized controlled clinical trial. *DARU Journal of Pharmaceutical Sciences*, *20*(1), 39. https://doi.org/10.1186/2008-2231-20-39

John, N. R., Gala, V. C., & Sawant, C. S. (2013). Inhibitory effects of plant extracts on multi-species dental biofilm formation in-vitro. *International Journal of Pharma and Bio Sciences*, *4*(2). https://doi.org/10.17795/iji.38199.Research

Júnior, E. G., Landucci, L. F., Khalil, O., Arafat, K., Ranieri, R. V., & Jr, G. (2011). Antimicrobial Activity of Six Plant Extracts from the Brazilian Savanna on Periodontal Pathogens. *International Journal of Odontostomatology*, *5*(3), 249–256.

Karim, B., Bhaskar, D., Agali, C., Gupta, D., Gupta, R., Jain, A., Kanwar, A. (2014) 'Effect of *Aloe vera* mouthwash on periodontal health: triple blind randomized control trial', Journal of Oral Health and Dental Management, 13(1): pp. 14-19. PMID: 24603910 [PubMed]

Karygianni, L., Cecere, M., Skaltsounis, A. L., Argyropoulou, A., Hellwig, E., Aligiannis, N., … Al-Ahmad, A. (2014). High-level antimicrobial efficacy of representative Mediterranean natural plant extracts against oral microorganisms. *BioMed Research International*, *2014*(July). https://doi.org/10.1155/2014/839019

Kaur, S., Bright, R., Proudman, S., Bartold, M. (2014). Does periodontal treatment influence clinical and biochemical measures for rheumatoid arthritis? A systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism* 44: 113-122, http://dx.doi.org/10.1016/j.semarthrit.2014.04.009

Kondo *et al.* (2014) 'A high-fiber, low-fat diet improves periodontal disease markers in high risk subjects: a pilot study', *Nutrition Research*, Jun;34(6):491-8. doi:10.1016/j.nutres.2014.06.001.

Kouidhi, B., Al Qurashi, Y. M. A., & Chaieb, K. (2015). Drug resistance of bacterial dental biofilm and the potential use of natural compounds as alternative for prevention and treatment. *Microbial Pathogenesis*, *80*, 39–49. https://doi.org/10.1016/j.micpath.2015.02.007

Lazar, V., Saviuc, C., & Chifiriuc, M. C. (2016). Periodontitis and Periodontal Disease - Innovative Strategies for Reversing the Chronic Infectious and Inflammatory Condition by Natural Products. *Current Pharmaceutical Design*, *22*(2), 230–237.

Mahyari, S., Mahyari, B., Emami, S. A., Malaekeh-Nikouei, B., Jahanbakhsh, S. P., Sahebkar, A., & Mohammadpour, A. H. (2016). Evaluation of the efficacy of a polyherbal mouthwash containing *Zingiber officinale*, *Rosmarinus officinalis* and *Calendula officinalis* extracts in patients with gingivitis: a randomized double-blind placebo-controlled trial. *Complementary Therapies in Clinical Practice*, *22*, 93–98. https://doi.org/10.1016/j.ctcp.2015.12.001

Mallikarjun, S., Rao, A., Rajesh, G., Shenoy, R., & Pai, M. (2016). Antimicrobial efficacy of Tulsi leaf (*Ocimum sanctum*) extract on periodontal pathogens: an *in vitro* study. *Journal of Indian Society of Periodontology*, *20*(2), 145–150. https://doi.org/10.4103/0972-124X.175177

Mankar, C. D., Shah, M. U., & Doshi, Y. S. (2016). Evaluation of antimicrobial activity of orange peel extract against oral biofilm forming organisms: an *in vitro* microbial study and scanning electron microscopic assessment. *International Journal of Basic and Clinical Pharmacology*, *5*(5), 1917–1923.

Mindell, E. (2000) *The New Herb Bible.* London: Vermillion

Moghaddam, H. K., Mirzaii, M., Khaksari, M., Fazli, M., Rahimi, F., & Behzadi, A. A. (2015). Antibacterial and anti-adherent activity of Great Mullein (*Verbascum thapsus* L.) ethanolic extract on *in vitro* biofilm formation of three oral Streptococci. *International Journal of Health Studies*, *1*(2), 34–37.

Muñoz-González, I., Thurnheer, T., Bartolomé, B., & Moreno-Arribas, M. V. (2014). Red wine and oenological extracts display antimicrobial effects in an oral bacteria biofilm model. *Journal of Agricultural and Food Chemistry*, *62*(20), 4731–4737. https://doi.org/10.1021/jf501768p

Murray Michael, & Pizzorno Joseph. (2013). The Encyclopedia of natural medicine. https://doi.org/10.1017/CBO9781107415324.004

Naiktari, R. S., Gaonkar, P., Gurav, A. N., & Khiste, S. V. (2014). A randomized clinical trial to evaluate and compare the efficacy of triphala mouthwash with 0.2% chlorhexidine in hospitalized patients with periodontal diseases. *Journal of Periodontal and Implant Science*, *44*(3), 134–140. https://doi.org/10.5051/jpis.2014.44.3.134

National Health Service (2015). *Gum disease.* Available at: http://www.nhs.uk/Conditions/Gum-disease/Pages/Introduction.aspx (Accessed: 20 November 2015)

Nguyen, C.M., Kim, J.W.M., Quan, V.H., Nguyen, B.H., Tran, S.D. (2015) Periodontal associations in cardiovascular diseases: the latest evidence and understanding. *Journal of Oral Biology and Cardiovascular Research*, *5*:203-206. http://dx.doi.org/10/1016/j/jobcr.2015.06.008

Palombo, E. A. (Swinburne U. of T. (2011). Traditional medicinal plant extracts and natural products with activity against oral bacteria: potential application in the prevention and treatment of oral diseases. *Evidence-Based Complementary and Alternative Medicine*, *2011*, 15 pp. http://doi.org/10.1093/ecam/nep067

Patra, J. K., Kim, E. S., Oh, K., Kim, H.-J., Kim, Y., & Baek, K.-H. (2014). Antibacterial effect of crude extract and metabolites of *Phytolacca americana* on pathogens responsible for periodontal inflammatory diseases and dental caries. *BMC Complementary and Alternative Medicine*, *14*(September 2014), 343. https://doi.org/10.1186/1472-6882-14-343

Petersen P.E. & Ogawa H. (2012) The global burden of periodontal disease: towards integration with chronic disease prevention and control. *Periodontology, 60*(2012), 15–39. doi: 10.1111/j.1600-0757.2011.00425.x.

Petrovic, M. S., Kesic, L. G., Kitic, D. V, Milasin, J. M., Obradovic, R. R., Bojovic, M. D., & Simonovic, A. A. (2015). Periodontal disease and phytotherapy. *Journal of Oral Hygiene & Health*, *3*(1), 1–4. https://doi.org/10.4172/2332-0702.1000172

Philstrom, B., Michalowicz, B. & Johnson, N. (2005) *Periodontal diseases*. Lancet 366:1809-1820. http://dx.doi.org/10.1016/S0140-6736(05)67728-8.

Pizzorno, J. & Murray, M. (2013) *Textbook of natural medicine.* St. Louis: Churchill Livingstone/Elsevier.

Preshaw, P. M. (2000). Host response modulation in periodontics. *Periodontology*, *48*(2008), 92–110.

Projan, S. J., & Youngman, P. J. (2002). Antimicrobials: new solutions badly needed. *Current Opinion in Microbiology*, *5*, 463–465.

Radvar, M., Moeintaghavi, A., Tafaghodi, M., Ghanbari, H., Fatemi, K., Mokhtari, M. R. & Farazi, F. (2016). Clinical efficacy of an herbal mouth wash composed of *Salix alba*, *Malva sylvestris* and *Althaea officinalis* in chronic periodontitis patients. *Journal of Herbal Medicine*, *6*(1), 24–27. https://doi.org/10.1016/j.hermed.2016.01.001

Rassameemasmaung, S., Sirikulsathean, A., Amornchat, C., Maungmingsook, P., Rojanapanthu, P., & Gritsanaphan, W. (2008). Topical application of *Garcinia mangostana* L. pericarp gel as an adjunct to periodontal treatment. *Complementary Therapies in Medicine*, *16*, 262–267. https://doi.org/10.1016/j.ctim.2007.12.004

Robbins, C. (1995) *The Household Herbal – A Complete Practical Guide to Plants that Heal.* London: Bantam Press.

Saini, P., Al-Shibani, N., Sun, J., Zhang, W., Song, F., Gregson, K. S., & Windsor, L. J. (2012). Effects of *Calendula officinalis* on human gingival fibroblasts. *Homeopathy*, *101*(2), 92–98. https://doi.org/10.1016/j.homp.2012.02.003

Salam, R., Khokon, J. U., & Mussa, S. B. M. T. (2014). Effect of neem and betel leaf against oral bacteria. *International Journal of Natural and Social Sciences*, *1*, 52–57.

Saleem, H. G. M., Seers, C. A., Sabri, A. N., & Reynolds, E. C. (2016). Dental plaque bacteria with reduced susceptibility to chlorhexidine are multidrug resistant. *BMC Microbiology*, *16*(1), 214. https://doi.org/10.1186/s12866-016-0833-1

Schwach-Abdellaoui, K., Vivien-Castioni, N., & Gurny, R. (2000). Local delivery of antimicrobial agents for the treatment of periodontal diseases. *European Journal of Pharmaceutics and Biopharmaceutics*, *50*(1), 83–99. https://doi.org/10.1016/S0939-6411(00)00086-2

Shafiei, Z., Shuhairi, N. N., Md Fazly Shah Yap, N., Harry Sibungkil, C. A., & Latip, J. (2012). Antibacterial activity of *Myristica fragrans* against oral pathogens. *Evidence-Based Complementary and Alternative Medicine*, *2012*(August). https://doi.org/10.1155/2012/825362

Sharma, R., Hebbal, M., Ankola, A. V, Murugaboopathy, V., & Shetty, S. J. (2014). Effect of two herbal mouthwashes on gingival health of school children. *Journal of Traditional and Complementary Medicine*, *4*(4), 272–8. https://doi.org/10.4103/2225-4110.131373

Shetty, Av., Anand, G., Ravinanthan, M., & Basaviah, R. (2015). *In vitro* antimicrobial and cytotoxic effects of *Anacardium occidentale* and *Mangifera indica* in oral care. *Journal of Pharmacy and Bioallied Sciences*, *7*(1), 69. https://doi.org/10.4103/0975-7406.148780

Sofrata, A., Lingstrom, P., Baljoon, M., and Gustafsoon, A. (2007). The effect of miswak extract on plaque pH. An *in vivo* study. *Caries Res*. 41, 451-454. doi: 10.1159/000107931

Somu, C.A., Ravindra, S., Ajith, S., & Ahamed, M.G. (2012). Efficacy of a herbal extract gel in the treatment of gingivitis: a clinical study. *Journal of Ayurveda*

Sravani, K., Suchetha, A., Mundinamane, D. B., Bhat, D., Chandran, N., & Rajeshwari, H. R. (2015). Plant products in dental and periodontal disease: an overview. *International Journal of Medical and Dental Sciences*, *4*(2), 913–921.

Srinath, J., & Lakshmi, T. (2014). Application of spices in dentistry - a literature review. *International Journal of Drug Development and Research*, *6*(2), 1–9.

Süntar, I., Oyardı, O., Akkol, E. K., & Ozçelik, B. (2015). Antimicrobial effect of the extracts from *Hypericum perforatum* against oral bacteria and biofilm formation. *Pharmaceutical Biology*, *209*(June), 1–6. https://doi.org/10.3109/13880209.2015.1102948

Tyler, V.E. (1999) *Herbs of Choice - the Therapeutic Use of Phytomedicines.* New York: Pharmaceutical Products Press

Vangipuram, S., Jha, A., & Bhashyam, M. (2016). Comparative efficacy of *Aloe vera* mouthwash and chlorhexidine on periodontal health: A randomized controlled trial. *Journal of Clinical and Experimental Dentistry*, *18*(4), 442–447. https://doi.org/10.4317/jced.53033

Vieira, D. R. P., Amaral, F. M. M., Maciel, M. C. G., Nascimento, F. R. F., Libério, S. A., & Rodrigues, V. P. (2014). Plant species used in dental diseases: ethnopharmacology aspects and antimicrobial activity evaluation. *Journal of Ethnopharmacology*, *155*, 1441–1449. https://doi.org/10.1016/j.jep.2014.07.021

Waghmare, P. F., Chaudhari, A. U., Karhadkar, V. M., & Jamkhande, A. S. (2011). Comparative evaluation of turmeric and chlorhexidine gluconate mouthwash in prevention of plaque formation and gingivitis: A clinical and microbiological study. *Journal of Contemporary Dental Practice*, *12*(4), 221–224. https://doi.org/10.5005/jp-journals-10024-1038

Walker, J., Imboeck, J. M., Walker, J. M., Maitra, A., Haririan, H., Rausch-Fan, X., … Somoza, V. (2016). *Magnolia officinalis* L. Fortified Gum Improves Resistance of Oral Epithelial Cells Against Inflammation. *The American Journal of Chinese Medicine*, *44*(6), 1167–1185. https://doi.org/10.1142/S0192415X16500658

Wan Nordini Hasnor, W., Fathilah, A., & Rahim, Z. (2013). Plant Extracts of *Psidium guajava*, *Mangifera* and *Mentha* sp. inhibit the growth of the population of single-species oral biofilm. *Alternative and Integrative Medicine*, *2*(1), 1–6. https://doi.org/10.4172/2327-5162.1000102

Webb, G.P. (2012) *Nutrition-Maintaining and Improving Health*. 4th edition. London: Holder Arnold

Wood, M. (2009) *The earthwise herbal. A complete guide to new world medicinal plants.* Berkeley: North Atlantic Books.

Yamanaka, A., Kouchi, T., Kasai, K., Kato, T., Ishihara, K., and Okuda, K. (2007). Inhibitory effect cranberry polyphenol on biofilm formation and cysteine proteases of *Porphyromonas gingivalis. J. Periodont. Res.* 42, 589-592. doi: 10.1111/j.1600-0765.2007.00982.x

Yarnell, E. Abascal, K. and Rountree, R. (2009) *Clinical Botanical Medicine: Revised and Explained.* New York: Mary Ann Liebert.

Yeturu, S. K., Acharya, S., Urala, A. S., & Pentapati, K. C. (2016). Effect of *Aloe vera*, chlorine dioxide, and chlorhexidine mouth rinses on plaque and gingivitis: A randomized controlled trial. *Journal of Oral Biology and Craniofacial Research*, *6*(1), 55–59. https://doi.org/10.1016/j.jobcr.2015.08.008

TABLE 1. HERB SPECIES INDICATED FOR TREATMENT & MANAGEMENT OF PERIODONTAL DISEASE IN AT LEAST 3 DIFFERENT CONTEMPORARY HERBAL TEXTS

Herb species	Alexander & Straub-Bruce, 2014	Pizzorno & Murray, 2013	Braun, 2010	McIntyre, 2010	Yarnell, 2009	Fisher, 2009	Wood, 2008 & 2009	Chevallier, 2007	Hoffman, 2003	Mills & Bone, 2003	Barnes *et al.*, 2002	Barker, 2001	Weiss, 2001	Blumental, 2000	Mindell, 2000	Tyler, 1999	Bartram, 1995	Robins, 1995	Count
Achillea millefolium	◯			◯			◯												3
Azadirachta indica	◯														◯	◯			3
Calendula officinalis	◯		◯	◯	◯	◯				◯		◯							7
Camellia sinensis		◯	◯		◯											◯			4
Centella asiatica		◯			◯	◯													3
Commiphora molmol	◯			◯		◯	◯	◯	◯	◯	◯		◯		◯	◯	◯		12
Echinacea purpurea	◯			◯	◯	◯			◯								◯		6
Hydrastis canadensis	◯														◯	◯	◯	◯	5

Matricaria recutita	○		○		○	○						○		○			○		7
Mentha piperita	○			○	○														3
Myrica spp.										○					○		○		3
Plantago major	○			○								○							3
Quercus spp.	○					○	○										○	○	5
Salvia officinalis	○			○	○	○	○				○		○		○	○	○	○	11
Sanguinaria canadensis		○			○	○										○	○		5
Symphytum spp.					○	○											○		3
Thymus vulgaris	○			○	○														3
Vaccinium myrtilis		○				○		○					○				○		5
SPECIES COUNT	12	4	3	8	10	10	3	3	2	3	2	3	3	1	5	6	10	3	**18**

TABLE 2. SUMMARY OF *IN VITRO* STUDIES

Source plant	Author	Year	Supragingival micro-organisms tested	Subgingival micro-organisms tested	Other cells tested	Biochemicals tested	Review/Comments
Mangifera indica (mango), *Anacardium occidentale* (cashew)	Anand *et al.*	2015	*Streptococcus mutans*		*Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Candida albicans*		
Coffea arabica, Coffea canephora	Antonia *et al.*	2010	*Streptococcus mutans*				
Camellia sinensis (green tea)	Araghizadeh *et al.*	2013	*Streptococcus mutans* (20 strains)	*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia* (20 strains each)			Minimal inhibitory concentration for *S. mutans* 6.25 mg/ml, whilst other micro-organisms was 12.5 mg/ml
Artemisia herba-alba (white wormwood), *Opuntia focus-indica* (Indian fig), *Camellia sinensis* (green tea), *Phlomis*	Arbia *et al.*	2017		*Porphyromonas gingivalis, Prevotella intermedia*			Minimal inhibitory concentration range 0.03 to 591 mg/ml, For *P. gingivalis*, *A. herba alba* and *O. ficus-indica* were most effective; for *P. intermedia, O. ficus-indica* and *C. sinensis* were most effective

crinita (Jerusalem sage)							
Copaifera reticulata (copaiba)	Bardaji *et al.*	2016	*Streptococcus mutans, S. salivarius, S. mitis*	*Fusobacterium nucleatum, Prevotella nigrescens, Porphyromonas gingivalis*	*Lactobacillus casei*		
Quercus infectoria (gall oak)	Basri *et al.*	2012	*Streptococcus mutans, S. salivarius*	*Porphyromonas gingivalis, Fusobacterium nucleatum*			*Quercus* galls used in traditional Indian medicine to treat toothache and gingivitis. Minimial inhibitory concentration 0.16 to 0.63 mg/ml in methanol or acetone extracts. Galls (plant cancers) effective against oral pathogens, *S. Salivarius* most susceptible.
Acacia nilotica (gum arabic tree), *Murraya koenigi* (curry tree), *Psidium guajava* (guava)	Chandrashekar *et al.*	2017	*Streptococcus mutans, S. sanguis, S. salivarius*	*Porphyromonas gingivalis, Fusobacterium nucleatum*	*Lactobacillus acidophilus*		
Cymbopogon citrates (lemongrass), *Plectrathus amboinicus* (Mexican mint), *Conyza bonariensis* (hairy fleabane)	Da Silva *et al.*	2012	*Streptococcus mutans, S. salivarius, S. oralis*		*Lactobacillus casei*		

Punica granatum (pomegranate), *Glycyrrhiza glabra* (liquorice), *Equisetum arvense* (horsetail), *Stryphnodendron barbatimam*	De Oliveira *et al.*	2013	*Streptococcus* spp.	*Porphyromonas gingivalis, Aggregatibacter actinomycetemcoitans, Prevotella intermedia*	*Candida* spp., cultured mouse macrophage (cell viability and inflammation response)		Minimal inhibitory concentrations (MIC) of *S. mutans* were 12.5 mg/ml for *P. granatum*. 3.13 mg/ml *S. barbatimam*, 25 mg/ml *E. arvense*, 100 mg/ml *G. glabra*
Salvadora persica (toothbrush tree)	Esfahani *et al.*	2014		*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans*			
Aloe vera (aloe)	Fani and Kohanteb	2012	*Streptococcus mutans*	*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Bacteroides fragilis*			*Aloe vera* gel had MIC for *S. mutans* of 12.5 ug/ml, and for *A. actinomycetemcomitans, P. gingivalis* and *B. fragilis* of 25-50 ug/ml ($P<0.01$)
Psidium cattleianum (cherry guava), *Myracrodruon urundeuva* (timber tree)	Gaetti-Jardim, Jr. *et al.*	2011		*Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum*			
Glycyrrhiza uralensis (Chinese liquorice)	Gafner *et al.*	2011	*Streptococcus mutans, S. sobrinus*	*Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum*			

Psacalium decompositum (Indian plantain)	Garcio-Palencia *et al.*	2016	*Streptococcus mutans*	*Porphyromonas gingivalis, Prevotella intermedia*			
Geum urbanum (wood avens)	Granica	2016			Polymorphonuclear lymphocytes		
Morus alba (mulberry)	Gunjal *et al.*	2015		*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia*			
Citrus sinensis (orange)	Hussain *et al.*	2015		*Prevotella intermedia, Porphyromonas gingivalis, Aggregatibacter actinomyctemcomitans*			
Moringa oleifera (drumstick tree), *Murraya koenigii* (curry tree), *Psidium guajava* (guava), *Eclipta prostata* (false daisy), *Phyllanthus fraternus* (gulf leaf-flower)	John *et al.*	2013	*Streptococcus mutans, S. salivarius, S. mitior, S. sanguinis, S. mitis, S. milleri*				
Pistacia lentiscus (mastic gum)	Karyagianni *et al.*	2014		*Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum*			

Terminalia chebula (myrobalan)	Lee *et al.*	2017					
Ocimum sanctum (tulsi)	Mallikarjun *et al.*	2016		*Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans*			
Citrus reticulata (orange)	Mankar *et al.*	2016		*Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans*			

TABLE 2. SUMMARY OF *IN VITRO* STUDIES (CONTINUED)

Source plant	Author	Year	Supragingival micro-organisms tested	Subgingival micro-organisms tested	Other cells tested	Biochemicals tested	Review/Comments
Azadirachta indicum (neem), *Mimusops elengi* (bakul), *Tinospora cardifolia* (giloy), *Ocimum sanctum* (tulsi)	Mistry *et al.*	2017	*Streptococcus mutans*				
Verbascum thapsus (mullein)	Moghaddam *et al.*	2015	*Streptococcus mutans, S. sanguinis, S. salivarius*				
Vitis vinifera (grape vine)	Munoz-Gonzalez *et al.*	2014	*Streptococcus mutans, S. oralis, Actinomyces oris*	*Fusobacterium nucleatum*		red wine, grape seed extract	Grape seed extract exhibited high activity against *F. nucleatum, S. oralis* and *A. oris*. Red wine good against *F. nucleatum* and *S. oralis*
Zingiber officinale (ginger)	Park *et al.*	2008		*Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella intermedia*			
Phytolacca americana (american pokeweed)	Patra *et al.*	2014	*Streptococcus mutans*	*Porphyromonas gingivalis, Escherichia coli*			

Robinia pseudoacacia (black locust)	Patra *et al.*	2015	*Streptococcus mutans*	*Porphyromonas gingivalis*			
Azadirachta indicum (neem), *Piper betel* (betel)	Salam *et al.*	2014	*Streptococcus mutans*	*Enterococcus faecalis*	*Pseudomonas aeruginosa*		
Myristica fragrans (nutmeg)	Shafiei *et al.*	2012	*Streptococcus mutans, S. mitis, S. salivarius*	*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum*		ethanol and ethyl acetate extracts	
Salvadora persica (toothbrush tree)	Solnata *et al.*	2007		*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Haemophilus influenza*		benzyl isothionyate	
Copaifera langsdorffii (Salam tree)	Souza *et al.*	2011		*Porphyromonas gingivalis*			
Hypericum perforatum (St. John's wort)	Suntar *et al.*	2015	*Streptococcus mutans, S. sobrinus*	*Enterococcus faecalis, Lactobacillus plantarum*			Water extract 8 ug/ml showed strong activity against *S. sobrinus* and *L. plantarum*, and moderate activity against *S. mutans* and *E. faecalis*
Punica granatum (pomegranate), *Psidium guajava* (guava) and *Schinus terbinthifolius*	Vieira *et al.*	2014	*Streptococcus mutans*				*Chenopodium ambrosioides* had no antimicrobial effects

(Brazilian pepper-tree)							
Magnolia officinalis (magnolia)	Walker *et al.*	2016		*Porphyromonas gingivalis*			
Psidium guajava (guava), *Mangifera spp*. (mango), *Mentha spp.* (mint)	Wan Nordini Hasnor *et al.*	2013	*Streptococcus sanguinis, S. mitis*				
Vaccinium macrocarpon (cranberry)	Yamanaka *et al.*	2007	*Streptococcus spp.*	*Porphyromonas gingivalis*			

TABLE 3: COMPARISON OF THERAPUTIC GOALS SET FOR TREATMENT OF PERIODONTAL DISEASE IN HERBAL AND SCIENTIFIC APPROACHES

Therapeutic goals for periodontal disease in herbal approach	**Therapeutic goals for periodontal disease in scientific approach**
Promote wound healing (vulnerary)	Inhibit growth of oral pathogens (anti-bacterial)
Improve membrane and collagen integrity	Reduce development of dental plaque
Decrease inflammation in the mouth (anti-inflammatory)	Reduce adhesion of microbial pathogens to the tooth surface
Improve immune status (immunomodulatory)	Down-regulate host-immune inflammatory response (new adjunct therapy)
Reduce bleeding of gums (anti-haemorrhagic)	
Reduce pain (analgesic)	
Inhibit growth of oral pathogens (anti-bacterial)	
(Compiled from sources: Hoffman 2003, Palombo 2011, Yarnell 2009, Pizzorno & Murray 2013, Shinwari *et al.* 2014)	

Appendices

Appendix 1: Detailed summary of 26 clinical trials

Author	Year	Country	Herbs Tested	Type of Preparation	Study Topic	Type of Study	Trial Size	Participant Inclusion Criteria	Study Duration	Dosage	Results/P-value
Abdulbaqi *et al.*	2016	Malaysia	*Salvadora persica* (toothbrush tree), *Camellia sinensis* (green tea)	aqueous herbal extracts as mouthwashes	Evaluation of *Salvadora persica* and gree tea effect on plaque	Double-blind randomized controlled crossover clinical trial	n=14; polyherbal; 0.12% chlorhexidine; placebo	25-40 year olds in good health and more than 20 teeth	24 hours	0.25 mg/ml green tea and 7.82 mg/ml S persica aqueous extracts	Polyherbal significantly better than chlorhexidine 1.317 +/- 0.344 (P<0.0167)
Amioan *et al.*	2010	Iran	*Salvadora persica* (toothbrush tree)	chewing gum with extract of *Salvadora persica*	Evaluation of effectiveness of *Salvadora persica* in gingivitis	Double blind randomised clinical trial	n=72	female high school students aged 15-18 years old, with plaque-induced moderate gingivitis	14 days	chew gum three times a day after brushing teeth for at least 1 hour	showed significant results in reduction of gingival index (P<0.001), bleeding index (P<0.005), but no significant results in reducing

											plaque index (P<0.579).
Aspalli *et al.*	2014	India	*Salvadora persica* (toothbrush tree), *Terminallia bellerica* (bibhitaka), *Piper bitel* (nagavalli), Gandhapura taila, Ela, Peppermint satva, Yavani satva	polyherbal mouthwash	Evaluation of the effectiveness of a polyherbal mouthwash compared to scaling procedure only	Randomised clinical trial	n=100: n=50 polyherbal mouthwash plus scaling; n=50 scaling only	Generally healthy, with minimum 20 teeth, diagnosed with mild to moderate gingivitis	21 days	15ml for 30 sec twice daily	greater reduction in plaque index scores, gingival index scores, and gingival bleeding scores in G2 (P<0.05)
Balappanavar *et al.*	2013	India	*Camellia sinensis* (green tea) & *Azadirachta indica* (neem)	mouthwash with single herb extract	Evaluation of the effectiveness of a mouthwash with green tea and neem extrats against chlorhexidine 0.2%	Randomised controlled clinical trial	n=30: n=10 2% neem extract; n=10 green tea extract; n=10 0.2% chlorhexidine	18-25 years old, generally healthy, diagnosed with mild to moderate gingivitis, minimum of 20 teeth, no	21 days	700ml 2% neem extract; 0.5% green tea extract; 500 ml 0.2% chlorexidine	0.5% tea showed better effectiveness (P<0.05) followed by 2% neem and then 0.2% chlorhexidine mouthwash.

								antibiotics in the last 6 months			
Batista *et al.*	2014	Brazil	*Punica granatum* (pomegranate) & *Matricaria recutita* (chamomile)	mouthwash with single herb extract	Evaluation of chamomile and pomegranate mouthwashes	Randomised controlled clinical trial	n=55 divided randomly into 3 groups: n=19 chamomile extract; n=18 pomegranate extract; n=18 0.12% chlorhexidine mouthwash	Over 18 years old, patients with periodontal disease, but no periodontal treatment or antibiotics for at least 3 months	9 months	not available	Pomegranate and chamomile mouthwash were as effective as chlorhexidine 0.12% (P<0.001)
Bedi *et al.*	2011	India	*Azadirachta indica* (neem)	herbal extract	Evaluation of neem extract for subgingival irrigation	Randomised controlled clinical trial	n=20: n=10 subgingival irrigation with neem extract plus scaling and root planing; n=10 scaling and root planing	30-55 years old, chronic generalised periodontitis with probing pocket depth of 5mm	30 days	not available	Neem extract showed significant (P<0.05) improvement on gingival index, clinical attachment level, reduction of pocket depth

											and aspartate transaminase levels - thus better results than using mechanical debridement alone
Bhat *et al.*	2011	India	*Aloe vera*	gel	evaluation of the efficacy of injecting *Aloe vera* into periodontal pocket	Randomised controlled clinical trial	n=15	20 to 35 years old, generally healthy with moderate periodontitis, no antibiotics or periodontal treatment in past 6 months, probing depth of 5 mm plus bleeding on probing	3 months	not available	Significant decrease ($P<0.05$) in pocket depth and relative decrease in gingival and plaque indexes at 1 month and 3 months

Chandrahas *et al.*	2012	India	*Aloe vera*	mouthwash	evaluation of *Aloe vera* mouthwash on plaque reduction comparing to 0.2% chlorhexidine	Randomised controlled double blind clinical study	n=120 persons; both sexes; aged 18-25 years randomly divided into 3 groups: G1 - 100% Aloe vera; G2- placebo/distilled water; G3 - 0.2% chlorhexidine	gingivitis or mild periodontitis, generally healthy, at least 1 maxillary quadrant full with premolars and molars, no pocket depth greater than 3mm, no recent antibiotic use, no history of systemic diseases	14 days induction phase, 22 days intervention phase	10ml twice daily for a minute	Significant (P<0.05) reduction in plaque index and gingivial index and effect comparable to chlorhexidine
Farjana *et al.*	2014	India	*Curcuma longa*	Curcumin extract oral gel	Evaluation of curcumin on bleeding index, bleeding on probing	Pilot clinical study	n=10	severe gingivitis	21 days	applied herbal gel twice a day for 3 weeks after brushing and leave gel in mouth for at least 10	Curcumin gel reduced bleeding on probing (P<0.001)

										minutes before rinsing	
Grbic *et al.*	2011	USA	*Centella asiatica* (gotu cola); *Echinacea purpurea*; *Sambucus nigra* (elderberry)	transmucosal herbal patch	evaluation of the efficacy of using transmucosal herbal patch with polyherbal extracts in treatment of gingivitis	Randomised double blind controlled trial	n=53: herbal transmucosal patch and placebo patch	18 to 65 years old, at least 3 posterior teeth in both maxillary quadrants, no hormonal treatment, no antibiotics, no anti-inflammatory therapy, no systemic conditions	15 days	not available	Gingival index was significantly (P<0.009) decreased in persons using the herbal patch; an effective and safe agent for reducing topical gingival inflammation

Gupta *et al.*	2015	India	*Cinnamomum verum*	herbal extract	Evaluation of cinnamon extract on plaque and gingival health	Triple blind randomized controlled clinical trial	n=105: n=35 cinnamon; n=35 chlorhexidine; n=35 distilled water		4 weeks	not available	Chlorhexidine reduced PI and GI more than cinnamon, but this was not statistically significant
Gupta *et al.*	2015	India	*Terminalia chebula*	herbal extract mouthwash	Evaluation of Terminalia chebula on plaque and gingival inflammation	Double-blind randomised control trial	n=90: n=30 terminalia chebula mouthwash; n=30 0.2% chlorhexidine; n=30 distilled water	undergraduate students	30 days	not available	Terminalia is as effective as chlorhexidine (P<0.05) at BI and PI reduction at 15 and 30 days vs placebo
Gupta and Gupta	2015	India	*Acacia nilotica*	*Streptococcus mutans*	Evaluation of *Acacia nilotica* on *Streptococcus mutans*	Double-blind Randomised Control Trial	n=90: n=30 50% A nilotica; n=30 0.2% chlorhexidine; n=30 saline water	high-caries risk volunteers	60 days	10 ml rinse for 30 days	Significant decreases in Strep mutans by A nitotica and chlorhexidine (P<0.0001)
Gupta *et al.*	2014	India	*Ocimum sanctum* (holy basil)	mouthwash	Evaluation of the effectiveness of a mouthwash with holy basil extrats against	Randomised triple blind controlled clinical trial	n=108: n=36 holy basil 4% mouthwash; n=36 0.12% chlorhexidine mouthwash; n=36 placebo mouthwash	generally healthy individuals, mild to moderate gingivitis, no antibiotic or anti-	30 days	10ml twice a day of *Ocimum sanctum* for 30 days	*Ocimum santcum* mouthwash prevented plaque as well as 0.12% clorehexidine (P<0.059)

					chlorhexidine 0.12%			inflammatory therapy history for past 3 months, no systemic diseases			
Gupta *et al.*	2014	India	*Aloe vera*	mouthwash	Evaluation of *Aloe vera* mouthwash for dental plaque reduction	Randomised double blind controlled clinical trial	n=300: n=100 *Aloe vera* mouthwash; n=100 chlorhexidine mouthwash; n=100 saline/placebo	generally healthy wth gingivitis, no antibiotic therapy for past 2 weeks	4 days	10 ml twice a day *Aloe vera* 100% juice used as a mouthwash	*Aloe vera* mouthwash (100% juice) was as effective as chlorhexidine
Author	**Year**	**Country**	**Herbs Tested**	**Type of Preparation**	**Study Topic**	**Type of Study**	**Trial Size**	**Participant Inclusion Criteria**	**Study Duration**	**Dosage**	**Results/P-value**

Hattarki *et al.*	2013	India	*Camellia sinensis* (green tea)	dental strips	Evaluation of effectiveness of green tea catechins in periodontal disease	Randomised controlled clinical trial and microbiological study	n=20: n=10 study group *Camellia sinensis*; n=10 control group received scaling and root planing	otherwise healthy, periodontal pockets of 5mm or more, at least 20 natural teeth, no antibiotics or antimicrobial drugs in past 6 months, no smokers, not pregnant	5 weeks	Hydroxy propyl cellulose strips containing catechin extract; dosage not specified	Statistically significant (P<0.001) reduction in periodontal pocket depth index, gingival index and plaque index. Reduction of periodontal bacteria *Tannerella forsythus* and *Porphyromonas gingivalis*
Jenabian *et al.*	2012	Iran	*Camellia sinensis* (green tea)	mouthwash	Evaluation of green tea extract mouthwash in treatment of gingivitis	Randomised single-blind controlled clinical trial	50 high school students aged 14-16 years old were randomly divided into 2 groups: G1 n=25 green tea 5% mouthwash; G2 n=25 saline/placebo	generally healthy, but with gingivitis	6 weeks	5ml *Camellia sinensis* extract twice a day	A herbal mouthwash with *Camellia sinensis* showed reduction in gingival index and inflammation

Karim *et al.*	2014	India	*Aloe vera*	mouthwash	Evaluation of Aloe vera mouthwash for reduction of dental plaque and gingival index	Randomise x tripple-blind control clinical trial	345 persons were randomply divided into 3 groups: G1= Aloe vera mouthwash (n=115); G2= chlorhexidine (n=115); G3=placebo/distilled water (n=115)	generally healthy with signs of gingivitis included, but exluded if had dental treatment, antibiotic or anti-inflammatory therapy in the last 3 month, if have systemic diseases and if smoke.	30 days	10ml twice a day for 1 minute and not to rinse with water afterwards	Aloe vera mouthwash showed equally effective results to that of chlorhexidine mouthwash in reducing gingivial, bleeding and plaque indixes
Mahyari *et al.*	2016	Iran	*Zingiber officinalis* (ginger); *Rosmarinus officinalis* (rosemary); *Calendula officinalis* (marigold)	polyherbal mouthwash	Evaluation of the effectiveness of a polyherbal mouthwash with ginger, rosemary and	Randomised double blind controlled trial	60 persons aged 18-65 were randomly divided into 3 groups: G1 n=20 polyherbal mouthwash; G2 n=20 chlorhexidine mouthwash;	generally healthy with gingivitis, but not on antibiotic or anti-inflammatory therapy for the past 14	14 days	twice a day	Polyherbal mouthwash was found to be as effective as chlorhexidine but with no side effects

					marigold (5%) extracts		G3 n=20 placebo	days, not pregnant and with no Sjogren's syndrome			
Moktasi *et al.*	2016	Iran	*Salix alba* (white willow); *Malva sylvestris* (Common mallow); *Althea officinalis* (marshmallow)	polyherbal mouthwash	Evaluation of polyherbal mouthwash with white willow, mallow and marshmallow extracts as an adjunct to scaling and root planing on patients with chronic periodontitis and gingivitis	Randomised double blind pilot study	Chronic periodontitis study: over 45 years old n=30: n=10 polyherbal mouthwash with scaling and root planing; n=10 chlorhexidine mouthwash with scaling and root planing; n=10 scaling and root planing; Gingivitis study: mean age 27.76; n=34: same groups as periodontitis study	Periodontitis study: periodontal patients with pockets and attachment loss in all quadrants, no antibiotics anti-inflammatory drugs or periodontal therapy in last 3 months, no smokers, no pregnancy.	14 days	10 ml of mouthwash twice daily	Polyherbal mouthwash was found to be as effective as chlorhexidine, especially in gingivitis patients. P-value is not available.

								Gingivitis study: Gingivitis patients, same exclusion criteria as periodontitis study			
Naiktari	2014	India	Triphala Amalaki (*Phyllanthus emblica*, aka *Emblica officinalis*), Haritaki (*Terminalia chebula*) and Bahera (*Terminalia bellirica*)	herbal mouthwash	Evaluation of *Phyllanthus emblica, Terminalis chebula* and *Terminalis bellirica*	Double-blind randomized multi-centre clinical trial	n=120: n=40 triphala; n=40 0.2% chlorhexidine; n=40 distilled water	hospitalised patients with periodontal disease	15 days	mouthwash 1 minute twice daily for 2 weeks	No significant difference between triphala and chlorhexidine ($P<0.05$). But both PI and GI had a significant reduction compared with distilled water.

Radvar *et al.*	2016	Iran	*Salix alba, Malva sylvestrais* and *Althaea officinalis*	polyherbal mouthwash	Evaluation of *Salix alba, Malva sylvestrais and Althaea officinalis* on periodontitis and gingivitis	Randomised clinical trial	n=30 periodontitis study, after 6 weeks of scaling and root planing: n=10 herbal mouthwash; n=10 chlorhexidine; n=10 placebo mouthwash; gingivitis study n=34: same groups as periodontitis study	chronic periodontitis patients with pocketing and attachment loss in all quadrants, all over 45 years old; gingivitis patients with signs of gum inflammation but no attachment loss or bone recession	periodontitis study: 4 weeks. gingivitis study: 2 weeks	100% ethanol extracts of 5 parts A. officinalis: 1.25 parts S. alba: 1 part M. sylvestris, dried and diluted 5% weight/volume to 0.31% g in 2ml H2O	herbal mouthwash and root planing reduced periodontitis indices more than root planing alone, but this reduction was not statistically significant. For gingivitis patients, herbal mouthwash significantly reduced BOP and GI, by same level as chlorhexidine. There was tooth and tongue staining with chlorhexidine

Rassameemasmaung *et al.*	2008	Thailand	*Garcinia mangostana* (purple mangosteen)	gel	Evaluation of the effectiveness of purple mangosteen gel applied topically	Randomised double blind pilot study	n=31; n=16 herbal gel plus scaling and root planing; n=15 only scaling and root planing	otherwise healthy, at least 2 periodontal pockets of 7-9mm, but 5-6 mm for rest, no antibiotics in 3 months, no periodontal treatment in 6 months	3 months	not available	Test group had greater reduction in periodontal pocket depth, gingival and bleeding indices, but both groups had good results (P<0.05) after 3 months of treatment
Sharma *et al.*	2014	India	*Azadirachta indica* (neem), *Mangifera indica* (mango)	Indigenously-prepared neem and mango chewing stick mouthwashes	Evaluation of neem and mango on plaque and gingival indices	Triple-blind randomised controlled trial	n=105: n=35 neem; n=35 mango; n=35 0.2% chlorhexidine	school children aged 12-15	4 months	not available	Neem possesses equivalent efficacy to chlorhexidine in reducing plaque, whilst chlorhexidine has superior antigingivitis properties

Sofrata *et al.*	2011	Sweden, Saudi Arabia	*Salvadora persica*	chewing stick	Evaluation of S persica on plaque and gingivitis, subgingival microbiota and GI	Double-blind randomised clinical trial	n=68: n=30 S persica; n=28 = control	over 18 years age, at least 24 teeth, no systemic disease, antibiotics, in last 6 months, no pregnancy	3 weeks	not applicable	active S persica actively reduced plaque (P=0.007)
Vangipuram	2016	India	*Aloe vera*	Aloe vera mouthwash	Evaluation of *Aloe vera* on plaque and gingival indices	Randomised controlled trial	n-390: n=130 Aloe vera; n=130 chlorhexidine; n=130 placebo	dental students	30 days	not available	No significant difference between Aloe vera and chlorhexidine (P<0.05)
Waghmare *et al.*	2011	India	Turmeric	herbal mouthwash	Evaluation of turmeric in preventing plaque formation and gingivitis	unknown	n=100: n=50 chlorhexidine; n=50 for herbal mouthwash	25-35 year olds, with fair to poor gingival index scores and plaque index >1	21 days	not available	chlorhexidine reduces PI better than turmeric mouthwash (P<0.05), but these had same results for GI and total microbial count

Walker *et al.*	2016	Austria	*Magnolia officinalis L.*	bark extract in fortified chewing gum	Evaluation of *Magnolia officinalis* chewing gum in reducing inflammatory response in oral epithelial cells	Four-armed parallel designed human intervention trial, with double-blind study for chewing gum intervention	n=40: n=10 *Magnolia* bark chewing gum; n=10 normal chewing gum; n=10 Colgate toothpaste with 0.3% triclosan; n=10 control	healthy volunteers	14 days	chewing two "dragees" of Magnolia bark gum for at least 10 minutes five times per day	Magnolia gum more effective than normal chewing gum at reducing lipopolysaccharide-induced inflammation and oral stress of epithelial cells by 73.4%
Yeturu *et al.*	2016	India	*Aloe vera*	unspecified	Evaluation of *Aloe vera* on plaque and gingivitis	Single blind randomized single-centre parallel group controlled trial	n=90: n=30 *Aloe vera*; n=30 chlorhexidine; n=30 chlorine dioxide	outpatients from periodontal department under fixed orthodontic treatment	15 days	not available	*Aloe vera* reduced PI scores by 20.38% (+/- 16.74) in 14 days, but this was significantly less than ($P<0.05$) for chlorhexidine (31.59% (+/- 16.58) or chlorine dioxide; and for GI score at 9.88% reduction (+/- 8.77)

											significantly less than for chlorhexidine at 16.3% (+/- 9.98)