

# Novel natural product based oral topical rinses and toothpastes to prevent periodontal diseases

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## Abstract

Over the past years, the public interest in natural or herbal based healthcare products is increasing. This trend is not only visible in the supermarkets, our dental practices, but also in the scientific world. More and more clinical trials are being conducted to validate the claims about these products on periodontal health. Among single component preparations, aloe vera and green tea are the most studied natural ingredients. Concerning polyherbal mixtures, triphala is the most popular product. The effects of these natural products on periodontal health seems encouraging, with almost all studies showing an inhibitory effect on plaque accumulation and improvement in gingival health. However, more studies are needed to be able to design clinical guidelines about the effect of these natural products on periodontal parameters. For most of these products solely one study is available and, moreover, the available studies are limited in duration, number of participants and the specific composition of the natural product is often not in detail described.

## Introduction

Dental plaque, a biofilm, is the nemesis of oral health. It is one of the important etiological factors for the most prevalent diseases of the mouth, namely tooth decay and periodontal diseases. Effective biofilm control is therefore of prime importance to maintain oral health. The search for adequate, quick and easy tools to control or remove dental plaque has been a real quest for many scientists and clinicians. However, after decades of research, it is clear that there is no ready-made solution.

In order to provide optimal control of the oral biofilm, different oral hygiene tools have been developed and marketed. The oldest tool, the toothbrush, is thought to have its roots around 3500BC in ancient Egypt [60]. However, after more than 5000 years of development, even the most advanced electric toothbrushes are not able to remove the biofilm completely. Williams and co-workers (2004) demonstrated that 3 minutes brushing with an electric toothbrush only removes 31% of the biofilm [53, 131]. A recent meta-review –a summary of the findings of high quality systematic reviews- showed a mean biofilm reduction of 46% after brushing with an electric toothbrush [126]. Manual toothbrushes perform even worse [126]. These findings underline that tooth brushing alone is insufficient to remove all plaque. When adding an interdental brush into the equation, 32% more plaque is removed than when only a toothbrush is used [110]. This additional effect on biofilm removal could not be shown with dental floss, wooden toothpicks or oral irrigators [110]. The reasons for this lack of clinical effectiveness of mechanical biofilm control for the majority of the populations are numerous with limited time of usage, lack of motivation, poor manual dexterity, crowding, tooth alignment being major factors [65, 104].

Given the importance of plaque bacteria in initiating oral diseases, the incorporation of chemical agents to boost the oral biofilm removal and/or its pathogenicity is a logical development [25]. In a meta-analysis Serrano and co-workers (2015) showed that chemical agents used for at least 6 months adjunctive to tooth brushing significantly improve gingival, bleeding and plaque indices [112]. The most commonly used compounds are chlorhexidine, essential oils, triclosan and cetylpyridium chloride embedded either in toothpastes or mouthwashes [50, 52, 59, 109, 132]. However, to date, there is no universally applicable chemical agent that can completely inhibit biofilm formation. Additionally, a wide range of side effects have been reported for almost every compound such as extrinsic tooth staining, increased calculus formation, transient taste disturbances, numbness and erosive or desquamative effects on the oral mucosa.

There is thus a need for exploring novel alternative adjunctive compounds for dentifrices and mouth rinses to boost oral biofilm removal and improve clinical indices for oral and periodontal health.

## Natural products

The last decade there is a renewed interest from patients in natural oral health products. A possible explanation for this could be that nowadays the oral health care provider has been replaced as the only source of oral health information by the internet, social media, ... [6, 61, 82]. These platforms often promote natural products because of their alleged benefits: the lack of alcohol, artificial preservatives, flavors and colors. It is therefore not surprising that the public interest in natural or herbal based healthcare products has grown dramatically over the years [34, 41, 57]. A large scale online survey in the US, showed that approximately 35% of the 26157 respondents reported the current use of herbal medicines [106]. A focus group discussion in Germany revealed that herbal based medicine is predominately used for treating mild to moderate diseases and to prevent illnesses/promote health. The most important reason why herbal medicine is preferred is dissatisfaction with conventional medicine [130]. Furthermore other arguments for this are positive experiences with herbal medicine in the past, and positive aspects and beliefs associated with herbal products, such as the believe that they are safer than regular products [21, 49, 130]. Another specific aspect is the importance of family traditions ("it was always done this way"). Family members are one of the most important sources of information concerning herbal medicine [130].

Dentifrices and mouthwashes labelled as natural typically do not contain ingredients such as synthetic sweeteners, artificial colours, preservatives, additives, synthetic flavours and fragrances. They are formulated from naturally derived components. The term "herbal" on the label implies that most of the active ingredients are plant based [41, 71]. While most chemical agents control plaque and gingivitis via anti-bacterial mechanisms, some natural compounds have additionally anti-inflammatory and anti-oxidant properties. Furthermore, there are many more claimed benefits of these: anti-nociceptive, saliva stimulant, anti-halitosis and anti-caries effects [36].

The use of herbal products is, however, not new. Humans have sought cures for diseases in nature since ancient times [22]. This tradition of using plants/herbs for medicinal purposes is particularly strong in certain regions, such as Asia and South-America. In India, the use of herbal compounds is one of the characteristics of Ayurveda medicine. Ayurveda, literally translated from the Sanskrit as the knowledge of life or the science of perfect health, is the historical system of personalized medicine, which emphasizes disease prevention and health promotion [91]. In this tradition, different key historical documents, including the "Rigveda", the "Charaka", "Sushruta Smahita" describe the use of *Ocimum sanctum*, triphala, green tea, chamomile, ... for various oral and dental problems [47, 77, 78]. In South-America, the use of medicinal plants dates back before the settlement by Spaniards [22]. Persian medicine encourages the use of herbs as *salvadora persica*, *acacia arabica*, *aloe vera*, ... or combinations thereof for healthy gums and oral health [111]. But also

in the Western world, the use of plants in dentistry is more common than one thinks. The use of Eugenol in the dental practice has been established for a long time [22]. Additionally, Listerine mouthwash can be found in many households across the globe.

Despite the long tradition of using herbs for medicinal and dental indications, the underlying evidence is often sparse. However, the growing demand for evidence based therapies has resulted in an increase in randomized clinical trials examining herbal/natural products. The number of randomized clinical trials concerning herbal/natural products increased from 2013 to 2015 by 143% [36]. The most covered oral health conditions involve oral mucositis, periodontal diseases and tooth decay, but interventions on oral candidiasis, malodour, aphthous stomatitis, and xerostomia are also reported. The most frequently used natural product containing formulations in these trials are mouthwashes (47%), toothpastes (7%), patches (7%) and oral gels (6%) [36].

The purpose of the present review was to provide a comprehensive overview of different natural products (and combinations thereof) described in recent (the last five years) randomized, clinical studies examining their usefulness in maintaining or obtaining periodontal health. An overview of all natural products is given in table 1. Table 2 and 4 respectively show the characteristics of studies concerning toothpastes and mouthwashes and table 3 and 5 display the results of these studies.

### *Acacia arabica*

*Acacia arabica* is a tree which grows in the Indian subcontinent, the Middle East and North Africa. The branches of this tree are used in India as chewing sticks ('Babul' or 'Kikar' datun) [115]. The trees are primarily planted for their bark which yield a gum known as Acacia arabica gum or Babul gum, used by many communities in daily oral hygiene [115, 122, 125]. The leaves, the bark and the gum of the tree all have claimed medicinal properties [122]. They contain gallic acid, calcium, magnesium, potassium salts of Arabic acid, tannins, cyanogenic glycosides, oxidases, peroxidases and pectinases, which all contribute to the claimed antibacterial, antihistaminic, anti-inflammatory, astringent and haemostatic properties [19, 68, 92, 95, 115, 122, 125]. Although the use of *Acacia arabica* is considered to be safe, in 2013 a case report was published in which the use of an *Acacia arabica* containing toothpaste was linked to plasma cell gingivitis in a 17 year old female patient. Discontinuation of the herbal toothpaste resolved the symptoms within 2 weeks [75].

The effect of *Acacia arabica* incorporated in a toothpaste was tested in gingivitis patients. In a cross-over study on 60 patients with established gingivitis, it was shown that the use of an *Acacia arabica* containing toothpaste for 4 weeks reduced plaque levels, gingivitis levels and bleeding on probing better than a control toothpaste [122].

Next to the traditional oral hygiene products (toothpastes and mouth rinses), *Acacia arabica* is also incorporated in gels and powders [92, 95]. A double-blind placebo-controlled clinical trial on patients with mild to moderate periodontitis showed the clinical effectiveness of the local application of an *Acacia arabica* containing gel after scaling and root planing [115]. After three months of usage of this product, the moderate pockets, plaque and gingival index were statistically significantly improved more than in the control group using a placebo gel.

### *Aloe Vera*

Aloe vera is a succulent, cactus like plant with mucilaginous tissue in the centre of the leaf that grows in tropical climates all around the world [16, 127, 132]. It is an accepted natural product for medical, cosmetic, and nutraceutical purposes based on its antibacterial and anti-inflammatory properties, easy availability and absence of known adverse effects [93, 132]. The use of aloe vera in dentistry is said to date back to 1966 when Noskova and co-workers used Aloe vera to treat early stages of periodontitis [88]. In vitro, antibacterial activity of Aloe vera against important oral pathogens such as *Candida albicans*, *Streptococcus mutans*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, *Prevotella intermedia*, *Peptostreptococcus anaerobius* and *Streptococcus mitis* has been demonstrated [39].

Recent literature showed that rinsing with Aloe vera mouthwashes reduced both plaque and gingivitis [3, 16, 127, 132]. Additionally, it reduces these clinical scores significantly better than distilled water [16] or a placebo mouthwash [127]. However, Aloe vera seems less effective than chlorhexidine in reducing plaque and gingival inflammation [16, 132] although Vangipuram and co-workers failed to confirm these findings. They showed that both an aloe vera and a chlorhexidine mouthwash were equally as effective in reducing plaque and gingival indices [127].

Besides the addition of *Aloe vera* to mouthwashes, it has also been added to many other dental products such as toothpastes and dental gels. The results found with these products also point to a positive effect of *Aloe vera* on the periodontium. An improvement in periodontal condition could be found after subgingival administration of an *Aloe vera* gel [12]. Additionally, *Aloe vera* toothpastes also reduce plaque and gingivitis levels in patients [27, 93]. This effect was comparable to a classic fluoridated or triclosan containing toothpaste [27, 93].

### *Anacardium occidentale* Linn.

*Anacardium occidentale* Linn is a tropical tree growing in many regions over the world, but originally indigenous and commonly found in the Northeast of Brazil [42]. Different parts of this plant (the fruits, stem bark, leaves) have been used in folk medicine for the treatment of a wide range of

medical and oral conditions [42]. In vitro, this natural product showed antimicrobial activity against *S. mutans*, *Streptococcus sobrinus*, *C. albicans* and *Lactobacillus acidophilus* [7, 15].

In a cross-over study on 30 patients with more than 20% of the sites bleeding on probing, it was shown that the use of an *Anacardium occidentale* Linn containing mouthwash for 4 weeks reduced plaque levels, and bleeding on probing better than a placebo rinse. This effect was comparable to the effect found after rinsing with a chlorhexidine mouthwash [42].

### *Azadirachta indica* (neem)

*Azadirachta indica* (neem) is a medicinal herb that can be found in most of the tropical and subtropical countries. Various parts of this tree, like the leaves, bark, flowers, fruits, twigs, gum, seeds pulp, oil and roots are used for their anti-inflammatory, antipyretic, analgesic, immunostimulant, antiulcer, hypoglycaemic, antifertility, antimalarial, antifungal, antibacterial, antiviral, anticarcinogenic, hepatoprotective and antioxidant activities [31].

In traditional Indian medicine it has been used as a chewing stick (miswak) [31]. In vivo research of neem chewing sticks showed that these possess antibacterial properties against *S. mutans*, *Streptococcus salivarius*, *S. mitis*, and *Streptococcus sanguis* [99].

The, to our knowledge, first and only controlled clinical trial about the effect of a 2% neem mouthwash on periodontal parameters showed encouraging results. Balappanavar and co-workers reported that the 3-weeks usage of a neem mouthwash in 10 young adults resulted in a significant reduction in plaque and gingivitis levels. The effect seen with the neem mouthwash exceeded the effects seen with a 0.2% chlorhexidine mouthwash used for 2 weeks [11].

### *Calendula*

*Calendula officinalis* is a plant in the genus *Calendula* of the Asteraceae family [5]. It is also known under the popular name 'pot marigold'. *Calendula officinalis* is believed to be native to the Mediterranean region, but is widely spread through the world in regions with a warm tepid climate [66]. Its yellow to orange flowers have been used in Europe for centuries for medicinal purposes in various applications such as infusions, tinctures, liquid extracts, creams or ointments [70]. Crude extracts of the plant contain polysaccharides, otenoids, lutein, lycopene, rutin, ubiquinone, xanthophylls, flavonoids, triterpene alcohols, phenol acids, tannins, glycosides, sterols, carotenoids and saponisides [5, 66]. Quercetin and triterpenoid are considered the most important molecules since they possess anti-inflammatory and anti-oxidant properties [29, 72, 107]. In vitro calendula extracts have shown to have antimicrobial [56, 73], antifungal [33, 38], anti-inflammatory [100], anti-oxidant [20, 101] and wound healing enhancing [102] effects.

In theory there are no contraindications or known drug interactions but individuals with known sensitivity to the Compositae family may be predisposed to allergic reactions [66].

In a large scale randomized controlled clinical involving 240 gingivitis patients, participants were asked to rinse either with a Calendula tincture or with distilled water for six months. Rinsing with a tincture of calendula showed more pronounced and strong reductions in dental plaque, gingivitis and bleeding on probing scores than rinsing with distilled water [66].

### *Curcuma longa/ turmeric*

Turmeric, commonly known as haldi, is a widely used household spice, well-known for its deep orange-yellow colour and used as flavouring agent in many Asian cuisines. Its most important compound is curcumin, which is claimed to have anti-inflammatory, anti-oxidant, antibacterial, antiviral, antifungal, anti-tumour, antispasmodic, hepato-protective, and wound healing properties [76, 119].

In a controlled clinical trial, Mali and co-workers compared the effects of the 3 week use of a 0.1% turmeric mouthwash to the effects of a 0.2% chlorhexidine mouthwash in 60 mild to moderate gingivitis patients. They showed that a 0.1% turmeric mouthwash was effective in reducing plaque and gingivitis levels. This plaque and gingivitis reduction was comparable to that of a chlorhexidine mouthwash [76]. Muglikar and co-workers [81] found comparable results. They divided 30 gingivitis patients in three groups: all patients underwent mechanical cleaning. In one group, this was the only treatment, in the second group this was followed with the 21-day usage of a chlorhexidine mouthwash and in the third group by a curcumin mouthwash for 21 days. After 21 days, the improvements in plaque and gingivitis scores were similar in the chlorhexidine a curcumin mouthwash group.

Broader than the scope of this article, also the use of turmeric gel in dentistry seems promising due to its anti-plaque and anti-inflammatory properties and the better acceptance by patients compared to chlorhexidine gel [64, 114, 119]

### *Cymbopogon*

*Cymbopogon*, popularly known as lemongrass, is an aromatic plant used in Brazilian popular medicine [129]. Lemongrass has a plethora of claimed medicinal properties such as antibacterial, antifungal, antioxidant, antiseptic, astringent, anti-inflammatory, analgesic and antipyretic [24]. Lemongrass oil also showed anti-biofilm properties in an in vitro biofilm model with *Candida dubliniensis* [124]. This is attributed to its various constituents (citral, limonene,...) that alter the permeability of membranes, resulting in major surface alternations and morphological modifications,



leading to reduced adherence capacity of pathogens, an important step in biofilm formation [24, 124].

A double-blind parallel clinical trial from India showed that 0.25% lemongrass oil could be a herbal alternative to 0.2% chlorhexidine mouthwashes [24]. Twenty gingivitis patients rinsing with lemongrass oil for 3 weeks showed a decrease in gingivitis and plaque indices comparable to the decrease seen with 20 patients rinsing with a chlorhexidine mouthwash for 3 weeks [24].

### *Eugenia uniflora*

Due to its adaptability to different weather and soil conditions *Eugenia uniflora*, a plant belonging to the Myrtaceae family and native to Brazil, can be found today all over South America [62, 63]. This plant is known by different names of which the most common are pitanga or Surinam cherry [62, 63]. For decades, its leaf extracts are used in traditional South American medicine for the treatment of digestive disorders and hypertension [62]. Next to the leaves, also extracts from the fruits and stems are used in medicine based on their promising antimicrobial, anti-oxidant and anti-inflammatory activities [28, 35, 63].

A randomized controlled clinical trial with a *Eugenia uniflora* toothpaste included 50 10- to 12-year old children with gingivitis. They were asked to brush their teeth 3 times a day for 7 day with either a *Eugenia uniflora* toothpaste or with a control 0.3% triclosan toothpaste. After 7 days, there was no effect of the *Eugenia uniflora* toothpaste on plaque levels but a marked reduction in bleeding upon probing was noted. This reduction was comparable to the reduction seen with the use of the triclosan dentifrice [63]. In this clinical trial no adverse effects were reported confirming the results of an in vitro study that showed that the consumption of *Eugenia uniflora* is safe [23, 63].

### *Matricaria chamomile* L

One of the most consumed herbs in the world, not necessarily for its medicinal properties, is undoubtedly *Matricaria chamomilla*, better known as chamomile. Millions of cups of chamomile tea are drunk all over the world each day [118]. Its' most important phytochemicals are terpenoids and flavonoid, to which anti-inflammatory, analgesic and antioxidant effects are attributed [40, 113, 118]. Due to this properties, it is commonly used for human ailments, including hay fever, inflammation, muscle spasms, menstrual disorders, insomnia, ulcers, wounds, gastrointestinal disorders, rheumatic pain and haemorrhoids [118]. Extensive reviews on the therapeutic effects of chamomile are written, e.g. by Srivastana and co-workers in 2010 or more recently by Miraj and Alesaeidi [79, 118]. Chamomile is generally recognized as safe by the Food and Drug administration. However a low percentage of people seem to be sensitive for chamomile and develop allergic reactions. It mainly concerns contact allergies [118].

For oral problems, several applications of chamomile have been demonstrated. For example the use of a chamomile mouth rinse helps to control the pain and burning sensation in aphthous stomatitis patients [113]. Furthermore chamomile appears to be a promising alternative for the treatment of oral mucositis [43].

To our knowledge, only one recent clinical trial is available in the periodontal field by Goes and co-workers. In this randomized placebo controlled clinical trial, 30 orthodontic patients with fixed appliances with gingivitis were asked to rinse their mouth 2 times a day for 15 days. The patients who were using the 1% chamomile mouthwash experienced a reduction in plaque index and in bleeding upon probing. Despite the fact that the plaque inhibition was lower in the chamomile group than in the chlorhexidine group, this difference was not statistically significant. The bleeding on probing reduction was similar between both mouthwashes [40].

### Magnolia

Like many substances described in this review, also the use of magnolia extracts (*Magnolia officinalis*) has a long history. For more than 2000 years, it has been used in oriental medicine [14]. Magnolia bark extract is used in the treatment of various diseases such as acute pain, diarrhoea, coughs and urinary problems [14]. Its pharmacological properties, such as its anti-inflammatory effect, are attributed to its two main constituents: magnolol and honokiol [14, 53].

The use of magnolia extracts in dentistry seems promising, as its' inhibitory effect on oral pathogens has been repeatedly demonstrated. An effect on *P. gingivalis*, *Aggregatibacter actinomycetemcomitans*, *P. intermedia* and *Fusobacterium nucleatum* has been shown [17, 44, 45, 54]. Additionally, in vivo experiments showed that chewing gums with magnolia bark extracts reduce total salivary bacterial load and the salivary mutans streptococci concentration [14, 45].

A 6 month randomized placebo controlled clinical trial testing a 0.3% magnolia toothpaste on 51 gingivitis patients showed a larger reduction in gingival and plaque indexes when compared to the placebo toothpaste [53].

### *Ocimum sanctum*

As many plants in this review, also *Ocimum sanctum* is one of these herbs that has been used in India and other parts of Asia for centuries [47]. This medicinal plant is known as "queen of herbs", however it is better known under its popular names as "holy basil" or "tulsi". The various phytochemicals with vitalizing properties, ensure that this plant is also known as the "elixir of life". *Ocimum sanctum* has been used traditionally for a wide range of disorders, including those of the mouth and throat, lungs, heart, blood, liver, kidney, and the digestive, metabolic, reproductive and nervous systems.

Gupta and co-workers examined the effect of a four week usage of a 4% *Ocimum sanctum* mouthwash on patients with high plaque levels (Turesky >1.5). When compared to a saline control mouthwash, the *Ocimum sanctum* mouthwash significantly reduced plaque and gingivitis indices. The magnitude of this reduction was similar to what was achieved by rinsing with a 0.12% chlorhexidine mouthwash [47].

### Propolis

Propolis is a glue-like substance made by honeybees for building and preservation of their hive from buds, sap from plants and trees (mostly resin), and other botanical sources [67]. The chemical composition of propolis differs based on the botanical origin, more than 200 compounds have been identified in different samples, such as fatty and phenolic acids and esters, substituted phenolic esters, flavonoids, terpenes, ...[13] It is believed that these biologically active components have antibacterial, antiviral, fungicidal, anti-inflammatory, antitumor, and wound healing properties [13, 67]. In vitro, propolis has an antimicrobial activity against *P. intermedia*, *Prevotella melaninogenica*, *P. gingivalis*, *A. actinomycetemcomitans*, *Capnocytophaga gingivalis* and *F. nucleatum* [4].

The effect of a 2% propolis rinse was examined in a randomized, double-blind, controlled experimental gingivitis trial in twins by Bretz and co-workers in 2014 [13]. After three weeks of non-brushing, the gingival inflammation in the twins using the propolis mouthwash was comparable to the gingival inflammation in the twins rinsing with a positive control 0.05% sodium fluoride, 0.05% cetylpyridinium chloride mouthwash.

### *Punica granatum*

*Punica granatum* var. *pleniflora* (also known as golnaar) is a subspecies of the pomegranate. It is the male version of this plant and therefore it only blooms but does not bear fruits [111]. The use of pomegranate has a long history in Persian medicine and is repeatedly described in medical and pharmaceutical literature [111]. In the dental field, the antibacterial effect of pomegranate against certain streptococci (e.g. *S. mutans* and *S. sanguinis*) has been shown in vitro [51, 128]. However, to our knowledge, it is never shown that pomegranate has antibacterial effects against specific periodontopathogens.

Recently the effect of a golnaar mouthwash was compared to a 0.2% chlorhexidine mouthwash in diabetic patients with gingivitis. After 21 days of rinsing, a comparable improvement in plaque and gingivitis indices and in bleeding upon probing was seen in both groups of patients with both mouthwashes [111].

### *Schinus terebinthifolius* (Brazilian pepper tree)

*Schinus terebinthifolius*, popularly known as the Brazilian pepper tree, is native to South America and belongs to the cashew family, Anacardiaceae [37]. It is believed that this plant has antimicrobial, anti-inflammatory and antiulcerogenic properties. Therefore, it is used in the management of venereal diseases, womb inflammation, urinary tract infections, skin wounds, diarrhoea, and gastroduodenal ulcers [32, 37]. In the dental field, the use of *Schinus terebinthifolius* seems promising in the treatment of alveolitis (dry socket) as shown in a rat study [26].

A randomized clinical trial by Freires Ide and co-workers compared the 10 day use of a 0.31% *Schinus terebinthifolius* and a 0.12% chlorhexidine mouthwash in 31 gingivitis patients. Although the experimental mouthwash could not reduce the biofilm, a clear reduction in gingival inflammation was seen. Additionally, an intergroup comparison did not show a difference between the *Schinus terebinthifolius* and a chlorhexidine mouthwash concerning the efficacy in reducing bleeding on probing. However, the chlorhexidine mouthwash significantly reduced the biofilm accumulation [37].

### *Salvadora persica*

The *Salvadora persica* tree grows in the Middle East. Sticks from its roots, miswak sticks, have been used for centuries as a traditional method for cleaning the teeth [117]. The habitual use of this chewing stick is still widely spread throughout parts of Asia, Africa and the Middle East [116]. It is demonstrated that a *Salvadora persica* chewing stick reduces the dental plaque and gingival inflammation better than an inactivated miswak stick [116]. This century-long, traditional use of *Salvadora persica* translated more recently to a scientific interest in this shrub. At this moment various studies are available studying its' in vitro antibacterial effect [117]. The results are diverse, probably due to the variation in preparation methods of the *Salvadora persica* extracts and the used analysis methods [117]. However, all together, it seems that *Salvadora persica* has antibacterial effects, especially against Gram negative bacteria [18, 117].

Abdulbaqi and co-workers examined the effect of green tea and *Salvadora persica* in vitro and in a clinical trial. In vitro they showed the antibacterial (against *S. mitis*, *S. sanguinis* and *Actinomyces viscosus*) and anti-adherent effect of this two-component mouthwash [1]. In the clinical study, less plaque regrowth was detected with a green tea and *Salvadora persica* mouthwash than with a chlorhexidine or placebo (distilled water) mouthwash [2]. The effect on gingival parameters was, however, not examined in this study.

### Tea

Originating from China, tea has conquered the world over the past 2000 years [11]. This drink, with its long history as traditional botanical medicine, is today's second most consumed beverage in the

world after water [11, 103]. Tea is made from the leaves of the plant "*Camellia sinensis*". There are several variants of tea of which white, green and black tea are the most famous. These differences are based on the processing and oxidation of the tea leaves. Green tea has undergone minimal oxidation, which results in higher concentration of catechins [65] than for example black tea. Catechins are the most abundant polyphenols in tea, to which antioxidant and antibacterial capacities are attributed. Based on these characteristics it is therefore believed that green tea reduces the incidence of cardiovascular disease, strokes, obesity, diabetes and cancer [65, 103].

In the dental field, it was shown that green tea inhibit the growth of certain periodontal pathogens such as *P. gingivalis*, *P. intermedia* and *Prevotella nigrescens* and inhibit their production of virulence factors [8]. Additionally, green tea can inhibit also the adherence of *P. gingivalis* onto human buccal epithelial cells in vitro [8, 108]. An inverse association between the daily intake of green tea and probing pockets depth was shown in an epidemiologic study [69].

There are several recent controlled clinical trials comparing green tea mouthwashes with chlorhexidine. Although these studies differ in many areas, such as the patient population, the treatment duration, the green tea concentration, they all describe positive results of green tea on plaque and gingivitis parameters [2, 11, 65, 103, 104]. Additionally, these effects are comparable to those seen with chlorhexidine mouthwashes.

In the oldest of these studies, Balappanavar and co-workers, controlled clinical trial about the effect of a 0.5% tea mouthwash on periodontal parameters showed encouraging results. Balappanavar and co-workers reported that the 3-weeks usage of a tea mouthwash in 10 young adults resulted in a significant reduction in plaque and gingivitis levels. The effect seen with the tea mouthwash exceeded the effects seen with a 0.2% chlorhexidine mouthwash used for 2 weeks on plaque levels. [11]. Kaur and co-workers [65] compared the effect of 1 week rinsing with either a 0.25% green tea catechin or a 0.12% chlorhexidine mouthwash in a cross-over trial including 30 persons with a healthy periodontium. They found comparable plaque indices for the green tea and chlorhexidine group after the study period. In a randomized controlled trial involving 30 gingivitis patients, Priya and co-workers compared a 5% green tea mouthwash to a chlorhexidine mouthwash [103]. After a month, they could not find statistically significant differences in the reduction in gingival and plaque index between the green tea and chlorhexidine mouthwash. However, the green tea mouthwash showed statistically significant better reduction in bleeding on probing. Similarly, Radafshar and co-workers compared a mouthwash containing 1% of tannins from green tea to a 0.12% chlorhexidine mouthwash in 40 gingivitis patients. After 28 days, also this green tea based mouthwash was as effective as chlorhexidine for its plaque inhibitory and bleeding upon probing reducing actions [104]. Finally, there is one study describing a mouthwash with green tea and *Salvadora persica*, that

demonstrated less plaque regrowth than seen with a chlorhexidine or placebo (distilled water) mouthwash.

### *Terminalia chebula*

*Terminalia chebula* is a tree originating from South Asia. This plant is called the 'King of Medicine' in Tibet because of its extraordinary healing power [48]. *Terminalia chebula* has a long history of use and is considered safe [46]. Tannins are the major constituents of the ripe fruit of *Terminalia chebula*. They are a group of polymeric phenolic substances releasing gallic acid as main component which is well recognized for its antimicrobial and astringent properties [46, 58]. Furthermore, it is believed that *Terminalia chebula* has also have antidiabetic, hepatoprotective, anti-inflammatory, antioxidant and many other effects [46]. For oral diseases, its fruits have been used in the prevention and treatment of caries, gingivitis and stomatitis [46, 58]. In vitro and in vivo, the antimicrobial effect of *Terminalia chebula* against *S. mutans* has been shown [58, 85-87].

Gupta and co-workers (2014) compared the effect of 2 weeks of rinsing with a 10% *Terminalia chebula* or a 0.12% chlorhexidine mouth rinse to rinsing with saline in a randomized controlled trial including 26 patients in each arm. The results showed that the *Terminalia chebula* mouth rinse could reduce gingival inflammation without having an effect on plaque levels. The effect seen with this product was not significantly different from the effect of the chlorhexidine mouthwash [46].

A 10% *Terminalia chebula* mouthwash was compared with a 0.2% chlorhexidine mouthwash and a placebo in a randomized controlled clinical trial by Gupta and co-workers (2015). After 30 days of the usage of the herbal and the chlorhexidine mouthwash a significant decrease in plaque and gingivitis scores was seen in both groups. No difference could be found between both groups, but both reduced the gingivitis and plaque score significantly better than distilled water.

### Polyherbal products

In addition to mouthwashes and toothpastes with one main active natural substance, a plethora of oral hygiene tools containing polyherbal formulations exist. The most studied polyherbal product in dentistry is triphala, combining three natural products.

Triphala (Sanskrit; tri = three and phala = fruits) is a combination of the fruits of three medicinal trees native to the Indian subcontinent: *Emblica officinalis* (amalaki), *Terminalia bellirica* (behera/ bibhitaki) and *Terminalia chebula* (haritaki) [78, 83, 96]. Triphala has been used in traditional medicine in India for over 1000 years and it is believed to promote longevity and rejuvenation in patients of all constitutions and ages [91].

A myriad of positive effects are attributed to triphala. Triphala is considered to have antioxidant, anti-inflammatory, antibacterial, immunomodulating, gastric hyperacidity reduction, antipyretic,

analgesic, antimutagenic, antistress, adaptogenic, hypoglycaemic, and anticancer effects [91]. In this light, this polyherbal preparation is used in gastrointestinal treatments, in stress reduction, for weight loss, reduction of body fat and many other applications [91].

A recent review described the role of triphala in dentistry, showing that this product has also several applications in the dental field such as root canal irrigation or as anti-caries product [97, 121]. The influence of this product on plaque accumulation and improving gingival health is also repeatedly reported [10, 84]

Three recent studies compare a Triphala mouthwash with a chlorhexidine mouthwash [78, 83, 96]. Naiktari and co-workers showed the effect of 2 weeks of rinsing with triphala on 40 patients with clinical signs of gingival inflammation in a randomized clinical trial. Triphala reduced gingival inflammation indices and plaque levels to a similar degree as a 0.2% chlorhexidine mouthwash and better than when patients were rinsing with distilled water [83]. Similar results were obtained by Pradeep and co-workers who compared 60 days of rinsing with a 6% triphala mouthwash to the effects of rinsing with a 0.2% chlorhexidine mouthwash or a placebo mouthwash. In this randomized controlled clinical trial, 90 patients suffering from generalized chronic gingivitis were included. The data showed similar reductions in gingivitis and plaque indices for the triphala and chlorhexidine mouthwash [94]. Mamgain and co-workers compared 60 gingivitis patients in a randomized clinical trial examining the effect of a combination of a triphala and Ela decoction with the effect of a chlorhexidine mouthwash. Both mouthwashes showed significant reductions in gingivitis and plaque indices with no difference between them [78]. In general, all these studies showed a significant decrease of plaque and gingival inflammation after use (from 15 to 60 days) of triphala in gingivitis patients. These differences were comparable to those seen with the chlorhexidine mouthwashes.

Arimedadi oil (Irimedadi Taila) is another polyherbal product which includes manjishtha (*Rubia cordifolia*), khadira (*Acacia catechu*), til oil (*Sesamum indicum*) and clove (*Syzygium aromaticum*), amongst others [77]. Analgesic, astringent, anti-inflammatory, antimicrobial, anti-plaque and anti-gingivitis properties have been assigned to each of these ingredients [77, 89]. Based on these properties, it is used in patients with stomatitis, glossitis, aphthous ulcers, dental caries, pyorrhea, gingivitis, hyperemia of gums and for stain removal [105].

A recent 3-arm randomized controlled clinical trial including 45 patients with mild to moderate gingivitis showed comparable effects after 21 days of rinsing with Arimedadi oil and chlorhexidine. Both products reduced the plaque levels and gingival inflammation significantly and to the same degree [77].

This effect was also seen when a topical arimedadi taila oil was used to gently massage the gums after scaling in gingivitis patients [89]. This reduced the gingivitis scores significantly better than scaling alone, although this did not lead to better plaque reduction.

Besides triphala and arimedadi oil, there are also many other polyherbal products on the market. Six recent controlled clinical trials compare the use of a polyherbal toothpaste/mouthwash with one containing chlorhexidine and/or a negative control [30, 55, 74, 98, 120, 123]. More details about these studies can be found in table 2 & 4 and the results in table 3 & 5. Except from two of them that both use the HiOra mouthwash, they all use different polyherbal products containing three to nine herbal components.

In four of these studies a commercially available polyherbal products were used. Tatikonda and co-workers used Dabur red of which the specific composition was not mentioned in the article [123]. A toothpaste with nine herbs, registered as Sudantha<sup>®</sup> and containing *Acacia chundra* Willd., *Adhatoda vasica* Nees., *Mimusops elengi* L., *Piper nigrum* L., *Pongamia pinnate* (L.) Pirerre, *Quercus infectoria* Olivier., *Syzygium aromaticum* L., *Terminalia chebula* Retz., *Zingiber officinale* Rosce was used by Howshigan and co-workers [55]. Finally, the HiOra mouthwash was studied by Prasad and Deshmukh [30, 98]. According to Prasad this contains pilu (*S. persica*), bibhitaka (*Terminalia bellirica*), Nagavalli, ela (cardamom), pippement satva, bellenic myrobalan (vibhitaki) [98]. For all these commercial mouthwashes, it was not mentioned in detail why these specific herbs were selected for these products.

Tadikonda and co-workers used a toothpaste with papain, bromelain, miswak and neem [120]. These last two ingredients are common in herbal products with one specific active component and discussed earlier. Papain is a natural enzyme derived from papaya fruit. It hydrolyses large proteins into peptides and amino acids [120]. Bromelain is extracted from the pineapple plant and is known for its anti-inflammatory effects [120]. Medically papain and bromelain in conjunction with animal proteases like trypsin and chymotrypsin offer a wide spectrum of therapeutic effects [120]. Laboratory and human studies showed collective anti-oedematous, anti-inflammatory, anti-thrombotic and fibrinolytic actions [120].

Mahyari and co-workers used a mouthwash with *Zingiber officinale*, *Rosmarinus officinalis* and *Calendula officinalis* [74]. *Calendula officinalis* or pot marigold is already discussed into detail earlier. Rosemary (*Rosmarinus officinalis*) has antibacterial and antioxidant properties, whereas ginger (*Zingiber officinale*) can reduce prostaglandin biosynthesis and has antibacterial properties against certain periodontal pathogens [74].



These six studies found that for all these polyherbal products, their effect on gingivitis, plaque and bleeding on probing indices seems comparable to chlorhexidine products and superior to a negative control such as saline [30, 55, 74, 98, 120, 123].

## Concluding remarks

For centuries natural products are empirically used to treat various diseases and to promote health. The past years, there is an increased scientific interest in these natural products and one tries to validate the health claims of these based on clinical studies. In the dental field, this led to a plethora of primarily short term clinical trials investigating the use of natural product based toothpastes and mouthwashes as antiplaque and antigingivitis agents. The results of most of these studies suggest that these products have positive effects on the plaque biofilm formation and gum health.

Although the results of the current clinical trials seem encouraging, it became apparent from this review that many of these studies suffer from issues related to their design. Therefore it is very hard, not to say impossible at the moment to draw firm conclusions. It is clear that more well-conducted clinical trials are needed to be able to draft clinical guidelines concerning the use of natural products for periodontal health. At this moment, there are few clinical studies published about each natural product. Additionally, for the active components studied in different clinical trials, it is impossible to compare these, because they are extremely heterogeneous in terms of their origin but also and more importantly in the set-up of the studies. Looking to the studies about Aloe Vera for example, each study used a different patient population ranging from dental student to orthodontic patients with gingivitis. Also the period of usage varied widely going from 7 days to 3 months. In addition, although all studies studying "Aloe Vera" used an Aloe Vera containing product, not one of them was identical. The concentration of Aloe Vera in the products used varied from 0.25% to 5% [65, 103]. Even more, in two studies, the specific composition of the used Aloe Vera oral hygiene product was not even mentioned [3, 132].

When future studies are designed it is important to adhere to existing generic and specific guidelines [9, 80, 112]. To the best of our knowledge, none of the clinical studies about natural oral health products fulfil all the requirements specified in these guidelines. In the future, to start with, it is important to select a sufficiently large and representative patient sample. Also, the origin and purity of the natural product should be described in detail and how this was processed into an oral hygiene product in order to obtain a reproducible product. The study duration should be at least 3 months, but preferably 6 months [9, 112]. The side effects of these natural products need to be examined and reported in detail in the literature. Additionally, it should be investigated if the mode of delivery (toothpaste versus mouth rinse) matters and what is the ideal concentration of each natural product. Finally, what has not been studied until now, is the effects of these products on the microbiological composition of the oral biofilms.

Based on the available literature, although the usage of natural products for periodontal health seems encouraging, at this moment there is not enough evidence to shift from products approved by regulatory dental bodies to natural oral hygiene products. Future research should focus on the standardization of the study design, investigated parameters and participants to reduce the heterogeneity.

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## Acknowledgements

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## Tables

Table 1: Natural products

Scientific name (Family name)*	Common name	Properties
<i>Acacia Arabica</i> (Fabaceae)	Babul	Antibacterial, antihistaminic, anti-inflammatory, astringent and hemostatic. [122]
<i>Aloe Vera</i> (Asphodelaceae)	Aloe Vera	Anti-inflammatory, antibacterial, antioxidant, immune-boosting antiulcer activity, astringent effect, hypoglycemic and possibility of reducing scars and enhancing wound healing [16, 127, 132]
<i>Anacardium occidental</i> Linn. (Anacardiaceae)	Cashew	Antinociceptive, anti-inflammatory, and antimicrobial. [42]
<i>Azadirachta indica</i> (Meliaceae)	Neem	Anti-inflammatory, antipyretic, analgesic, immunostimulant, antiulcer, hypoglycemic, antifertility, antimalarial, antifungal, antibacterial, antiviral, anticarcinogenic, hepatoprotective and antioxidant activities.[31]
<i>Calendula officinalis</i> (Asteraceae)	Pot marigold	Antibacterial, antifungal, wound healing and re-epithelization, anti-inflammatory, antioxidant, immunomodulatory and anti-mutagenic properties. [66]
<i>Curcuma longa</i> (Zingiberaceae)	Turmeric, haldi	Anti-inflammatory, anti-oxidant, antimicrobial properties [76].
<i>Cymbopogon</i> (Poaceae)	Lemongrass	Antibacterial, antifungal, antioxidant, antiseptic, astringent, anti-inflammatory, analgesic, antipyretic and carminative properties. [24]
<i>Eugenia uniflora</i> (Myrtaceae)	Surinam cherry, pitange	Antimicrobial, anti-oxidant and anti-inflammatory properties. [35, 63]
<i>Camellia sinensis</i> (Theaceae)	Green tea	Anti-oxidant, antibacterial [65, 103, 104]
<i>Matricaria chamomilla</i> (Asteraceae)	Chamomile	Anti-inflammatory, analgesic and antioxidant effects. [40, 113, 118]
<i>Magnolia officinalis</i> (Magnoliaceae)	Magnolia	Anti-inflammatory, antimicrobial and anti-oxidant [53]
<i>Ocimum sanctum</i> (Lamiaceae)	Holy basil/ tulsi	Anticancer, antidiabetic, antifungal, antimicrobial, cardioprotective, analgesic and antispasmodic actions [90]
	Propolis	Antibacterial, antiviral, fungicidal, anti-inflammatory, antitumor, and wound healing properties [13]
<i>Punica granatum</i> (Lythraceae)	Golnaar	Antibacterial [51, 128]

<i>Schinus terebinthifolius</i> (Anacardiaceae)	Brazilian peppertree, Christmas berry	Antimicrobial, anti-inflammatory, and antiulcerogenic [32, 37]
<i>Salvadora persica</i> (Salvadoraceae)		Antibacterial, antifungal, and antiviral effects. [2, 116]
<i>Terminalia chebula</i> (Combretaceae)		Antimicrobial, anticariogenic, antidiabetic, hepaprotective, anti-inflammatory, and antioxidant effects. [46]

\* Familiennaam gevonden via <http://www.tropicos.org/>

Table 2: natural toothpastes: characteristics of the studies

Reference	Study type	Ingredients	N°		Age F/M	Gingival health	Evaluation points	Super-vised	Additional oral hygiene instructions	Additional treatments	Conclusion
			Bl	End							
<b>Hellström and Ramberg, 2014, Sweden</b>	RCT 6 mo	0.3% Magnolia extract 2x/d, for 6mo	51	46	29/17 20-65yrs (mean: 43)	Gingivitis	BL 3 mo 6 mo	No	Apply 2 cm of the dentifrice on the brush at each time of brushing and to continue their regular self-performed plaque control measures twice a day.	NR	Six months' unsupervised use of a dentifrice containing 0.3% Magnolia extract resulted in significantly greater gingivitis reduction than a corresponding control dentifrice
		Placebo 2x/d, for 6mo	51	48	30/18 24-61 (mean: 42)						
<b>Howshigan et al., 2015, Sri Lanka</b>	RCT 24 wks	Ayurvedic toothpaste (Sudantha <sup>®</sup> , combination of nine herbs) for 24wks	40	34	18/16 24.5+-4.7 yrs	Generalised chronic gingivitis	BL 4 wks 8 wks 12 wks 24 wks	No	Instructions for brushing	Full-mouth prophylaxis	This study provides robust evidence of the beneficial antiplaque and antigingivitis effects of the test herbal toothpaste (Sudantha <sup>®</sup> ) on patients with chronic gingivitis.
		Placebo for 24wks	40	32	20/12 24.5 +- 4.8 yrs						
<b>Jovito et al., 2016, Brazil</b>	RCT (phase II)	<i>Eugenia uniflora</i> linn. (Surinam cherry) 3x/d for 7d	25	25	17/8 10-12yrs old	Gingivitis	BL 7d	Yes (1x/d & personal and	The patients were instructed as	NR	In conclusion, <i>E. uniflora</i> dentifrice showed anti-gingivitis properties in

	7d	Triclosan 0.3% (Colgate Total 12®) 3x/d for 7d	25	25	12/13 10-12yrs old			telephonic contact with parents)	to the number of three daily brushings.		children aged 10-12 years. Thus, it may be a potentially efficient and safe product to be used alternatively in preventive dental practice.
<b>Tangade et al., 2012 India</b>	CO 28d	Babul ( <i>Acacia arabica</i> ) toothpaste 2min 3x/d for 4wks	60	ND	18-37 28.8 ± 3.28	Gingivitis	BL 28d	No	Use of oral hygiene items was instructed.	10 wk wash-out between R/	Brushing with <i>Acacia arabica</i> -containing toothpaste may help inhibit gingivitis. It can be recommended for daily oral hygiene procedures.
		Regular toothpaste 2min 3x/d for 4wks									
<b>Tatikonda et al., 2014, India</b>	RCT 30d	Herbal toothpaste (Dabur Red) 3 min 2x/d for 30d	15	15	15/15 35-43 yrs	Gingivitis	d0 30d	No	Bass method	Professional prophylaxis	After 30 days of trial, both test and control groups showed effective reduction of plaque and gingivitis, which was statistically significant. No adverse reactions to dentifrices products were observed during the trial. It was concluded that herbal dentifrice was as effective as non-herbal dentifrices in the control of plaque and gingivitis.
		Conventional toothpaste (Pepsodent) 3 min 2x/d for 30d	15	15							
<b>Tadikonda et al., 2017, India</b>	RCT 30d	Toothpaste with Papain, Bromelain, Miswak and Neem 2x/d for 2-3 min for 30d	26	24	12/12 20yrs	Orthodontic subjects with visible plaque and gingivitis	BL 30d	No	Charters method of tooth brushing.	NR	The efficacy of the test dentifrice in limiting plaque and gingivitis suggests that it can be used as a home based adjunct to clinical therapy in orthodontic patients.
		Control toothpaste 2x/d for 2-3 min for 30d	26	26	17/9 20.23yrs						

RCT: randomized controlled clinical trial, CO: cross-over, min: minutes, d: day, wks: weeks, mo: months, yrs: years, BL: baseline

NR: not reported

Table 3: natural toothpastes: results of the studies

	Groups	Gingival index				Plaque index				BOP			
		Type	Site s/tooth	Teeth	Change	Type	Site s/tooth	Teeth	Change	Type	Site s/tooth	Teeth	Change
<b>Hellström and Ramberg 2013</b>	Magnolia extract	LS	6	All	20% decrease	Turesky	6	All	12% decrease	NR	NR	NR	NR
	Placebo				8% decrease				4% decrease				NR
<b>Howshigan et al., 2015</b>	Ayurvedic, polyherbal toothpaste	NR	NR	NR	NR	Turesky	6	All	52% decrease	BOP	6	All	77% decrease
	Placebo				NR				15% decrease				36% decrease
<b>Jovito et al., 2016</b>	<i>Eugenia uniflora</i> linn.	NR	NR	NR	NR	OHI-S	NR	NR	0% decrease	Ainamo	NR	NR	65% decrease
	Triclosan				NR				13% decrease				63% decrease
<b>Tangade et al., 2012</b>	Babul ( <i>Acacia arabica</i> ) 1	LS	4	All (3M)	47% decrease	Turesky	4	All (3M)	33% decrease	Ainamo	4	All (3M)	21% decrease
	Regular toothpaste 1				5% decrease				9% decrease				13% decrease
	Babul ( <i>Acacia arabica</i> ) 2				26% decrease				21% decrease				26% decrease
	Regular toothpaste 2				No change				6% decrease				7% decrease
<b>Tatikonda et al., 2014</b>	Polyherbal toothpaste	LS	2	All	27% decrease	Turesky	2	All	19% decrease	NR	NR	NR	NR
	Conventional toothpaste				38% decrease				17% decrease				NR
<b>Tadikonda et al., 2017</b>	Papain, Bromelain, Miswak and Neem	LS	NR	NR	42% decrease	mLSPI	NR	NR	40% decrease	NR	NR	NR	NR
	Control toothpaste				25% decrease				21% decrease				NR

LS: gingival index according to Loë and Silness, 1963, Turesky: Turesky modification of Quigley and Hein plaque index, OHI-S: simplified Oral hygiene index, mLSPI: modified Silness and Loe plaque index according to William et al., 1991

BOP: bleed on probing, Ainamo: Ainamo and bay bleeding index

NR: not reported, ND: not deductible



Table 4: natural mouth rinses: characteristics of the studies

Reference	Study type	Ingredients	N°		F/M Age	Gingival health	Evaluation points	Super-vised	Additional oral hygiene instructions	Additional R/	Conclusion
			Bl	End							
<b>Ajmera et al. 2013 India</b>	RCT 3 mo	Aloe Vera mouthwash 2x/d for 3mo	15	15	NR 18-65yrs	Plaque-induced gingivitis	BL 1 mo 3 mo	NR	NR	Scaling in two groups	It was concluded that aloe vera had a significant anti-inflammatory property. Thus, it can be used as an adjunct to mechanical therapy for treating plaque-induced gingivitis.
		Scaling	15	15							
		Aloe vera mouthwash 2x/d for 3mo and scaling	15	15							
<b>Abdulbaqi et al., 2016, Malaysia</b>	CO 24h	<i>Salvadora persica L</i> & green tea 30s with 15 mL, twice	14	14	13/1 25-39yrs	24h plaque regrowth	BL 24h	Fist (of two) rinses was supervised.	No	Polishing to have plaque free surfaces at baseline.	The test mouthwash has an anti-plaque effect for a 24h period. Longer-term clinical studies are highly encouraged to investigate its anti-plaque effect for longer periods.
		0.12% CHX 30s with 15 mL, twice	14	14							
		Placebo 30s with 15 mL, twice	14	14							
<b>Balappanavar et al., 2013, India</b>	RCT 3 wks	0.5% tea, 3 wks	10	10	15/15 18-25yrs, mean: 20.94 +- 0.26	Gingivitis	BL After 1st rinse 1 wk 2 wks 3 wks	Yes	BL: oral hygiene instruction: brush 2x/d with horizontal scrub method & rinse toothbrush under running water	NR	The effectiveness of 0.5% tea was more compared to 2% neem and 0.2% chlorhexidine.
		2% neem, 3 wks	10	10							
		0.2% chlorhexidine gluconate, 2 wks	10	10							
<b>Bretz et al., 2014, Brazil (&amp;US)</b>	RCT 21d	2% propolis rinse, 2x 25ml for 30s/d, 3 wks	21	19	22/16 13-22yrs	Induced gingivitis in twins	-14d (BL)	Yes (1x/d)	14d oral hygiene promotion	At end of study: prophylaxis	Use of a 2% propolis rinse was equivalent to a positive

		0.05% sodium fluoride & 0.05% cetylpyridinium chloride rinse, 2x 25ml for 30s/d, 3 wks	21	19			0 (after hygiene phase) 21d (after no-hygiene phase)		(with 1x/d supervised brushing), followed with 21d gingivitis induction phase		control rinse during a 21-day non-hygiene period.
<b>Chandras et al., 2012 India</b>	RCT 7d	100% Aloe vera, 10ml, 2x 1min/d, 7d	120	120	62/58 18-25	Experimental gingivitis (BL-14d: induction phase, d15-d22: intervention phase)	BL 7d 14d 22d	No	No	7d before BL: professional cleaning	Aloe vera mouthwash can be an effective antiplaque agent and with appropriate refinements in taste and shelf life can be an affordable herbal substitute for chlorhexidine.
		Distilled water, 2x 1min/d, 7d									
		0.2% CHX, 2x 1min/d, 7d									
<b>Dany et al., 2015, India</b>	RCT 21d	2x 1 min/d 0.25% lemongrass oil mouthwash for 21d	20	20	NR/NR 25-45yrs old	Gingivitis	BL 14d 21d	NR	Modified bass method. New toothbrushes of same make and brand to maintain uniformity.	Oral prophylaxis	Lemongrass oil mouthwash can also be used as a good herbal alternative to CHX mouthwash, so further studies are needed.
		2x 1min/d 0.2% chlorhexidine mouthwash for 21d	20	20							
		-	20	20							
<b>Deshmukh et al., 2017, India</b>	RCT 14d	Herbal (HiOra) 2x15mL 60s/d for 14d	15	ND	8/7 18-21 yrs	NR	BL 7d 14d	Yes	Similar toothbrush and toothpaste	Supragingival scaling	Herbal and probiotic mouthwashes can prove to be effective alternatives to CHX with minimal side effects.
		0.2% CHX 2x10mL 60s/d for 14d	15	ND							
		Probiotic 2x20mL 60s/d for 14d	15	ND							
<b>Freires Ide et al., 2013, Brazil</b>	RCT Phase II 10d	10mL 0.3125% <i>Schinus terebinthifolius</i> , 1x/d for 1min, 10d	16	14	7/7 9-13 yrs (mean: 10.9yrs)	Gingivitis	BL 10d	No	NR	No	ST mouthwash showed significant anti-inflammatory activity (equivalent to CHX),

		10mL 0.12% CHX, 1x/d for 1min, 10d	15	13	9/4 9-13 yrs (mean: 11.2yrs)						but it was not able to reduce biofilm accumulation.
<b>Goes et al., 2016, Brazil</b>	RCT 15d	1% <i>Matricaria chamomilla</i> L 2x 15mL/d for 1 min for 15d	10	10	26-4 10- 40yrs (mean: 28.8)	Gingivitis in orthodontic patients with fixed appliances	BL 15d	Written recommendations to follow at home	NR	NR	MTC reduced biofilm accumulation and gingival bleeding in patients with gingivitis, probably because of its antimicrobial and anti-inflammatory activities.
		0.12% CHX 2x 15mL/d for 1 min for 15d	10	10							
		Placebo 2x 15mL/d for 1 min for 15d	10	10							
<b>Gomes et al., 2016, Brazil</b>	CO 30d	10% <i>Anacardium occidentale</i> linn. 2x 1 min/d	30	27	15/15 18-32 yrs	Bleeding index $\geq$ 20%	BL 30d	NR	Rinse 30 min after tooth brushing. New toothbrush, habitual technique	NR	Mouthwash containing 10% AO was effective as an antiplaque and antigingivits agents, in a similar manner than 0.12% CHX.
		0.12% chlorhexidine digluconate 2x 1 min/d	27	NR							
		Placebo 2x 1 min/d	27	NR							
<b>Gupta et al., 2014b, India</b>	RCT 30d	10mL 4% <i>Ocimum sanctum</i> , 2x/d for 60s, 30d	36	36	16/11 18-27 yrs, mean: 22.75	Turesky PI $>$ 1.5 and DMFT: 3 to 5	BL 15d 4 wks	NR	NR	No	The results of the present study indicate that <i>Ocimum sanctum</i> mouth rinse may prove to be an effective mouthwash owing to its ability in decreasing periodontal indices by reducing plaque accumulation, gingival inflammation and bleeding. It has no side effect as compared to chlorhexidine.
		10mL 0.12% Chlorhexidine 2x/d for 60s, 30d	36	36							
		10mL Saline 2x/d for 60s, 30d	36	36							

<b>Gupta et al., 2014a, India</b>	RCT 14d	<i>Terminalia chebula</i> 10% 10mL 2x 60s/d for 2 wks	26	26	39/39 19-25 yrs	NR	0 7d 14d	No	No	NR	This study demonstrated that <i>Terminalia chebula</i> mouth rinse is effective in reducing microbial plaque, gingival inflammation and neutralizing salivary pH
		0.12% chlorhexidine, 10mL 2x 60s/d for 2 wks	26	26							
		Saline 10mL 2x 60s/d for 2 wks	26	26							
<b>Gupta et al. 2015, India</b>	RCT 30d	<i>Terminalia chebula</i> 10% 10mL 2x 60s/d for 30d	30	30	NR 22.16yrs	Turesky PI >1.5 and DMFT: 3 to 5	BL 15d 30d	No	No	No	The results of the present study indicate that <i>Terminalia chebula</i> may prove to be an effective mouthwash. <i>Terminalia chebula</i> extract mouth rinse can be used as an alternative to chlorhexidine mouthrinse as it has similar properties without the side-effects of the latter.
		0.2% chlorhexidine 10mL 2x 60s/d for 30d	30	30	NR 21.71yrs						
		Distilled water 2x 60s/d for 30d	30	30	NR 22.13yrs						
<b>Kaur et al., 2014, Brazil</b>	CO 1 wk	0.25% green tea catechin for 1 wk	30	30	NR/NR 18-25 yrs	Healthy periodontium	BL 1 wk	No	NR	Profession al oral hygiene (scaling and root planing with polishing)	This study supports the effectiveness of green tea catechin mouthwash as an antiplaque agent. It should be explored as a cost-effective, long-term antiplaque rinse with prophylactic benefits.
		0.12% chlorhexidine gluconate for 1 wk	30	30							
<b>Khairnar et al., 2013, India</b>	RCT 6 mo	2 ml of tincture of calendula with 6ml of distilled water, 6mo	120	120	20- 40yrs	Gingivitis	BL 3 mo 6 mo	No	Not to bring any additional reinforcement into their oral hygiene practice.	3mo: thorough scaling procedure	Within the limits of this study, it can be concluded that calendula mouthwash is effective in reducing dental plaque and gingivitis adjunctive to scaling.
		8 ml distilled water, 6 mo	120	120							

<b>Mahyari et al. 2016, Iran</b>	RCT 14d	10mL 2x/d for 30s Polyherbal mouthwash ( <i>Z. officinale</i> , <i>R. officinalis</i> and <i>C. officinalis</i> ) for 14d	20	20	12/8 36.2	Gingivitis	BL 7d 14d	NR	NR	NR	Polyherbal mouthwash containing hydroalcoholic extract of <i>Z. officinale</i> , <i>R. officinalis</i> and <i>C. officinalis</i> (5%) was effective in the treatment of gingivitis and its efficacy was comparable to that of chlorhexidine mouthwash.
		10mL 2x/d for 30s 0.2% CHX for 14d	20	20	12/8 35.9						
		10mL 2x/d for 30s Placebo for 14d	20	20	11/9 35						
<b>Mali et al., 2012 India</b>	CCT 21d	0.1% tumeric mouthwash, 10ml, 2x 1min/d 30 min after brushing for 21d	30	30	NR	Mild to moderate gingivitis	BL 14d 21d	No	BL-1mo: Instructions for maintenance of oral hygiene.	BL-1mo: Thorough scaling and polishing after BL measurements.	Chlorhexidine gluconate as well as turmeric mouthwash can be effectively used as an adjunct to mechanical plaque control in prevention of plaque and gingivitis. Both the mouthwashes have comparable anti-plaque, anti-inflammatory and anti-microbial properties.
		0.2% chlorhexidine gluconate, 10ml, 2x 1min/d 30 min after brushing for 21d	30	30							
<b>Mali et al., 2016, India</b>	RCT 21d	Arimedadi oil 10 mL 2x/d for 21d	15	ND	NR 18-21 yrs	Mild to moderate gingivitis	BL 7d 14d 21d	NR	Oral hygiene instructions. Similar toothbrush and toothpaste	Scaling and polishing	Arimedadi oil is equally effective to CHX gluconate as an adjunct to mechanical plaque control in prevention of plaque accumulation and gingivitis. Arimedadi oil could be an effective and safe alternative to 2% chlorhexidine gluconate mouthwash due to its prophylactic and therapeutic benefits.
		0.2% CHX 10 mL 2x/d for 21d	15	ND							
		-	15	ND							

<b>Mamgain et al., 2016, India</b>	RCT 21d	Trifala and Ela decoction 2x 60s/d for 21d	30	ND	NR	Gingivitis	BL 14d 21d	NR	Standardized oral hygiene protocol	NR	Triphala and Ela decoction is organic, easy to prepare economical and equally effective as compared to chlorhexidine mouthwash.
		CHX 2x 60s/d for 21d	30	ND							
<b>Muglikar et al., 2013 India<sup>2</sup></b>	CT 21d	20% curcumin moutwash 2x/d for 21d	10	10	NR 20-40 yrs	Chronic generalised gingivitis	BL 7d 14d 21d	NR	Oral hygiene instruction: modified Bass brushing and dental floss.	Scaling and root planing	Curcumin is comparable to chlorhexidine as an anti-inflammatory mouthwash. This, it can be considered as an effective adjunct to mechanical periodontal therapy.
		CHX 2x/d for 21d	10	10							
		-	10	10							
<b>Naiktari et al., 2014, India</b>	RCT 15d	10mL Triphala, 2x/d for 2 wks	40	40	42-78 20-65yrs	Clinical signs of gingival inflammation	0 15d	No	Continue with their routine oral hygiene measures and to keep a gap of 30 minutes between tooth brushing and rinsing.	No	The triphala mouthwash is an effective antiplaque agent like 0.2% CHX. It is significantly useful in reducing plaque accumulation and gingival inflammation, thereby controlling periodontal diseases in every patient. It is also cost effective, easily available, and well tolerable with no reported side effects.
		10mL 0.2% chlorhexidine, 2x/d for 2 wks	40	40							
		10mL of distilled water, 2x/d for 2 wks	40	40							
<b>Pradeep et al., 2016, India</b>	RCT 60d	15mL, 2x/d, 6% triphala	30	30	17/13 30.17 +- 6.1yrs	Chronic generalized gingivitis	BL 7d 30d 60d	Bring empty bottles with them at the time of follow-up visits to assess for compliance.	Mouthwash twice daily 30 to 45 minutes after brushing. Individuals were also instructed to refrain from any forms of	NR	TRP mouthwash was found to decrease inflammatory parameters from baseline to follow-up intervals. Because improvement in gingivitis was comparable with that of CHX mouthwash, TRP mouthwash can be considered a potential
		15mL, 2x/d, 0.2% CHX	30	30	15/15 29.9 +- 5.6yrs						
		15mL, 2x/d, Placebo	30	30	16/14 29.7 +- 6.2yrs						

									oral hygiene aids, including dental floss and chewing gum, during the study.		therapeutic agent in the treatment of gingivitis.
<b>Prasad et al., 2015, India</b>	RCT 4d	2x/d 5 mL Herbal mouthwash (Hiora) for 4d	50	ND	NR	No oral hygiene ('de novo' plaque formation)	d1 5d	NR	NR	Thorough oral prophylaxis	Within the limitation of this study chlorhexidine gluconate and herbal mouthwash showed similar anti plaque activity with latter showing no side effects.
		2x/d 10 mL 0.2% chlorhexidine gluconate for 4d	50	ND							
		2x/d 5 mL Saline for 4d	50	ND							
<b>Priya et al., 2015, India</b>	RCT 1 mo	5% Green tea	15	NR	NR/NR 18-24 yrs	Gingivitis patients	BL 15d 1 mo	NR	Modified Bass method was demonstrated on study models. Written and verbal oral hygiene instructions were administered to all the patients.	NR	The green tea-containing mouthwash is equally effective in reducing the gingival inflammation and plaque to CHX.
		CHX	15	NR							
<b>Radafshar et al., 2017, Iran</b>	RCT 28d	15mL 2x 1 min/d green tea mouthwash containing 1% tannin for 28d	20	20	9/11 18-25yrs	Dental students without clinical signs	BL 1 wk 4 wks	Daily usage had to be reported	No changes in regular tooth brushing methods.	Supragingival staining and dental polishing	The 1% tannin green tea mouthwash could be a safe and feasible adjunct to mechanical plaque control. The tested green tea

		15 mL 2x 1 min/d 0.12% CHX for 28d	20	20	8/12 18- 25yrs	of periodontitis					mouthwash could be considered a good alternative for chlorhexidine in contraindicating situations.
<b>Sedigh-rahimabadi et al., 2017, Iran</b>	RCT 4 wks	<i>Punica granatum</i> var <i>pleniflora</i> (Golnaar) 10mL for 2min/day, 2 wks	40	36	50/30 20- 65yrs	Type 2 diabetic patients with gingivitis	BL 2 wks 4 wks	Time of brushing had to be noted in the daily reminder sheet.	Educated about the principles of oral hygiene and correct method of tooth brushing and flossing by a trained person.	Scaling after 2 wks (just after mouthwash usage)	Golnaar mouthwash is safe and effective in treatment of gingivitis in diabetic patients although further studies are recommended.
		0.2% CHX 10mL for 2min/day, 2 wks	40	34							
<b>Vangipuram et al., 2016, India</b>	RCT 30d	2x 10mL/d Aloe Vera for 30d	130	130	210/180 18-40 yrs	Dental students	BL 15d 30d	NR	Similar toothbrush and toothpaste	NR	Being an herbal product Aloe Vera has shown equal effectiveness as Chlorhexidine. Hence can be used as an alternative product for curing and preventing gingivitis.
		2x 10mL/d CHX 0.12% for 30d	130	130							
		2x 10mL/d distilled water for 30d	130	130							
<b>Yeturu et al., 2016, India</b>	RCT 15d	10mL 2x 1 min/d Aloe vera for 15d	30	30	18/12 21 +- 3.41	Gingivitis during orthodontic treatment	BL 15d	NR	NR	NR	Chlorine dioxide can be a suitable and economical alternative for chlorhexidine. Further long-term studies are recommended for evaluating their effectiveness.
		10mL 2x 1 min/d Chlorine dioxide for 15d	30	25							
		10mL 2x 1 min/d CHX for 15d	30	30							

RCT: randomized controlled clinical trial, CO: cross-over, min: minutes, d: day, wks: weeks, mo: months, yrs: years, BL: baseline

CHX: chlorhexidine

NR: not reported





Table 5: natural mouth rinses: results

	Groups	Gingival index				Plaque index				BOP			
		Type	Site s/t oot h	Teeth	Change	Type	Site s/t oot h	Teeth	Change	Type	Site s/t oot h	Teeth	Change
<b>Ajmera et al. 2013 India</b>	Aloe vera	LS	NR	NR	50% decrease	NR	NR	NR	NR	GBI	NR	NR	34% decrease
	Scaling				50% decrease				NR				32% decrease
	Aloe vera & scaling				66% decrease				NR				40% decrease
<b>Abdulbaqi et al., 2016</b>	<i>Salvadora persica L</i> & green tea	NR	NR	NR	NR	Turesky	2	All (3M)	ND	NR	NR	NR	NR
	CHX				NR				ND				NR
	Placebo				NR				ND				NR
<b>Balappanavar et al., 2013</b>	Neem	LS	NR	NR	60% decrease	LSPI	NR	NR	71% decrease	NR	NR	NR	NR
	Tea				59% decrease				93% decrease				NR
	CHX				54% decrease				47% decrease				NR
<b>Bretz et al., 2014</b>	Propolis rinse	PBS	1	All (3M)	43% increase	NR	NR	NR	NR	NR	NR	NR	NR
	Sodium fluoride & cetylpyridinium chloride				30% increase				NR				NR
<b>Chandrasah et al., 2012</b>	Aloe vera	MGI	4	1 <sup>st</sup> and 2 <sup>nd</sup> PM & M teeth in 1 maxillary quadrant	51% decrease*	Turesky	4	1 <sup>st</sup> and 2 <sup>nd</sup> PM & M teeth in 1 maxillary quadrant	13% decrease*	Saxton	4	1 <sup>st</sup> and 2 <sup>nd</sup> PM & M teeth in 1 maxillary quadrant	46% decrease*
	Distilled water				27% decrease*				3% increase*				12% decrease*
	CHX				46% decrease*				25% decrease*				58% decrease*
<b>Dany et al., 2015</b>	Lemongrass oil	LS	NR	NR	28% decrease	LSPI	NR	NR	36% decrease	NR	NR	NR	NR
	CHX				25% decrease				35% decrease				NR
	-				9% decrease				24% decrease				NR
<b>Deshmukh et al., 2017</b>	Herbal	LS	NR	NR	80% decrease	LSPI	NR	NR	ND	NR	NR	NR	NR
	CHX				79% decrease				ND				NR
	Probiotic				78% decrease				ND				NR

<b>Freires Ide et al., 2013, Brazil</b>	<i>Schinus terebinthifolius,</i>	NR	NR	NR	NR	OHI-S	NR	NR	3% decrease	Ainamo	NR	NR	31% decrease
	CHX				NR				33% decrease				29% decrease
<b>Goes et al., 2016</b>	<i>Matricaria chamomilla</i> L	NR	NR	NR	NR	Ainamo PI	4	12 teeth	26% decrease	Ainamo	4	12 teeth	30% decrease
	CHX				NR				40% decrease				32% decrease
	Placebo				NR				10% increase				23% increase
<b>Gomes et al., 2016</b>	<i>Anacardium occidentale</i> linn.	NR	NR	NR	NR	Turesky	2	All	31% decrease	Ainamo	2	All	57% decrease
	CHX				NR				30% decrease				56% decrease
	Placebo				NR				6% decrease				30% decrease
<b>Gupta et al., 2014b</b>	<i>Ocimum sanctum</i>	LS	NR	NR	39% decrease	Turesky	NR	NR	17% decrease	NR	NR	NR	NR
	CHX				40% decrease				20% decrease				NR
	Saline				No difference				3% increase				NR
<b>Gupta et al., 2014a</b>	<i>Terminalia chebula</i>	LS	NR	NR	27% decrease*	Turesky	NR	NR	7% decrease*	NR	NR	NR	NR
	CHX				27% decrease*				12% decrease*				NR
	Saline				No change*				11% increase*				NR
<b>Gupta et al., 2015</b>	<i>Terminalia chebula</i>	LS	NR	NR	37% decrease	Turesky	NR	NR	14% decrease	NR	NR	NR	NR
	CHX				44% decrease				18% decrease				NR
	Distilled water				2% increase				8% increase				NR
<b>Kaur et al., 2014</b>	Green tea	NR	NR	NR	NR	Turesky	NR	NR	ND	NR	NR	NR	NR
	CHX				NR				ND				NR
<b>Khairnar et al., 2013,</b>	Calendula	LS	4	All (3M)	89% decrease	Turesky	2	All (3M)	94% decrease	GBI	4	All (3M)	86% decrease
	Distilled water				36% decrease				40% decrease				31% decrease
<b>Mahyari et al. 2016</b>	Polyherbal mouthwash	MGI	4	All	ND	Turesky	6	All	ND	GBI SvdO	3	All	ND
	CHX				ND				ND				ND
	Placebo				ND				ND				ND
<b>Mali et al., 2012</b>	Tumeric	LS	NR	NR	63% decrease	Turesky	NR	NR	69% decrease	NR	NR	NR	NR
	CHX				61% decrease				64% decrease				NR
	Arimedadi oil	LS	NR	NR	63% decrease	LSPI	NR	NR	59% decrease	NR	NR	NR	NR

<b>Mali et al., 2016</b>	CHX				63% decrease				61% decrease				NR
	-				16% decrease				17% decrease				NR
<b>Mamgain et al., 2016</b>	Trifala and Ela	LS	NR	NR	70% decrease	LSPI	NR	NR	56% decrease	NR	NR	NR	NR
	CHX				69% decrease				60% decrease				NR
<b>Muglikar et al., 2013 India<sup>2</sup></b>	Curcumin	LS	NR	NR	50% decrease	LSPI	NR	NR	33% decrease	NR	NR	NR	NR
	CHX				53% decrease				33% decrease				NR
	-				35% decrease				31% decrease				NR
<b>Naiktari et al., 2014</b>	Triphala	NR	NR	NR	32% decrease	NR	NR	NR	35% decrease	NR	NR	NR	NR
	CHX				26% decrease				25% decrease				NR
	Distilled water				1% increase				1% increase				NR
<b>Pradeep et al., 2016</b>	Triphala	ND	NR	NR	68% decrease	Quigley	NR	NR	57% decrease	NR	NR	NR	NR
	CHX				70% decrease				60% decrease				NR
	Placebo				34% decrease				37% decrease				NR
<b>Prasad et al., 2015</b>	Herbal	LS	4	All (3M)	46% increase	Quigley	4	All (3M)	41% increase	NR	NR	NR	NR
	CHX				38% increase				25% increase				NR
	Saline				82% increase				56% increase				NR
<b>Priya et al., 2015</b>	Green tea	LS	NR	NR	39% decrease	Turesky	NR	NR	45% decrease	Ainamo	NR	NR	74% decrease
	CHX				42% decrease				41% decrease				61% decrease
<b>Radafshar et al., 2017</b>	Green tea	NR	NR	NR	NR	Turesky	NR	NR	22% decrease	Ainamo	NR	NR	21% decrease
	CHX				NR				27% decrease				19% decrease
<b>Sedigh-rahimabadi et al., 2017</b>	<i>Punica granatum var pleniflora</i>	MGI	NR	NR	97% decrease	LSPI	NR	NR	90% decrease	GBI	NR	NR	89% decrease
	CHX				93% decrease				90% decrease				93% decrease
<b>Vangipuram et al., 2016</b>	Aloe Vera	LS	All	Index teeth	21% decrease	LSPI	All	Index teeth	42% decrease	NR	NR	NR	NR
	CHX				23% decrease				44% decrease				NR
	Distilled water				8% decrease				9% decrease				NR
<b>Yeturu et al., 2016</b>	Aloe vera	LS	NR	NR	10% decrease	mLSPI	NR	NR	20% decrease	NR	NR	NR	NR
	Chlorine dioxide				12% decrease				30% decrease				NR
	CHX				16% decrease				32% decrease				NR

\* calculated based on graphs

LS: gingival index according to Loë and Silness, 1963, PBS: Papillary bleeding score, MGI: Modified gingival index as described by Lobene et al., 1986

Turesky: Turesky modification of Quigley and Hein plaque index, OHI-S: simplified Oral hygiene index, LSPI: plaque index according to Silness and Loe, mLSPI: modified Silness and Loe plaque index according to William et al., 1991, Ainamo PI: Ainamo & Bay, 1975 plaque index, Quigley: Quigley and Hein plaque index, GBI SvdO: gingival bleeding index by Saxton & van der Ouderaa

ND: not deductable, NR: not reported

PM: premolars, M: molars