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Review Article

DENTAL DISEASE AND ITS CURE: A Review

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ABSTRACT

Oral diseases are major health problems with dental caries and periodontal diseases among the most important preventable global infectious diseases. Oral health influences the general quality of life and poor oral health is linked to chronic conditions and systemic diseases. The association between oral diseases and the oral micro biota is well established. The development of dental caries involves acidogenic and aciduric Gram-positive bacteria (mutans streptococci, lactobacilli and actinomycetes). Periodontal diseases have been linked to anaerobic Gram-negative bacteria (Porphyromonas gingivalis, Actinobacillus, Prevotella and Fusobacterium). Several agents are commercially available these chemicals can alter oral micro biota and have undesirable side-effects such as vomiting, diarrhea and tooth staining. Hence, the search for alternative products continues and natural phytochemicals isolated from plants used as traditional medicines are considered as good alternatives. In this review, plant extracts or phytochemicals that inhibit the growth of oral pathogens, reduce the development of bio films and dental plaque, influence the adhesion of bacteria to surfaces and reduce the symptoms of oral diseases.

Keywords: Periodontal diseases, oral pathogens, dental caries, dental plaque, periodontitis

INTRODUCTION

The relationship between the microorganisms found in dental plaque and the common dental disease of periodontitis has undergone numerous phases historically Early in the 19th century, it was felt that, like the situation with diseases such as tuberculosis, a specific bacterial species was responsible for the disease processes. The criteria by which a given bacterial species was associated with disease historically has been through the application of Koch's Postulates. These criteria were developed by Robert Koch in the late 1800's. The criteria are as follows:

1. A specific organism can always be found in association with a given disease.
2. The organism can be isolated and grown in pure culture in the laboratory.
3. The pure culture will produce the disease when inoculated into a susceptible animal.
4. It is possible to recover the organism in pure culture from the experimentally infected animal.

However, the concept that a specific bacterial species was responsible for periodontal diseases fell out of favor for several reasons[1]. First, despite numerous attempts, a specific bacterial agent was not isolated from diseased individuals. Rather, the organisms found associated with disease were also found associated with health. Good experimental animal model systems of periodontal disease were not available to test the pathogenicity of specific microorganisms (this, in fact, remains problematic today). Further, in the mid 1900's, epidemiological studies indicated that the older an individual was, the more likely they were to have periodontal disease. This led to the concept that the bacterial plaque itself, irrespective of the specific bacteria found in plaque, was associated with disease. This concept, known as the Non-Specific Plaque Hypothesis, held that all bacteria were equally effective in causing disease. Several important developments caused a change in this thinking. First, it was realized that organisms that are found as part of the "normal" bacterial flora (i.e., found in health), may function as pathogens under certain conditions. These organisms may be altered, or increase significantly in numbers relative to other non-pathogenic species, to function as pathogens[2]. This type of bacterial pathogen is referred to as an endogenous pathogen, in contrast to an organism that is not normally found in healthy states which is termed an exogenous pathogen. Secondly, tremendous advances were made in the 1960's and 1970's in techniques used to culture anaerobic microorganisms (bacterial species that cannot grow in the presence of oxygen) [3]. These advances were related to the anaerobic culturing conditions as well as the nutrients required in media to grow anaerobic species, which are typically very fastidious in their nutrient requirements. The growth of anaerobic microorganisms, and examination of their properties using in vitro and in vivo model systems, has now led us back to the understanding that different microorganisms have varying potential to cause disease[4]. Thus, the current concept of the processes involved in the development of periodontal diseases fall under the Specific Plaque Hypothesis. The Specific Plaque Hypothesis states that disease results from the action of one or several specific pathogenic species and is often associated with a relative increase in the numbers of these organism found in plaque.

Other species that have been implicated as pathogens, including Fusobacterium nucleatum, Prevotella intermedia, Eikenella corrodens, Campylobacter rectus, Bacteroides forsythus, and the oral spirochetes of the genus Treponema[5]. It is important to note that the disease processes involve not only pathogenic microorganisms, but also a susceptible host. Further, many microorganisms function to the benefit of the host, by inhibiting the growth of potential pathogenic species. One example of such an interaction is Streptococcus sanguis, which produces hydrogen peroxide that is lethal for Actinobacillus actinomycetemcomitans. Despite tremendous increases in our understanding of the pathogenic properties of specific plaque microorganisms and the role of specific microorganisms in the disease process, current therapy in periodontics is largely non-specific. The treatments that we utilize (e.g., oral hygiene measures, debridement by scaling and root planning, or even the currently available mouthwashes) are oriented towards reducing the accumulation of plaque on the teeth. Future developments in periodontics will involve the development of therapies which prevent the colonization or growth of specific microorganisms that are known to function as pathogens in this environment[6].

PERIODONTITIS

Periodontitis is now seen as resulting from a complex interplay of bacterial infection and hostresponse, often modified by behavioral factors . Advances in research over recent years have led to a fundamental change in the periodontal disease model. The prevailing model of periodontal disease in the 1960s suggested that all individuals are susceptible to severe periodontitis, that gingivitis progresses to periodontitis with consequent bone and tooth loss, and that the susceptibility to periodontitis increases with age[7]. All aspects of this model are under strong challenge from the results of more recent research. The belief in universal susceptibility has given way to the current view that only some 20% of any population suffer from severe generalized periodontitis, even though moderate disease affects a majority of adults. Risk factors, such as smoking, have a profound effect on the predisposition to periodontal disease[8]. There is now a clear association between smoking and periodontal diseases, independent of oral hygiene, age, or any other risk factor. Studies have shown that there is no difference between smokers and nonsmokers in amounts of plaque accumulation, or in the prevalence of the principal bacteria which are considered pathogenic for periodontitis. What smoking appears to do is suppress the vascular reaction which follows gingivitis. In effect this is a masking effect on the signs of inflammation. Smoking may also be a factor in the association between refractory periodontitis and a polymorph nuclear leukocyte defect in the peripheral blood. There is also some evidence that smoking is associated with osteoporosis; the link with dental alveolar bone loss is currently under study. In human periodontitis, there is no simple, direct pathogen-disease link. More than 500 bacteria have been identified within periodontal pockets. Moreover, it is impossible to accurately associate the complex microbiota in a periodontal lesion, in a given patient, with the bacterial species that may have contributed to development of that lesion. Much evidence suggests, however, that a finite set of pathogenic microbiota, sometimes working alone, or in combinations, cause periodontal diseases in humans[9]. Most pathogens associated with periodontal lesions are Gram-negative anaerobic rods, while some pathogens are also Gram-positive facultative and anaerobic cocci and rods, and Gram-negative facultative rods. Due to this mixed variety of pathogens, and their variability in sensitivity to antibiotics, simplistic antimicrobial chemotherapy is problematic. Three pathogens have an especially strong association with the presence of progressive periodontal disease: Actinobacillus actinomycetemcomitans, spirochetes of acute necrotizing gingivitis, and Porphyromonas gingivalis. One potential virulence factor recently ascribed to P. gingivalis and A. actinomycetemcomitans, which is shared by a number of respiratory and enteric pathogens, is the ability to enter mammalian cells[10]. These pathogens are very often the cause of continued loss of periodontal attachment despite diligent conventional mechanical periodontal therapy, as well as causing refractory periodontitis, localized juvenile periodontitis, and other types of early-onset periodontitis. Patients who suffer from these conditions may benefit from antibiotic therapy. Evaluation of the patient's periodontal status requires obtaining a relevant medical and dental history and conducting a thorough clinical and radiographic examination, with evaluation of extra oral and intraoral structures[11]. A medical history should be taken and evaluated to identify predisposing conditions that may affect treatment, patient management and outcomes. Such conditions include, but are not limited to, diabetes, hypertension, and pregnancy. Factors which may also play a role in treatment outcome are smoking, substance abuse and medications. Adult periodontitis is defined as inflammation of the gingiva and the adjacent dental attachment apparatus. The disease is characterized by loss of clinical attachment due to destruction of the periodontal ligament and loss of the adjacent supporting bone. As mentioned previously, dental plaque bacteria play a key role in what is now understood to be the complex process by which the common types of oral diseases occur dental caries and periodontal diseases[12]. As with other infectious diseases, there is a balance between the host immune responses on one hand and the microbial pathogenesis on the other hand. In health, host immune responses are sufficient to hold in check the pathogenic potential of both the normal resident microbial flora and exogenous microbial pathogens. Infectious diseases such as periodontal disease occur when this equilibrium is disturbed. Clinical features may include combinations of the following signs and symptoms: edema, erythema, gingival bleeding upon probing, and/or suppuration[13]. Adult periodontitis with slight to moderate destruction is characterized by a loss of up to 1/3 of the supporting periodontal tissues; a loss of over 1/3 of the periodontal supporting tissues is seen in advanced adult periodontitis. Radiographic evidence of bone loss is apparent in advanced adult periodontitis, and may be evident in adult periodontitis with slight to moderate destruction. Adult periodontitis with slight to moderate or advanced loss of periodontal supporting tissues may be localized, involving one area of a tooth's attachment, or more generalized, involving several teeth or the entire dentition[14]. A patient may simultaneously have areas of health and adult periodontitis with slight, moderate, and advanced destruction.

PERIODONTITIS ASSOCIATED WITH SYSTEMIC CONDITIONS

A number of systemic factors have been documented as capable of affecting the periodontium and/or treatment of periodontal disease. Systemic etiologic components may be suspected in patients who exhibit periodontal inflammation or destruction which appears disproportionate to the local irritants. Periodontal therapy may be modified based on the current medical status of the patients. Periodontal organisms may be the source of infections elsewhere in the body. Therefore, those infections may also affect systemic health[15]. The therapeutic goal is to achieve a degree of periodontal health consistent with the patients overall health status. Achieving this goal, however, may be directly affected by the degree of control of the systemic condition. The systemic and psychological status of the patient should be identified, therefore, to reduce medical risks that may compromise or alter the periodontal treatment.

The human oral cavity is a complex biological system in which members of a diverse microbial community interact with themselves as well as with different host structures and components. It has been reported that this cavity is colonized by approximately 500 bacterial species most of which are still poorly characterized. The bacterial flora of this human cavity includes a wide range of bacterial cell types as well as important fungi such as Candida albicans, while some of them are classified as opportunistic pathogens capable of causing severe infections in compromised patients. Although complex, the interactions among the members of the oral flora develop according to reproducible temporal and spatial patterns, a process that results in co-aggregation-mediated interactions and the formation of multi-species microbial biofilms known as dental plaques[16]. These cell arrangements allow microbial cells to prosper in a hostile environment, which is the case for the significant clinical bacterial pathogens that prosper in the human host. These cell structures are the result of specific microbial-microbial and microbial-host interactions, which play a role in the ability of microbial cells to evade the host response and resist antimicrobial agents. Furthermore, there is evidence that bio films play a significant role in the horizontal transfer of genetic material among members of these cell aggregates a process that facilitates their adaptation to different ecological niches. Most of the knowledge available to date with regard to the microbial and host factors and processes involved in these interactions has been obtained with classic approaches based on the utilization of molecular genetics and molecular biology. Although these approaches have produced important and novel information, they have provided a rather narrow picture of these complex interactions. In contrast, a holistic view of the genetic blueprint of a bacterial cell can be readily obtained once its entire genome is sequenced with automated methods and annotated by computer analysis of nucleotide sequences. This genome-wide approach, which uses tools such as genomics and bioinformatics, is based mainly in the comparative analysis of gene content and structure among different bacterial cells and gene expression under different physiological conditions using DNA arrays. Whole-genomic comparisons and transcriptome analysis have the benefit of providing wider and more comprehensive information regarding the genome structures and gene expression patterns that will facilitate the understanding of the evolution and adaptation of bacterial pathogens, and the complex mechanisms by which they interact with their hosts. For example, the application of DNA microarrays and global transcriptional analysis has facilitated the study of the genetic composition and the analysis of gene expression under different environmental conditions, respectively, of important bacterial pathogens such as Escherichia coli and Pseudomonas aeruginosa. These studies have provided novel and important information with regard to lateral gene transfer and the emergence of pathogens with new or different virulence attributes, the adaptation of bacteria to particular hosts and environmental niches through genome re-arrangements, the evolution of pathogens that share the same host niche, and potential bacterial targets for the development of new therapeutic agents and the design of vaccines to prevent microbial diseases. Similar approaches could be applied to dental pathogens once their genomes are completely sequenced and annotated, a process that is near completion for several of them. However, there are investigators who have not waited until the genomes of oral bacteria were completely annotated and published, and have already started these types of analyses with some oral pathogens[17].

Streptococcus mutans, a major pathogen of dental caries, has been detected in heart valves and isolated from the blood of patients with infective endocarditis (IE), suggesting its close relationship with infective endocarditis S. mutans is classified into four serotypes (c/e/f/k) based on the chemical composition of its cell surface serotype-specific rhamnose–glucose polymers (RGPs), which form a backbone of rhamnose polymers with side chains of glucose polymer. Serotype c is reported to be the most prevalent in oral isolates at approximately 70–80 %, followed by e, f and k. In our previous study, four S. mutans strains isolated from the blood of patients with bacteraemia after tooth extraction or IE were characterized; however, none of those strains were classified as serotype c. The serotype-specific RGPs of S. mutans were demonstrated to play important roles in streptococcal adherence to human monocytic and fibroblastic cells, and speculated to be its most efficient cytokine-stimulating components. In addition, the hydrophilic nature of RGPs is known to be associated with the resistance to phagocytosis by human polymorphonuclear leukocytes. Further, RGPs were shown to possess properties allowing them to bind directly to human platelets and trigger their aggregation in a dose-dependent manner. In our previous study, serotype k strains featured a drastic reduction in the amount of glucose side chains and were shown to be less susceptible to phagocytosis by human polymorphonuclear leukocytes than the parent strain. However, the virulence of each serotype of S. mutans in blood remains to be elucidated. Recently, the association of cardiovascular diseases and periodontitis has received attention because of results showing that periodontopathic bacterial DNA could be detected in the diseased cardiovascular tissues. We previously reported that not only periodontopathic bacterial species, but also several streptococcal species, were detected in cardiovascular specimens, such as heart valve and atheromatous plaque, and S. mutans was the most frequently detected. In the present study, detection of S. mutans in additional specimens, as well as serotype determination of S. mutans-positive specimens was carried out[18].

The main diseases of the teeth include plaque, caries and pyorrhoea. Proper dental care is necessary for eliminating tooth decay and periodental diseases. The people living in Indian subcontinent largely depend on the traditional systems for the treatment of toothache, caries and other diseases related to teeth. The traditional herbal preparations for dental care comprise of various types of herbal powders and chewing sticks made out of young woody stem or root pieces. Acacia catechu Catechu paste is used to treat the bleeding (Katha) gums and for tooth hypersensitivity. A. nilotica Fresh twig is used as tooth brush for keeping (Kikar) the gums and teeth healthy and clean. Achyrathes aspera Twing is used for brushing teeth. (Puthkanda, Latjira) to treat dental problems. Azadirachta indica Fresh twig is used as tooth (Neem) brush to prevent gum diseases and pyorrhoea. Aristolochia bracteolata Root juice is applied to the site (Kidamari) of toothache for relieving pain. Cinnamomum camphora Tender twigs are chewed or the paste of (Kapur) stem bark is applied in aching teeth. Cinnamomum verum Powdered stem bark is applied to (Dalchini) teeth in the treatment of caries and pyorrhoea. Curcuma longa Powder of rhizome is used in tooth (Turmeric) powder for curing pyorrhoea. Eucalyptus globulus To prevent tooth decay and (Karpoora) to provide relief form pain the leaf oil is applied to the site of pain. Ficus bengalensis Aerial root is used as (Bargad) tooth brush and the latex is applied in toothache. Juglans regia Stem bark is used in tooth (Akhrot) powders to make the teeth healthy. Madhuca longifolia Stem bark is used in tooth (Mahua) powder for gum pain and toothache. Mimusops elengi Bark is used in tooth (Maulsari) powder for the protection of gums and teeth. Myristica fragrans Fruit paste is applied on (Jaiphal) teeth to cure dental caries and pyorrhoea. Ocimum sanctum Leaves are chewed as such for (Tulsi) the treatment of bad breath and leaf paste is usefull for tooth hypersensitivity. Piper betel Leaf paste is suggested for (Pan) dentinal hypersensitivity. Piper longum Fruit in the form of powder (Piplamus) is applied for dental caries. Piper nigrum Fine powder of seeds is applied (Goal mirch) to teeth in toothache, pyorrhoea and gum bleeding. Potentilla fulgens Root powder is applied (Vajardanti) in gingivitis. Punica granatum Stem bark or fruits rind is used (Anar) as component of dental powder. Salvadora persica Twig is used as tooth brush (Pilu) for cleaning the teeth. Roots are used in dental caries, and to relieve toothache. Syzygium aromaticum Clove oil is applied for (Laung) toothache, dental caries and pyorrhoea. Spilanthes calva Flowers chewed in toothache. (Akarkara) Plant made into paste is applied in toothache. Zanthoxylum armatum Twig is used as tooth brush (Tejbal) for cleaning the teeth. Fruit powder is applied to teeth in toothache[19].

In the Indian subcontinent the commonest source of chewing sticks is Azadirachta indica. Salvador persica stems and roots are also widely used as chewing sticks. Chewing sticks obtained from A. indica contain essential oils and exert carminative, antiseptic and analgesic action. The tannins of chewing sticks have an astringent effect on mucous membrane.

Many plants are useful in pyorrhoea. Cinnamomum verum bark is an astringent and is thus useful for checking the bleeding of gums. The bark has essential oil and tannins. The essential oil of C. verum has antimicrobial and antibacterial properties. Accacia nilotica bark and ash of almond kernel can be pulverized together and mixed with common salt to make a highly effective preparation to contain pyorrhoea and for strengthening of gums by making them strong. Use of clove oil is recommended for the alleviation of toothache.

CURE FOR DENTAL DISEASES

Traditional Plant-Based Medicines

Medicinal plants have been used as traditional treatments for numerous human diseases for thousands of years and in many parts of the world. In rural areas of the developing countries, they continue to be used as the primary source of medicine. About 80% of the people in developing countries use traditional medicines for their health care. The natural products derived from medicinal plants have proven to be an abundant source of biologically active compounds, many of which have been the basis for the development of new lead chemicals for pharmaceuticals. With respect to diseases caused by microorganisms, the increasing resistance in many common pathogens to currently used therapeutic agents, such as antibiotics and antiviral agents, has led to renewed interest in the discovery of novel anti- infective compounds. As there are approximately 500 000 plant species occurring worldwide, of which only 1% has been phytochemically investigated, there is great potential for discovering novel bioactive compounds. There have been numerous reports of the use of traditional plants and natural products for the treatment of oral diseases. Many plant-derived medicines used in traditional medicinal systems have been recorded in pharmacopeias as agents used to treat infections and a number of these have been recently investigated for their efficacy against oral microbial pathogens. The general antimicrobial activities of medicinal plants and plant products, such as essential oils, have been reviewed previously. Therefore, the purpose of this review is to present some recent examples from the literature of studies that have served to validate the traditional use of medicinal plants with specific biological activity. In particular, traditional medicinal plant extracts or phytochemicals that have been shown to inhibit the growth of oral pathogens, reduce the development of dental plaque, influence the adhesion of bacteria to surfaces and reduce the symptoms of oral diseases will be discussed subsequently[20].

Antibacterial Activity of Total Plant Extracts

Many studies investigating the activity of traditional medicinal plants against oral pathogens have been limited to examination of crude aqueous or organic solvent extracts. In most cases, the investigators have simply sought to validate the traditional medicinal use of the plant. For example, the use of Drosera peltata (Droseraceae) leaves as a traditional treatment for dental caries was validated by a study which showed that chloroform extracts of the aerial plant parts showed broad spectrum activity against numerous bacteria of the oral cavity, with greatest activity against S. mutans and S. sobrinus.

Plumbagin was identified as the active component of this extract. Tichy and Novak investigated a collection of 27 medicinal and random plants extracts and identified a number that inhibited the growth of oral streptococci. The most active extracts included those from Abies canaden- sis (Pinaceae), Albizia julibrissin (Fabaceae), Chelidonium majus (Papaveraceae), Ginkgo biloba (Ginkgoaceae), Junipe- rus virginiana (Cupressaceae), Pinus virginiana (Pinaceae), Rosmarinus officinalis (Lamiaceae), Sassafras albidum (Lauraceae), Tanacetum vulgare (Asteraceae) and Thuja plicata (Cupressaceae). Bioautography indicated that a number of extracts contained common antimicrobial components, while other extracts possessed chemically different constituents[21].

A boiling water extract of Coptidis rhizoma (Ranun- culacea), a traditional Chinese medicinal plant, showed bactericidal activity against oral bacteria with particularly good activity against periodontopathogenic bacteria. assessed the ability of 10% decoctions and methanol extracts of a number of medicinal plants to inhibit bacterial isolates obtained from crevicular fluid of the periodontal pockets of periodontics patients. In general, the methanol extracts showed greater activity than the decoctions.

Terpenes bakuchiol isolated from the Chinese medicinal plant, Psoralea corylifolia (Fabaceae), has shown activity against numerous Gram-positive and Gram-negative oral pathogens. It was able to inhibit the growth of S. mutans under a range of sucrose concentrations, pH values and in the presence of organic acids in a temperature-dependent manner and also inhibited the growth of cells adhered to a glass surface[22].

Alkaloids the alkaloid berberine isolated from C. rhizoma (Ranunculacea) showed bactericidal activity against oral bacteria, with greatest activity against A. actinomycetem- comitan and P. gingivalis much less activity was observed against Lactobacillus and Streptococcus species. Berberine also inhibited the collagenase activity of A. actinomycetemcomi- tans and P. gingivalis.

Sugar Alcohols xylitol is a sugar alcohol naturally found in plants that is used as an artificial sweetener in many foods. Its anticariogenic properties were investigated by adding 0.78–50% xylitol to broth cultures of S. mutans, S. saliviarius and S. sanguis, incubating at 37◦C for 18 h and determining the optical density of the cultures. Streptococcus mutans was the only bacterium significantly inhibited by xylitol at 1.56%, while all bacteria showed statistically significant inhibition at levels above 1.56%. The study concluded that xylitol exhibited anticariogenic effects by inhibiting the growth of S. mutans while not affecting other streptococci that are part of the normal oral flora.

Antibacterial Activity of Propolis

Propolis has been shown to exhibit good antimicrobial activity against a range of oral bacteria and inhibit the adherence of S. mutans and S. sobrinus to glass. It was also shown to be a potent inhibitor of water-soluble glucan synthesis. In the same study, an extract of Arnica montana (Asteraceae) demonstrated no antimicrobial activity, nor did the extract affect adherence or glucan synthesis. the activity of propolis against a number of microorganisms, including S. mutans and S. sobrinus. Ethanol extracts of four samples of propolis collected from different geographical regions with activity likely to be due to the presence of numerous flavonoids. Propolis showed antimicrobial activity similar to chlorhexidine and greater than clove or sage extracts in a study investigating the ability of these chemicals to inhibit the growth of microbes obtained from the saliva of periodontally healthy subjects and those with chronic perodontitis. Nidus Vespae, the honey comb of Polistes olivaceous , P. japonicus de Saussure and Parapolybiavaria fabricius, is a traditional Chinese medicine that has a number of pharmacological properties. While Nidus Vespae is similar to propolis, it contains additional material including waxes and aromatic oils. Like propolis, extracts and fractions of Nidus Vespae have been shown to exert antimicrobial activity toward a number of oral microorganisms, in particular S. mutans[23].

Essential Oils with Activity against Oral Bacteria

The antibacterial properties of essential oils are well-known and activity against bacteria found in the oral cavity, including pathogens, has been documented. Indeed, there is evidence that commercial mouthwashes containing essential oils are useful in the long-term control of plaque and mild- to-moderate gingivitis and are preferred to those containing chlorhexidine for long-term daily use. A number of recent studies add to the evidence that essential oils may be suitable additives in products used for the maintenance of oral hygiene or prevention of dental disease.

The essential oil of Melaleuca alternifolia (Myrtaceae), known as tea tree oil (TTO), has been used medicinally for many years. TTO has antimicrobial properties and is used in the superficial treatment of skin infections. In addition to their inhibitory and bactericidal activities, most of the oils were able to inhibit the adhesion of S. mutans and P. gingivalis. Essential oils are also capable of enhancing the activity of chlorhexidine[24]. When used in combination, the essential oils of cinnamon and manuka were able to significantly reduce the amount of chlorhexidine required to inhibit the growth of oral pathogens. This enhanced activity was also seen against bacterial cultures grown as biofilms. Between 4- and 10-fold reductions of the amount of chlorhexidine required to inhibit biofilm bacteria was observed when used in combination with cinnamon, manuka and Leptospermum morrisonii oils[25].

CONCLUSIONS

The plant extracts, essential oils and purified phytochemicals have the potential to be developed into agents that can be used as preventative or treatment therapies for oral diseases. While it is encouraging to see a number of clinical trials of such products, further studies of the safety and efficacy of these agents will be important to establish whether they other therapeutic benefits, either alone or in combination with conventional therapies, that can help to reduce the overall burden of oral diseases worldwide. In particular, studies that address issues such as adequate statistical power, blinding, standardization of extracts or purified compounds, and quality control would be of great value.

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