

The Significance of Phytochemicals on Periodontal Health

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ABSTRAK

Penyakit periodontal adalah penyakit inflamasi tisu sokongan gigi yang menjejaskan hampir 90% penduduk di seluruh dunia. Rawatan penyakit periodontal melibatkan terapi mekanikal, pembedahan, dan pemberian antibiotik. Kos rawatan yang tinggi dan rintangan bakteria terhadap rejim antibiotik tertentu telah menyebabkan pencarian rawatan alternatif untuk mengatasi penyakit ini dengan kos yang lebih efektif dan kurang kesan sampingan. Produk semulajadi telah terbukti menjadi sumber penting dalam membangunkan ubat moden untuk menggalakkan kesihatan umum. Ekstrak tumbuhan herba telah digunakan secara meluas dalam kesihatan mulut terutamanya untuk mencegah pengumpulan plak bakteria dan karies gigi. Dalam penyakit periodontal, beberapa kajian telah mendokumentasikan bahawa ekstrak tumbuhan herba berpotensi untuk mencegah dan merawat periodontitis melalui bahan aktif ekstrak tumbuhan yang berkaitan dengan sifat antimikrobial, anti-inflamasi dan anti-oksidan. Sumber-sumber untuk mendapatkan herba adalah ekonomik dan mudah untuk dihasilkan serta dipasarkan. Sesetengah herba telah dipasarkan untuk penggunaan awam dalam bentuk ubat gigi dan kumur mulut. Kajian ini adalah satu usaha untuk menggariskan kepentingan herba dalam menyediakan ubat-ubatan berpotensi yang berkesan dan ekonomik untuk penyakit periodontal dan kepentingan untuk penyelidikan klinikal selanjutnya pada masa akan datang.

Kata kunci: anti-radang, antioksidan, penyakit gusi, perubatan herba, produk semulajadi

ABSTRACT

Periodontal disease is an inflammatory disorder of tooth-supporting tissues that affects almost 90% of the population worldwide. The treatment of periodontal

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disease involved mechanical therapy, surgery, and administration of antibiotics. The high cost of the treatment and bacterial resistance to certain antibiotics regime has led to the search for the alternative treatment to overcome the disease at less cost and side effects. Natural products had been proven to be an important source in developing modern medicine to promote general health. Herbal plant extracts had been widely used in oral health particularly to prevent bacterial plaque adherence and dental caries. In periodontal disease, several studies and reviews have documented that herbal plant extracts had the potential to prevent and treat periodontitis through their active ingredients associated with antimicrobials, anti-inflammatory, and anti-oxidant properties. The sources to obtain the herbs are readily available and economical to produce in the market. Some of the herbs had been marketed for public uses in the form of toothpaste and mouth rinses. This review is an attempt to outline the importance of herbal medicine to provide potential effective and economical medicaments for periodontal disease and its significance for further clinical research in the future.

keywords: anti-inflammatory, antioxidant, herbal medicine, natural product, periodontal disease

INTRODUCTION

Periodontal diseases are multifactorial inflammatory diseases that can lead to the damage of tooth-supporting tissues (Lindhe 1999). According to its established definition, chronic periodontal disease is “an infectious disease that causes inflammation in the supporting tissues of the teeth, gradual attachment loss and bone destruction. It is characterized by gingival pocket formation and/or recession” (Lindhe 1999). Common systemic diseases, such as diabetes and obesity, and osteoporosis in postmenopausal women, and social habit of smoking are relatively common risk factors to affect most patients with periodontal disease in dental clinical practices (Genco & Borgnakke 2013). Currently, robust evidence has supported the

strong relationship of periodontal disease among patients with poor oral hygiene and bacterial plaque control, patients diagnosed with diabetes mellitus and smokers.

Gingivitis and periodontitis are the most common periodontal diseases and are predominantly caused by infection of the bacteria in dental plaque biofilm. Dental plaque biofilm consisting of anaerobic Gram-negative bacteria, such as *Porphyromonas gingivalis*, *Prevotella sp.*, *Fusobacterium sp.*, and *Actinobacillus sp.*, has been well established as a true risk factor of periodontal disease (Tichy & Novak 1998). In periodontal disease, infection of the gingival crevice and below produces a cellular inflammatory reaction of the gingiva and underlying connective tissue, which can present as gingivitis (often observed as

bleeding of gingiva) or periodontitis (inflammatory responses resulting in damage of collagen attachment and bone destruction) (Loesche 2007). It can be summarized that the clinical manifestation of periodontal disease includes gingival redness, bleeding, abscesses and swelling, halitosis, mobile teeth, as well as ultimately tooth loss if left untreated.

Periodontal disease is amongst the most common oral illnesses, contributing to the worldwide chronic disease burden. The prevalence is very high, affecting up to 90% of the world population (Pihlstrom et al. 2005). Periodontal disease is a public health concern because of its high prevalence among adolescents, adults and the elderly (Sanz et al. 2010). In the United States (US), approximately 50% of the population in all age groups exhibit gingivitis (Albandar & Kingman 1999) with another report stating that high burden of periodontitis affects nearly half (45.9%) of the US population aged 30 years and older (Eke et al. 2016). According to the National Oral Health Survey for Adults in Malaysia, the prevalence of periodontal disease is 94%, with mild and severe periodontitis assessed to be at 30.3% and 18.2%, respectively. These findings were based on a countrywide household survey of 8,332 dentate adults aged 15 and older (NOHSA 2010).

Periodontal disease prevention has been established through community outreach programs and in healthcare facilities that promote oral health knowledge and habits among the public. Nonetheless, there are significant disparities in oral

health among continents, countries, and even within nations. These can be influenced by socioeconomic situation, ethnicity or race, gender, age or current state of health. While most dental disorders can be avoided, not everyone is aware of or able to benefit from efficient oral health promotion activities (Watt 2005).

Translating awareness and experience of disease control into intervention programs is the biggest challenge. Global, economic, and cultural contexts, as well as shifting population dynamics, influence the distribution of oral health services in nations and cultures, as well as how people care for themselves. Reducing inequalities requires broad, much further measures aimed at groups at higher risk of specific oral illnesses and increasing access to existing therapy. Meanwhile, providing basic dental care treatments inside the scope of general health care systems remains the most significant challenge in many developed countries (Watt 2005).

According to a survey to quantify the economic burden of periodontitis management in Malaysia, the cost of managing all cases of periodontitis at the national level from a sociological perspective was nearly MYR (Malaysian Ringgit) 32.5 million, compensating for 3.83% of the country's 2012 gross national product. It would cost the nation MYR 18.3 million for the treatment of mild periodontitis and MYR 13.7 million for managing patients with severe periodontitis (Mohd Dom et al. 2016).

Periodontal disease treatment is intended to relieve inflamed tissue,

decrease the number of pathogenic bacteria, and eradicate pathogenic periodontal pockets. Mechanical therapy, chemotherapy and systemic antibiotic administration are among the common therapies in clinical settings. However, factors such as the increase in the incidence of oral disease, financial considerations in developing countries, an increase in opportunistic infections in immunocompromised individuals and bacterial resistance to current antibiotics has led to research into alternative treatment approaches for oral diseases that are safe, economical, and most importantly, effective in curing the disease (Titchy & Novak 1998). Furthermore, according to the World Health Organization (WHO), around 65-80% of the global population live in developing nations predominantly rely on herbal medicine for primary healthcare due to underprivileged and poor access to modern medicine (Akererele 1993). The majority of commonly used antibiotics for treating oral infections, such as amoxicillin, metronidazole, erythromycin and tetracycline have been reported as having bacterial resistance (Bidault et al. 2007). In the prevention and management of oral infections, certain antibacterial agents, including cetylpyridinium chloride, amine fluoride chlorhexidine or merchandises comprising such agents, have been established as demonstrating toxicity, inducing dental staining, or being linked with oral cancer in the case of ethanol (Knoll-Kohler & Stiebel 2002; Lachenmeier 2008; McCullough & Farah 2008; Neumegen 2005). As a result, the quest

for new pharmaceuticals continues, and organic phytochemicals produced from botanicals used in herbal medicines are being considered as potential substitutes for synthetic compounds (Prabu et al. 2006).

In Malaysia, studies of alternative natural products for treatment of periodontitis have been documented through the study on Gelam honey's effect in periodontitis-induced rats. It was found that Gelam honey could reduce the level of interleukin-1 β systemically and has been verified to have the potential of reducing alveolar bone resorption by lessening the osteoclast activity in the experimental rats induced with periodontitis (Aziz et al. 2014; Hamzah et al. 2014). Another study done by Toker et al. (2008) has provided morphologic and histologic data showing that systemic administration of propolis which could avert alveolar bone resorption in the periodontitis-induced rat model. Recently, the efficiency of herbal leaf extract, *Ficus deltoidea* (or famously known as Mas Cotek among locals) in inhibiting alveolar bone resorption in ovariectomized rats has been investigated. The alveolar bone microarchitecture and histology were examined under micro-computed tomography and light microscope, respectively. It was shown that the antioxidant and anti-inflammatory properties of flavonoids from the herb extract was found to be capable of preventing alveolar bone loss in ovariectomy-induced osteoporosis mice by potentially retaining trabecular bone microarchitecture, decreasing osteoclast and increasing osteoblast

cell numbers (Omar et al. 2020).

MECHANISM OF ACTION OF HERB EXTRACT ON PERIODONTAL HEALTH

Antioxidant Property of Herb Extract on Periodontal Health

Green tea is made from *Camellia sinensis* leaves that have encountered negligible oxidation throughout production. It encompasses the largest concentrations of polyphenols, which have prodigious antioxidant property (Hrishi et al. 2016). Catechins are a type of polyphenol found in tea. Catechin, epicatechin, gallic acid, epigallocatechin gallate (EGCg), epigallocatechin, epicatechin gallate (ECg) are the six major catechin chemicals found in green tea. Due to its potent antioxidant property, EGCg has been the subject of intensive study among all other compounds (Narotzki et al. 2012). Bone resorption, which occurs in periodontitis, is mainly due to the imbalanced interaction between osteoblasts and osteoclasts. In an animal study, EGCg from green tea has been shown to reduce lipopolysaccharide-mediated bone resorption in both *in vivo* and *in vitro* conditions. It has also been shown that EGCg suppresses lipopolysaccharide (LPS)-mediated gene expression, such as nuclear factor-kappa-B ligand receptor activator (RANKL), cyclooxygenase-1 and PGE-2 cytokines in mouse osteoblasts. This clearly indicates that the presence of catechin in green tea is highly effective in preventing of bone resorption caused by an inflammatory

reaction, as seen in periodontitis (Tominari 2015). In addition, several research on the use of green tea in the treatment of periodontitis in various methods have been conducted. Pilot research on the application of green tea as a toothpaste and local drug delivery system have demonstrated an increase in periodontal health in patients with chronic periodontitis (Hrishi et al. 2016). In a clinical trial, green tea mouthwash has been shown to have similar antiplaque efficacy to the gold standard chlorhexidine gluconate, when used for a duration of one week (Kaur et al. 2014).

Alkaloid, which is found in plants such as *Piper longum* and *Piper nigrum*, has been demonstrated to have antioxidant and anti-inflammatory properties. In an animal periodontitis-induced study, when treated with piperine, LPS-stimulated mice showed decreases in tumor necrosis factor- α (TNF- α) levels and reduced nitrite level, which confirms the piperine's free radical scavenging activity (Pradeep & Kuttan 2003). Another research on the model for rat periodontitis showed that piperine significantly down-regulated interleukin-1 β , matrix metalloproteinases (MMPs), MMP-8 and MMP-13 production. Piperine explicitly prevented alveolar bone loss and, dose-dependent, reformed the trabecular microstructures. Histological staining has shown that piperine substantially decreases penetration of soft tissue inflammation (Dong et al. 2015).

Triphala, a well-known and highly efficient polyherbal Ayurvedic medication, consisting of fruit of the

plant species *Terminalia chebula* (Haritaki), *Emblica officinalis*, (Amalaki) and *Terminalia bellerica* (Bibhitaki), has significant antioxidant, antimicrobial and anti-collagenase effects. Triphala contains antioxidants, which reduces oxidative stress and protects cells from free radical damage (Peterson 2017). In addition, Triphala mouthwash has also been reported to be as effective as the gold standard 0.2% chlorhexidine mouthwash in anti-plaque and anti-inflammatory activities in a clinical trial (Naiktari et al. 2014).

Anti-inflammatory Property of Herb Extract on Periodontal Health

In the United States, *Ginkgo biloba* leaf extract is one of the most commonly accessible herbal supplements (Shankland 2009). It was reported in an animal study to reduce inflammation in periodontitis-induced rat model (Sezer et al. 2013). *Ginkgo biloba* leaf extract consists of ginkgo flavone glycosides (24%), terpenoids (6%) and ginkgolic acid. The alleged biological properties involve anti-inflammatory, the scavenging of free radicals and reduction of oxidative stress (Thorpe et al. 2011). In the ligature-induced periodontitis rat experimental study, the systemic treatment of *Ginkgo biloba* extract (28-56 mg/kg/day) has resulted in the reduction of osteoclast counts and inflammation as well as induced osteoblast activity (Sezer et al. 2013).

The effect of piperine, which is an alkaloid found in plants such as *Piper nigrum* (black pepper) and *Piper longum* (long pepper), on the

production of TNF- α and nitric oxide (NO) levels has been analysed using both *in vitro* and *in vivo* systems. Pradeep and Kuttan (2003) have shown that piperine has an inhibitory effect on the development of nitric oxide and TNF- α , both of which have an established role in the pathology of inflammation in periodontitis. *Piper nigrum* also presented with an anti-inflammatory property in the study by Jayashankar et al. (2011), which found that brushing with *Piper nigrum* herbal toothpaste for 12 weeks had shown a substantial reduction in gingival bleeding.

Chamomile (*Matricaria chamomilla*) and its use in the treatment of periodontal diseases have been documented by Berry (1995), helping to minimize periodontal tissue inflammation and decreases the number of unhealthy bacteria in the mouth. In the same study, it was suggested that drinking chamomile tea or the application of chamomile as a mouth rinse and toothpaste may overcome periodontal inflammation. Chamomile has the ability to prevent periodontal disease by decreasing inflammatory response and alveolar bone degradation by lowering TNF- α and IL-1 β , as well as inhibiting osteoclast activation via the RANKL-osteoprotegerin (OPG) axis without compromising bone anabolism (Guimaraes et al. 2016).

Punica granatum and *Centella asiatica* are well-known as medicinal herbs that aid in tissue repair and regulate host responses. The novel formulation of the two herbal extracts in the form of biodegradable chips as

a subgingival adjuvant to scaling and root planing has been shown in studies to have promising therapeutic benefits and have greatly improved the clinical symptoms of chronic periodontitis and interleukin-1 in maintenance patients when used as an adjunct to local delivery (Sastravaha et al. 2005).

Currently, a manufactured natural product toothpaste in stores, Parodontax® (GlaxoSmithKline, Middlesex, United Kingdom) has established pronounced consideration. It consists of sodium fluoride, sodium bicarbonate and herbal ingredients: Chamomile, which is thought to have anti-inflammatory effects and to reduce gingival inflammation; echinacea, which is considered to boost the immunological response; Sage and rhatany, which has anti-hemorrhagic qualities; myrrh, which is said to be a natural anti-septic; and peppermint oil, which has analgesic, anti-septic, and anti-inflammatory effects (Ozaki et al. 2006). In a randomized clinical trial to investigate the efficacy of herbal toothpaste in patients with established gingivitis, Parodontax® demonstrated a substantial declination in gingival bleeding and plaque formation (Ozaki et al. 2006).

Antimicrobial Property of Herb Extract on Periodontal Health

Green tea has been shown to have significant impacts on periodontal pathogens. The primary polyphenols in green tea, catechins, have been found to have bactericidal action against Gram-negative anaerobic rods, and the combination of mechanical treatment

with green tea catechins utilizing a slow-release local delivery method has proven beneficial in improving periodontal overall health (Hirasawa et al. 2002). Anaerobic bacteria such as *Porphyromonas gingivalis* and *Prevotella spp.* are the major etiological agents in periodontitis. *In vitro* experiments have shown that catechins hinder the development of *Porphyromonas gingivalis*, *Prevotella nigrescens* and *Prevotella intermedia* (Asahi et al. 2014). They also inhibit the adherence of *Porphyromonas gingivalis* onto human buccal epithelial cells and inhibit *Porphyromonas gingivalis*-derived collagenase activity (Sakanaka et al. 1996; Makimura et al. 1993).

An *in vitro* analysis assessed the antibacterial activity, in which 50 µg/ml Triphala concentrations inhibited *Streptococcus mutans* species (Ramesh et al. 2016). This antiplaque action may be attributed to tannic acid in Triphala, which is highly adsorbed on the bacterial cell wall, resulting in enzymatic hydrolysis and, finally, bacterial cell death (Jagadish et al. 2009). Triphala was also reported to inhibit the collagenases produced by polymorphonuclear leukocytes, which cause connective tissue destruction in periodontitis (Abraham et al. 2005). This has been supported by an *ex vivo* study in which tissue samples were treated with Triphala, kamilloosan extracts, doxycycline and gelatin zymography. The study results demonstrated that Triphala showed a 76.6% reduction in the activity of the MMP-9 while kamilloosan and doxycycline at concentrations of 1500 µg/ml, showed a reduction of 46.36%

and 58.7%, respectively (Abraham et al. 2005).

It was assumed that *Echinacea purpurea* strengthens the immune system by stimulating white blood cells (See et al. 1997). Three main groups of constituents including alkylamides/polyacetylenes, polysaccharides and caffeic acid derivatives can work together to improve the efficacy and function of white blood cells, such as lymphocytes and macrophages (See et al. 1997). The mouthwash of *Echinacea purpurea* is effective in periodontal disease when combined with sage, menthol, chamomile and peppermint oil (Modaraj et al. 2009).

Hammer et al. (1999) investigated the efficacy of tea tree oil (TTO) against a diverse range of oral bacterial isolates, calculating the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values ranging from 0.003% to 2.0% volume concentration of a solution (v/v). The time-kill assays in his study showed that exposing *Lactobacillus rhamnosus* and *Streptococcus mutans* to 0.5% v/v TTO resulted in a >3 log decrease in viable cells after 30 seconds.

Neems, also recognized as *Azadirachta indica*, has also proven a good efficacy in the treatment of periodontal disease by hindering insoluble glucan synthesis, which results in bacterial aggregation (Patel & Venkatakrishna 1988; Wolinsky et al. 1996). In a small-sample analysis, it was indicated that the use of a dental gel consisting of *Azadirachta indica* extract significantly decreased plaque levels, in particular the bacterial

count of *Streptococcus mutans* when compared to chlorhexidine 0.2% mouthwash as a positive control (Pai et al. 2004).

Meswak is a chewing stick that is used as a traditional oral hygiene toothbrush by many individuals from diverse backgrounds especially in developing countries. Meswak is produced from the Arak tree (*Salvadora persica*), which is found mostly in Saudi Arabia and other Middle Eastern countries. In recent years, meswak extract has been developed into dentifrices as it has been shown to have similar effects in plaque reduction and gingivitis to those of other conventional dentifrices (Gupta et al. 2012). The antibacterial effect of Meswak extract was demonstrated to be most effective against, *Aggregatibacter actinomycetemcomitans*, *Hemophilus influenza* and *Porphyromonas gingivalis* but less effective against *Streptococcus mutans* (Sofrata et al. 2011).

Aloe vera is a cactus plant that belongs to the *Liliaceae* family. There are over 300 varieties of aloe species. Various cosmetic and medicinal treatments have been developed in recent years from the gelatinous tissue found in the core of the aloe vera leaf, in the shape of aloe vera gel. As an adjunctive therapy, a combination of root surface debridement with aloe vera gel subgingival application has led to significant improvements in severe periodontitis by reducing periodontal pocket depth and gingival bleeding (Moghaddam et al. 2017). Significant reductions in the clinical criteria for periodontal pocket depth

and gingival bleeding index have explained the significant efficacy of aloe vera gel in improving the disease. (Bhat et al. 2011). In a report assessing the clinical effects of aloe vera, gingivitis and plaque formation had been substantially reduced after use as a mouth rinse (Villalobos et al. 2001).

Periocare® Gum Massage powder is another commercial herbal formulation product, which consists of *Cinnamon zeylanicum*, *Eugenia caryophyllata*, *Piper nigrum*, *Rubia cordifolia* and *Glycyrrhiza glabra*. The herbal composition in this powder has been individually shown to display antimicrobial and anti-inflammatory effects, which can be used to treat gingival inflammation and to decrease the microbial load. A research conducted by Suchetha and Bharwani (2013) concluded that mechanical plaque control coupled with multi-herbal formulations such as Periocare® is an efficient tool for controlling plaque and helping to preserve optimum periodontal health.

PLANTS EXTRACTION METHOD

Extraction is the isolation of medicinally active parts of plants using selected solvents and standard methods (Handa et al. 2008). Solvents play an important part in the technique of plant extraction in the separation of soluble plant metabolites, leaving behind the adherent cell debris (residue). Some of the extracts obtained initially may be suitable for use as therapeutic agents in the form of liquids and fluid extracts, while others require further processing to get their key metabolites,

such as glycosides, alkaloids, phenols, flavonoids and terpenoids (Azwanida 2015).

Maceration, Infusion, Decoction and Percolation

The maceration method involves immersing powdered or coarse plant ingredients inside a blocked jar holding solvent and allowing them to remain at room temperature for at least three days with continuous agitation (Handa et al. 2008). The method aims to loosen and shatter the plant's cell wall in order to extract soluble phytochemicals. Both infusion and decoction involves soaking in boiled or cold water followed by maceration. When compared to infusion and maceration, decoction is only suited for the extraction of heat-stable compounds, which are hard plant components such as barks and roots that generally result in more oil-soluble chemical compounds. Percolation is the fastest and simplest approach and involves the packaging of dry powder samples using a percolator device, mixed with boiling water, and macerated for two hours. In order to obtain the condensed extracts, the procedure is typically carried out at a modest speed of around 6 drops/min until the extraction is completed prior to evaporation (Rathi et al. 2006). Extraction of the *Psidium guayave L.* leaves using hydro-alcohol extracts (polar solvents) and ethanolic produced the largest extraction yield with the highest content of phytoconstituents (carbohydrates, alkaloids, saponins, flavonoids and tannins) relative to other

solvents, for example chloroforms, water and petroleum ethers (Arya 2012).

Soxhlet Extraction or Hot Continuous Extraction

In this procedure, the finely ground sample is placed in a porous or "thimble" bag made of durable cellulose or filter paper, which is then placed in the thimble chamber of the Soxhlet device. This technique uses less solvent than maceration (Handa et al. 2008). Conversely, the drawbacks of Soxhlet extraction include exposure to flammable and dangerous liquid organic solvents, with possible toxic contamination throughout extraction process, and the high purity of the solvents used in the extraction method, which may add to the expense (Azwanida 2015). Another concern is that the ultimate sample for Soxhlet extraction must be dry and finely split particles, with various variables such as solvent-sample ratio, temperature, and agitation speed (Amid et al. 2010). Soxhlet extraction of *Azadirachta indica* (Neem) leaf powder in methanol has been found to recover a variety of phytochemicals, primarily nonpolar molecules (Hossain et al. 2013).

Microwave-assisted Extraction (MAE)

Microwave-assisted extraction (MAE) uses microwave energy to enhance the distribution of analytes from the sample matrix to the solvent (Trusheva et al. 2007). This procedure decreases the extraction time and amount of

solvent required compared to the traditional form of extraction (Soxhlet extraction and maceration). The MAE method improved analyte recovery and repeatability, but it must be used under appropriate conditions to avoid heat deterioration (Kaufmann & Christen 2002). This method, however, is limited to phenolic compounds of small molecules, such as phenolic acids (gallic acid and ellagic acid), quercetin, isoflavones, and transresveratrol, because these molecules were sustainable under microwave heating temperatures of up to 100°C for 20 minutes (Azwanida 2015). Additional MAE cycles from two to ten seconds, to three to ten seconds resulted in a significant decline in phenolic and flavanone yields, primarily due to compound oxidation (Trusheva et al. 2007). Anthocyanins and tannins may be unsuitable for MAE as they deteriorate at high temperatures (Azwanida 2015). The evaluation of MAE as a new technique for extracting triterpene from *Centella asiatica* revealed an increase in yield, twofold in Soxhlet extraction using the following optimum condition: Absolute solvent ethanol at 75°C and a four-cycle irradiation capacity of 600 Watts (Puttarak & Panichayupakaranant 2013).

Ultrasound-assisted Extraction (UAE) or Sonication Extraction

Ultrasound-assisted extraction (UAE) makes use of ultrasound frequencies ranging from 20 to 2000 kHz (Handa et al. 2008). The mechanical impact of ultrasonic acoustic cavitation improves

surface contact between solvents and materials and promotes cell wall permeability. The chemical and physical characteristics of the products are altered in response to ultrasound, and they interact with the plant's cell wall, enabling compound release and increasing the mass transit of solvents to plant cells (Dhanani et al. 2017). The approach is a simple and low-cost method for extracting phytochemicals on a small and big scale extractions (Azwanida 2015). The benefits of UAE are primarily related to reduced solvent use and extraction time. Nevertheless, the use of ultrasonic energy in excess of 20 kHz would impact on active phytochemicals through the creation of free radicals (Handa et al. 2008). Higher phenolic effectiveness was found in *Cratogeomys formosum* ultrasonic extraction at 45 kHz, 50.33% ethanol volume/volume (v/v), and 15 minutes at temperature of 65°C (Yingngam et al. 2014). Nevertheless, it may be necessary to address the formation of free radicals at irradiation frequencies higher than 20 kHz (Azwanida 2015).

DISCUSSION

The Importance of Natural Product

A natural product is a chemical organic substance formed by natural living organisms that typically has a pharmacological or biological function that is beneficial to the development and design of pharmaceutical drugs (Table 1). The majority of novel medicines are derived from natural products (secondary metabolites) or chemicals isolated from natural sources

(Lahlou 2007). Historically, the earliest documented natural products as medicament were from Mesopotamia (2600 B.C.), whereby the oils from *Commiphora* species (myrrh) and *Cupressus sempervirens* (Cypress) were used to cure colds, cough and soreness (Cragg & Newman 2005). Avicenna, a Persian pharmacist and physician, had contributed significantly to the science of pharmacology and medication throughout his study in the *Canon Medicinae* (Newman & Cragg 2016).

Nowadays, the greatest example of a medicine generated from a natural substance would be the production of the anti-inflammatory compound acetylsalicylic acid, more often known as aspirin, which is derived from salicin extracted from the bark of the willow tree *Salix alba L* (DerMarderosian 2002). Aspirin's mechanism of action has been claimed to be inhibition of the cyclooxygenase (COX) enzyme activity, which is responsible for the production of prostaglandins (PGs), which cause pain, fever, inflammation and swelling (Vane 1971). Furthermore, pilocarpine, an L-histidine-derived alkaloid discovered in *Pilocarpus jaborandi* (Rutaceae), has been documented to create miotic activity that inhibits papillary block and has been utilized as a therapeutic medication in the treatment of glaucoma (Dias 2012). The Food and Drug Administration (FDA) authorized the oral formulation of pilocarpine in 1994 and 1998 for the treatment of xerostomia, a side effect of radiation therapy for head and neck malignancies, and Sjogren's syndrome, an autoimmune disease affecting the lacrimal and salivary glands (Dias

Table 1: The effects of herb extraction on in-vivo and in-vitro studies

Herbs/plants	Compounds/metabolites	Mechanism of action	Extraction method	In-vivo/in-vitro studies
<i>Camellia sinensis</i> (Green tea)	Polyphenols	Antioxidant Antimicrobial Anti-inflammatory	Soxhlet extraction Microwave-assisted extraction Ultrasound-assisted extraction	Reduce lipopolysaccharide-mediated bone resorption in both in-vivo and in-vitro conditions. Suppressed lipopolysaccharide (LPS) mediated gene expression such as nuclear factor-kappa B ligand receptor activator (RANKL), cyclooxygenase-1 and PGE-2 cytokines in mouse osteoblasts (Tominari 2015). Bactericidal activity against gram-negative anaerobic rods, and the combination use of mechanical therapy and green tea catechins using a slow-release local delivery system effectively enhanced periodontal health status (Hirasawa et al. 2002). Similar antiplaque efficacy to the gold standard, chlorhexidine gluconate when used for a duration of one week (Kaur et al. 2014).
<i>Piper longum</i> (Long pepper) <i>Piper nigrum</i> (Black pepper)	Alkaloid	Antioxidant Anti-inflammatory	Soxhlet extraction	Demonstrated free radical scavenging activity by decreases in nitrite level and reduces TNF- α levels (Pradeep & Kuttan 2003). Significantly down-regulated interleukin-1 β , MMP-8 and MMP-13 production (Dong et al. 2015).
<i>Terminalia chebula</i> , <i>Emblica officinalis</i> , and <i>Terminalia bellerica</i> (Triphala)	Flavonoids	Antioxidant Anti-inflammatory Antimicrobial	Soxhlet extraction	Has been reported to be as effective as 0.2% chlorhexidine in anti-plaque and anti-inflammatory activities (Naiktari et al. 2014). Triphala showed a 76.6% reduction in the activity of the matrix metalloproteinase-9 (MMP-9) while kamillosan and doxycycline showed 46.36% and 58.7%, respectively at concentrations of 1500 μ g/ml (Abraham et al. 2005).
<i>Ginkgo biloba</i>	Flavonoids Terpenoids	Anti-inflammatory	Ultrasound-assisted extraction	Systemic administration of <i>Ginkgo biloba</i> extract (28-56 mg/kg/day) has resulted in reduction of osteoclast counts and inflammation, and induced osteoblast activity (Sezer et al. 2013).

Herbs/plants	Compounds/ metabolites	Mechanism of action	Extraction method	In-vivo/in-vitro studies
<i>Matricaria chamomilla</i> (Chamomile)	Sesquiterpenes Flavonoids Coumarins Polyacetylenes	Anti-inflammatory Antioxidant	Soxhlet extraction Maceration	The 1% <i>Matricaria chamomilla</i> mouth rinse was found to improve the clinical and microbiological picture of chronic periodontitis. Its outcomes commensurate the gold standard mouth wash chlorhexidine (Agarwal & Chaudhary 2020). In rat periodontitis model study, Chamomile dry extract has ability to prevent periodontal disease by preventing the inflammation and alveolar bone resorption by reducing TNF- α and IL-1 β , preventing the osteoclast activation via the RANKL–Osteoprotegerin (OPG) axis, without interfering with bone anabolism (Guimaraes et al. 2016).
<i>Centella asiatica</i> and <i>Punica granatum</i>	Sterols Flavonoids	Antioxidant Anti-inflammatory	Maceration	In the form of biodegradable chips as a subgingival adjunct to scaling and root planning, <i>Centella asiatica</i> and <i>Punica granatum</i> have greatly improved the clinical symptoms of chronic periodontitis and interleukin-1 in maintenance patients when used as an adjunct to local delivery (Sastravaha et al. 2005).
<i>Ficus deltoidea</i> (Mas Cotek)	Flavonoids	Anti-inflammatory Antioxidant	Maceration	<i>Ficus deltoidea</i> can prevent alveolar bone loss in osteoporotic induced rats by its potential to preserve trabecular bone density, decrease osteoclast and increase osteoblast cell count to reduce bone resorption and stimulate bone formation, respectively (Omar et al. 2020).
<i>Echinacea purpurea</i>	Alkylamides / Polyacetylenes, Polysaccharides Caffeic acid	Antimicrobial	Ultrasound- assisted extraction Maceration	The mouthwash of <i>Echinacea</i> is effective in periodontal disease in combination with sage, menthol, chamomile and peppermint oil (Modaraj et al. 2009).
Tea tree oil	Terpinen-4-ol	Antimicrobial	Percolation	Time-kill assays demonstrated that exposure of <i>Streptococcus mutans</i> and <i>Lactobacillus rhamnosus</i> to 0.5% (v/v) tea tree oil resulted in >3 log reduction of viable cells within thirty seconds (Hammer et al. 1999).

Herbs/plants	Compounds/ metabolites	Mechanism of action	Extraction method	In-vivo/in-vitro studies
<i>Azadirachta indica</i> (Neem)	Flavonoids Terpenoids Coumarins Alkaloids	Antimicrobial	Microwave- assisted extraction	Dental gel containing <i>Azadirachta indica</i> extract greatly reduced the plaque level, in particular the bacterial count of <i>Streptococcus mutans</i> compared to chlorhexidine 0.2% as a positive control (Pai et al. 2004). Inhibits insoluble glucan synthesis which results in bacterial aggregation and It reduces the ability of <i>Streptococci</i> to colonize tooth surfaces (Wolinsky et al. 1996).
<i>Salvadora persica</i> (Meswak)	Flavonoids Alkaloids Terpenoids Tannins	Antimicrobial	Maceration	Presented with high bactericidal activity against the Gram-negative periodontal pathogens <i>A. actinomycetemcomitans</i> and <i>P. gingivalis</i> (Sofrata et al. 2011). In contrast to toothbrush, meswak significantly reduced the amount of <i>A. actinomycetemcomitans</i> in the subgingival plaque, which indicated that extracts from <i>Salvadora persica</i> might interfere with the growth and leukotoxicity of <i>A. actinomycetemcomitans</i> (Al-Otaibi et al. 2004).
Aloe vera	Aloin	Antioxidant Anti-inflammatory Antimicrobial	Ultrasound- assisted extraction	In-vitro study stated Aloe vera depleted the chemical and alternative pathways of complement activity to inhibit the production of free oxygen radicals by activated Polymorphonuclear leucocytes (PMNs) (Hart et al. 1988). Aloe vera is also shown to provide relief in swelling, bleeding gums and is an antiseptic for pockets and antifungal for thrush (Choonhakarn et al. 2008).
<i>Centella asiatica</i> and <i>Punica granatum</i>	Sterols Flavonoids	Antioxidant Anti-inflammatory	Maceration	In the form of biodegradable chips as a subgingival Adjunctive treatment to scaling and root planning, <i>Centella asiatica</i> and <i>Punica granatum</i> have greatly improved the clinical symptoms of chronic periodontitis and interleukin-1 in maintenance patients when used as an adjunct to local delivery (Sastravaha et al. 2005).

2012).

In a critical review of drug discovery by Lahlou (2013), the author stated that natural metabolites are better in terms of biological and pharmacological activities compared with randomly synthesized compounds. In another systematic review of natural ingredients as foundations of novel medications from 1981 to 2014, Newman and Cragg (2016) stated that Natural products serve a critical role in the creation and invention of medications for the treatment of human diseases. The exploration of and scientific investigation into the pharmacological use of natural products are significant as an initial step to develop new medicaments in preventing or treating diseases.

Herbs and General Health

Phytotherapeutic agents or phytomedicines are standardized herbal products composed of complex mixtures of one or more plants. Herbal drugs include active ingredients of raw or refined plant parts or materials plus other excipients such as solvents, diluents or preservatives (Akerele 1993).

Herbal extracts are well recognized for their contribution towards general well-being and have been shown to be efficient in the treatment and prevention of chronic disorder. The foxglove, *Digitalis purpurea L.*, was brought to Europe in the tenth century (Haefner 2003). Later, in the 1700s, it was discovered that cardiotonic glycoside, the active ingredient of digitoxin, may enhance cardiac

contractility by improving cardiac conduction (Haefner 2003). Digitoxin and its equivalents have long been used to treat congestive heart failure, although they may have long-term side effects and are being replaced by alternative medicine in treating "heart deficiency" (DerMarderosian 2002). In 2004, the United States FDA approved the use of the antimalarial drug quinine, which is extracted from the bark of *Cinchona succirubra* (Butler 2004). The bark was first used to cure malaria in the mid 1800s, and it has been used for hundreds of years to treat fever, malaria, fever, illnesses of the mouth and throat, indigestion, and malignancy (DerMarderosian 2002).

Herbs and Oral Health

The application of herbs in oral health has been utilized for centuries, particularly to prevent tooth decay, gum bleeding, halitosis and plaque accumulation. Herbs have been proven as one of the main ingredients in several commercialized toothpastes and mouthwashes, either for prevention or treatment of oral disease.

Beneficial effects of drinking green tea in preventing dental caries and gum disease have been reported in a number of studies and reviews. In dentistry, green tea leaves have been commercialized in the form of mouthwash for oral hygiene care. Magalhaes et al. (2009) observed that oral rinsing with 0.61% green tea extract had the same preventive effect for dentinal erosion and abrasion as mouth rinsing with 0.06% chlorhexidine extract or fluoride

extract (250 ppm), both of which are present in oral hygiene products. Furthermore, Ferrazano et al. (2011) found that oral rinsing with green tea (1.6 g crushed green tea in 40 ml water) for one week and three times a day was capable of considerably reducing the colony counts of cariogenic bacteria *Streptococcus mutans* and *Lactobacilli sp.* These findings demonstrate the effectiveness of green tea extract in reducing dental caries susceptibility.

Lippia sidoides Cham (Verbenaceae), also known as "Alecrim-pimenta", is a common shrub usually found in the northeast of Brazil (Bothelo et al. 2007). *Lippia sidoides* essential oil, carvacrol and thymol have been suggested by Bothelo et al. (2007) to be useful for maintaining a low level of plaque formation through their antibacterial activities against *Streptococcus mutans*, an essential cariogenic bacterium, which leads to caries or dental enamel demineralization. Mittal et al. (2010) recommended that a decoction of leaves and rootbark of guava (*Psidium guajava*) as a mouthwash makes an efficacious gargle for ulceration of the mouth as well as for swollen and bleeding gums.

Drosera peltata (Droseraceae) leaves, which have been identified as containing plumbagin as the active constituent of its extract, were used as traditional medicament for dental caries and it was found that chloroform derivatives of aerial plant parts displayed a wide range of action against various oral cavity bacteria, with the highest activity against *Streptococcus mutans* and *Streptococcus sobrinus* (Palombo 2011). An extract produced from tree

leaves in the form of medium-sized angiosperm in the Bignoniaceae family, *Newbouldia laevis*, was studied as a bactericide for bacteria involved in dental caries and it was observed that *Newbouldia laevis* had bactericidal activity against *Lactobacilli* and *Streptococcus mutans* (Okeke 2003).

In a study evaluating antibacterial efficacy against four common oral pathogens among the 20 traditional Chinese herbal medicines, Wong et al. (2010) found that 13 herbs demonstrated antimicrobial activity against *Porphyromonas gingivalis*, including *Cortex magnoliae officinalis*, *Cortex phellodendri*, *Flos lonicerae japonicae*, *Flos caryophylli*, *Fructus forsythiae suspensae*, *Fructus armeniaca mume*, *Herba menthae haplocalycis*, *Herba cum radice violae yedoensis*, *Pericarpium granati*, *Radix et rhizoma rhei* *Radix gentianae*, *Rhizoma cimicifugae* and *Ramulus cinnamomi cassia*.

The use of plant extracts in pharmaceutical products has been extensively discussed for their important antibacterial action against numerous microorganisms, including bacteria known for dental caries and periodontal disease. Phytochemicals with antimicrobial activities for the management and prevention of periodontal diseases, such as flavonoids, alkaloids, tannins, terpenoids and polyphenols, have been identified (Kumar et al. 2009). In addition, a recent review has reported the importance of herbs as antioxidants for combating oxidative stress in chronic periodontitis (Ramesh et al. 2016).

The application of herbal medications remains to spread exponentially around the world. Numerous herbal products or natural medicines have been used in different national healthcare settings for medical treatment. According to the World Health Organization (WHO), conventional herbal medicine is used by up to 80% of the world's population for their basic healthcare requirements. The utilization of medicinal plants and the development of indigenous medicines have significant economic benefits in the treatment of various disorders (Azaizeh 2000). Herbs and their derivatives are used in 25% of medicinal medicines in industrialized nations (Principe 1991).

The importance of herbal medicine as an alternative to treating disease can be stated being due to various factors such as: market demand for natural remedies; great interest in alternative therapies; concern about the adverse side effects of modern-day medications; communities' desire for preventive medication due to a rise in population age; the assumption that herbal remedies may be useful in the treatment of some diseases when conventional treatment and medications have been shown to be ineffective; the expensive expenditure of synthetic medicines; and the increased efficiency, evidence of effectiveness and safety of herbal medicines (Calixto 2000).

Periodontal disease is an inflammatory disease that if left untreated, it can result in the breakdown of tooth-supporting structures and ultimately, tooth loss.

In the elderly, individuals' quality of life is affected when they lose teeth, especially if it impacts their well-being, attractiveness, and nutritional condition (Saintrain & de Souza 2012). Mack et al. (2005) concluded that reduced dentition without replacing missing teeth with removable or fixed prosthodontics tends to reduce the physical quality of life index to the same extent as cancer or kidney disease.

Since numerous evidences have reported the valuable properties of antimicrobials, with their anti-inflammatory and antioxidant actions found in herb extracts, which are essential to prevent and treat periodontal disease, it can be summarized that herbal medicine plays an important role in providing potentially effective and economical medicaments for periodontal disease in the future. Since periodontal disease is a complex disorder, effective disease treatment necessitates a thorough understanding of all related risk factors as well as the pathophysiology of the disease. Modifiable risk factors that have been recognized, such as bacterial plaque, diabetes mellitus, tobacco smoking, drug-induced disorders, cardiovascular disease, obesity, and stress, need to be necessarily measured. Phytochemicals derived from herb extracts can be used as an adjunctive to standard periodontal therapy to treat periodontal disease and preserve periodontal health. However, public awareness and oral health promotion in preventing periodontal disease by encouraging them to have routine dental check-ups and treatment,

perform decent oral hygiene habit, and practice a healthy lifestyle are still the fundamental factors to consider and must not be left behind to complement the importance of phytochemicals in periodontal health.

CONCLUSION

Natural plant extract remains a vital component in the search and innovation of new, safe, effective, and economical medicaments. The application of herbal medicine has been widely documented to have beneficial use in the treatment and prevention of periodontal disease. This has been proven by its various essential ingredients and properties in reducing inflammation and oxidative stress, preventing plaque adherence and, most importantly, the antimicrobial effects. However, it is encouraging to have more clinical trials and additional studies on the efficacy and safety of the components in herbal extracts to support their beneficial therapeutic purpose, either alone or in conjunction with traditional treatments, which will help to minimize the total burden of periodontal disease worldwide.

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