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Review Article

Traditional Medicine and Micrornas Inperiodontal Disease: Bridiging the Gap

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Abstract

Traditional Medicine can be epitomized as knowledge, skill and practices based on the theories and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. MicroRNAs (miRNA) have become the spotlight of the biomedical research. The connection between the plant miRNAs and their ingestion in human tissues bestows a new unexplored relationship between the two kingdoms. Delving further into this zone, miRNA therapeutics could be the next best step toward identifying novel therapeutic options involving medicinal plants. Continuing efforts in this area will broaden our understanding of biological actions of herbal remedies and will open the way for the development of new approaches to prevent or treat human diseases by improving overall response and survival outcomes, especially when combined with conventional therapeutics.

Keywords: Periodontal disease; Traditional medicine; miRNA; Herbs

Introduction

Periodontal disease is a bacterial disease of the tooth supporting structures [1]. Among the important causative bacteria in periodontal disease are Porphyromonasgingivalis (Pg) and Actinobacillus actinomycetemcomitans (Aa), which adhere to tooth surfaces subsequent to the formation of stagnant biofilm. Pg and Aa produce an enzyme arginine-specific cysteine proteinase that can lead to disruption of the immune system, trigger an inflammatory response and eventually cause damage to the surrounding host tissue [2]. Treatment with mouthwashes and antibiotics have positive outcomes [4]; however, there are undesirable side effects like a metallic taste, allergies, developing bacterial resistance and systemic circulation of these [3,4].

One of the ways of minimizing the systemic distribution of therapeutic agents in the body is through the use of 'Local Drug Delivery Systems' for the release of antimicrobial agents [5]. In the area of infection, such as fibers, strips, films, gels, microparticles and nanoparticles. With the advent of these new technologies, costs of treatment increased. Consequently search for alternative therapies including natural phytochemicals, are being considered as desirable alternatives to synthetic chemicals [6]. The focus of this paper is to provide an in-depth knowledge of the development of traditional medicines and their current and potential applications for the prevention and treatment of periodontal disease. This paper also serves to establish a link between ethnic herbs and miRNAs. This relatively unexplored connection between plant-derived medicines with miRNAs can provide a newer dimension to the conventional traditional and complementary medicine therapeutics.

Traditional Plant Based Medicines

Tea

Green tea (*Camellia sinensis Theaceae*): A pilot study conducted in Egypt with 25 subjects established that green tea is effective as an antibacterial, anti-inflammatory and antioxidant agent [7]. In another investigation among adolescent females, it was found that mouthwashes containing 5% green tea had a positive effect on periodontal inflammatory indices [8].

Chamomile (*Matricaria recutita*): Results of controlled double-blind cross-over study to analyze the effects of German Chamomile mouthwash confirmed that this mouthwash used twice daily for four weeks was successful in reducing plaque build-up and gingival inflammation and hence can be given as an adjunctive daily supplement [9].

Chewing sticks

Guava (African chewing stick): An investigation to determine its antimicrobial properties concluded that guava extracts neutralized the leukotoxicity caused by A. actinomycetemcomitans [10]. Psidiumguajava is cultivated in the tropics and sub-tropics for its anti-oxidant, anti-inflammatory, anti-spasmodic and other important remedial properties [11]. An *in vitro* study demonstrated its broad-spectrum antimicrobial activity towards gram-negative and gram-positive bacteria [12]. In the rural areas of Nigeria, a large portion of the population use chewing sticks, which have an active component 'Fagara zanthoxyloides' known to inhibit periodontal pathogens *Porphyromonas gingivalis* and *Bacteroides melaninogenicus* [13].

Neem (*Azadirachta indicia*): As a mouth rinse, 0.19% Azadirachtaindica proved to have a comparable effect to that of chlorhexidine in reducing pathogenic microbes [14]. In a clinical study, after three weeks of brushing twice a day with toothpaste including neem leaf extracts, eight out of ten patients showed reduction in bacterial populations and elimination of halitosis without any toxic effects [15].

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Berries and fruits

A-Type Cranberry Proanthocyanidins: When tested on human oral epithelial cells, it was shown to reduce the inflammatory response caused by *P.gingivalis* [16]. The Memorial Sloan-Kettering Cancer Centre notes that Cranberry extracts have properties that can prevent bacterial plaque from colonizing and adhering to teeth by inhibiting the production of glucans and fructans [17].

Blackberry: An experiment using extracts from Hull blackberries proved that when *F. nucleatum* and *P. gingivalis* were exposed to 700 µg/ml of blackberry extract for a day, their metabolism reduced by 40% [18]. A double-blind randomized control trial was performed to determine the effectiveness of blackberry as part of a commercial product named Juice Plus+® and it was found that after 2 months, periodontal pocket depths, gingival crevicular fluid and bleeding on probing levels had significantly reduced [19].

Punica granatum (family *Punicaceae*): It is commonly called "pomegranate". A trial concluded that pomegranate extract gel not only completely prevented plaque formation, but also significantly reduced the amount of plaque [20]. Another study showed reduction in gingival bleeding when exposed to dentifrice containing pomegranate extract gel [21].

Grape (*Vitis spp.*) Resveratrol: It is one of the key polyphenols present in grapes, has known to inhibit the release of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-10, MCP-1, IFNα and IFNβ [22].

Essential oils

Frankincense or Olibanum with the functional component-Acetyl Keto Boswellic Acid (AKBA): which is known to selectively inhibit the lipo-oxygenase pathway [23]. In a randomized, double-blind investigation, it was proved that the anti-plaque properties of Frankincense were more effective than scaling and root planing and it may be used as an oral hygiene supplement [24]. In another clinical trial, Boswellia extract positively treated inflammatory disorders with minimal toxic effects [25].

Eugenia Caryophyllata (Clove oil): contains eugenol and several important active ingredients, including gallotannic acid, oleanolic acid, eugenin and vanillin, which may help relieve pain and cure infection [26]. An *in-vitro* experiment to study the influence of clove oil on oral bacteria confirmed that it acts as a superb antibacterial and anti-fungal agent and exhibits cytotoxicity [27].

Eucalyptus A double masked study revealed that subjects who consumed a eucalyptus chewing gum were relieved of the disease's symptoms, including a lesser amount of plaque accumulation, gingival bleeding and reduction in periodontal pocket depths [28,29]. In one of the clinical trials, it was verified that subjects who chewed a gum containing eucalyptus extract showed significantly reduced plaque when compared to those who chewed the control gum [30].

Lavender oil (*Lavandula angustifolia*): In an *in-vitro* study testing its anti-bacterial activity against a biofilm formed by gram negative and gram positive bacteria after 4 hours of exposure, terpinen-4-ol (an active ingredient of Lavender oil) was effective in reducing 90% of metabolic activity of the causative bacteria [31]. Another study states that inhaling lavender oil is widely used by aroma therapists to ease anxiety associated with dental procedures [32].

The essential oil of *Melaleuca alternifolia (Myrtaceae*), known as Tea Tree Oil (TTO): According to Cindy Jones, biochemist and author of the book "The Antibiotic Alternative", TTO is a powerful antiseptic and functions similar to an antibiotic in treating infections such as dental abscesses [33]. The activity of TTO against an extensive collection of oral bacterial isolates was investigated and results proved that exposure of *S. Mutans* and *Lactobacillus rhamnosus* to 0.5% (v/v) TTO resulted in reduction of viable cells within 30 seconds [34].

Functional foods

Garlic: contains two active organo sulfur elements namely diallyl sulfides and allicin, which function as anti-inflammatory, anti-microbial and anti-oxidant agents. An *in-vitro* research indicates that garlic is bactericidal towards *A. Actinomycetemcomitans*. Diallyl sulfides also add to the action of general antibiotics against drug-resistant bacteria [35]. In another similar study, it was found that garlic worked as an anti-microbial at concentrations of 5%, 10%, 20% and 100% and that no bacteria were resistant to this natural medicine. The study also proved that chlorhexidine was more effective but produced greater allergic reactions as compared to garlic [36].

Mushroom: Low molecular mass fractions of mushroom have been found to modify the proliferation and inflammation of gingival cells caused by pathogens such as *P. intermedia* and *A. naeslundii*, inhibit adhesion of plaque bacteria and biofilm formation [37]. Shiitake mushrooms (*Lentinula edodes*) were tested against six different periodontal pathogens and were found to have anti-biofilm effects even at low concentrations [38]. When mushroom extracts were incorporated in a mouthwash and tested on human volunteers, results revealed that the mouthwash interrupted biofilm formation, although its effect was less than that of Listerine [39].

Brazilian plant extracts

1. Propolis-A sample of Green Propolis taken from Southeast Brazil was studied as a component of toothpastes and it was concluded that 3% ethanol extract of propolis can alter the oral microbiota and be used in addition to scaling and root planing [40]. In another investigation, 20 volunteers diagnosed with chronic periodontitis were exposed to 20% propolis hydroalcoholic solution used as an irrigant in the periodontal pockets after scaling and root planning, confirmed that after two weeks of irrigation, there was signification reduction in the number of *P. gingivalis* [41]. An '*in vitro*' trial concluded that this herb was effective against a wide range of periodontal pathogens such as *F. nucleatum, P. gingivalis, P. intermedia, P. melaninogenica* and A. actinomycetemcomitans and proved to be more effective than antibiotics against all these bacterial strains [42].

2. Extracts of Equisetum arvense Leaf, Glycyrrhiza glabra Leaf and Stryphnodendron barbatimam Mart were capable of decreasing TNF-alpha levels, with G. glabra being the least cytotoxic. At different concentrations, these herbs proved to be bacteriostatic against gingival and periodontal pathogens [43].

Traditional chinese medicines

Zein and Shuanghuangbu: Zein-a protein found in maize and Shuanghuangbu-a traditional Chinese herb; have been used as a scaffold in periodontal tissue engineering procedures. It was concluded that Shuanghuangbu scaffold extracts at a concentration

of 100 mg/ml enabled PDL cell proliferation, thus facilitating tissue regeneration. These materials have proved to be compatible to oral tissues with no toxic effects [44]. Another research to study the effect of Shuanghuangbu on periodontal ligament cells confirmed that total protein content of PDL cells increased with an increase in concentration of the herb [45].

Terminalia chebula: An *in-vivo* study confirmed that a mouth wash comprising of *T.chebula* was effective against oral pathogens as the herb is well known for its immune modulatory, antibacterial and wound healing abilities [46]. In a Sri Lankan study, aqueous extracts from the fruit of *T. Chebula* when prepared as a mouthwash showed excellent anti-microbial activity against multi-drug resistant bacteria [47].

Japanese herbs

Enteromorpha linza: Studies validate that *E. Linza* has been effective against two periodontal pathogens- Prorphyromonas gingivalis and prevotella intermedia. In a randomized double-blind study to compare the anti-gingivitis effects of E. Linza with Listerine, results proved that a mouth rinse containing 1.5 mg/ml of *E. linza* extracts was as potent as the Listerine mouthwash and using it twice a day for one month extensively reduces plaque and gingival bleeding [48].

Orento: An *in-vitro* experiment evaluating the mechanism of action of Orento presented that it reduces the production of Prostaglandins and controls phospholipase A2 activity and that there has been no other antibiotic that has the ability to regulate PLA2 activity, making this herb a unique anti-inflammatory agent [49].

European herbal medicines

Rosemary, Sage, Thyme and BasilIn an *in-vitro* study conducted at Kingston University, it was assessed that these herbs contain phytochemicals such as Caffeic acid and Rosmarinic acid that have the ability to restrain Interleukin 8 activity, thus act against inflammation [50]. Another principal constituent, Carnosol, present in Rosemary and Sage is known to possess anti-oxidant and anti-inflammatory properties [51]. An experiment conducted at the Massachusetts Institute of Technology proved that Red Thyme had the potential to disrupt biofilms produced by Staphylococcus Aureus [52].

MicroRNAs in medicinal plants

MicroRNAs are small, non- coding RNAs that play crucial roles as regulators of gene expression [53]. They not only execute biological functions within their original system, but can also be transmitted across cross-kingdom, inducing a posttranscriptional repression of protein synthesis in the recipient [54]. Oral application is one of the predominant routes of application for herbal preparations. The plant RNA nexus could be internalized into the intestinal epithelia and become engulfed into exosomes [55]. These miRNAs that are packaged within exosomes could be taken up by either macrophages or intestinal stem cells. This inter-disciplinary miRNA regulation from the arena of medicinal plants might act as new bioactive components, interacting with the mammalian system [54]. In a study, 12 putative miRNAs were identified from Curcuma longa *L. Zingiberaceae* via bioinformatics and found to bind with various target genes in humans relating to diabetes mellitus type II, cardiovascular disorders, Alzheimer's, cancer and thalassemia. On another note, six miRNAs were identified from *G.arborea* (*Lamiaceae*), targeting the mammalian genes associated with cancer, blood borne disease and urinary tract infections. Certain conditions like stress, malnutrition, altered intestinal permeability due to GI tract disorders and traditional ethnic remedies can enhance the uptake of foreign miRNAs [56]. The most direct evidence of therapeutic effects of plant derived RNAs is where in MIR2911 (a plant-derived miRNA), is highly stable in the decoction of a Chinese herb honeysuckle and has been traditionally used in China for centuries to treat influenza infection [57].

Regulation of endogenous miRNAs by herbal medicine

Health related functions may be mediated by miRNAs by expressing their effects on the metabolome and the interactome within plants and/or modify the status of miRNAs within humans [53]. Treatment with Curcumin (belonging to the ginger family) could result in a>80% knockdown of miR-21 expression, increasing expression of several downstream target genes, including PTEN and PDCD4 and inducing apoptosis [58]. Resveratrol induces apoptosis by up-regulating miR-137 levels and subsequently reducing EZH2 expression in neuroblastoma. In another study, resveratrol induced apoptosis by suppressing miR-21 regulation of BCL-2 protein expression in pancreatic cancer cells. Treatment of carcinoma cells with green tea, leads to altered expression of miRNAs, due to its ingredient polyphenon-60 or epigallocatechin gallate [58,59]. Studies conducted by our lab and that of others have demonstrated that miRNAs regulate cell migration, myeloid cell differentiation, phagocytosis of various bacteria and opsonized antigens, TLR signaling, autophagy, regulation of actin cytoskeleton network, Want and PI3K signaling, etc [60-62]. Thus, by fine-tuning critical pathways involved in basic cell-biology, i.e. cell growth, cell survival and differentiation; and by modulating immune cells, alike, miRNAs can affect key genes involved in the periodontal inflammation and host response.

Discussion

Our study is one of the very few studies that summarize the use of traditional medicines employed across the globe for the management of periodontal disease. There is a rising inclination in North America and many European countries towards traditional healing techniques is attributable to factors such as reduced cost of treatment and lesser consumption of synthetic drugs [63]. 10% extracts from the Brazilian herb LippiaSidoides incorporated in a gel form was successful in reducing gingival inflammation by acting against dental plaque [64]. Gel formulations have also been used for subgingival application of extracts from Quercus brantii (oak bark) and Coriandrum sativum (coriander) [65]. Recent advances in the local delivery of herbal medicines have proved effective in a study where medicated chips were used for subgingival application of extracts from *Centella asiatica* and *Punica granatum* [66]. It is also the very first study trying to establish a possible link of effect of plant-miRNAs in periodontal disease; as well as the response of human miRNAs to the consumed oral ethnic herbs. Various studies comparing healthy *versus* diseased gingiva have demonstrated specific miRNA deregulations in periodontal tissue homeostasis and pathology targeting TLR and TNF alpha pathways [67,68]. Down regulation of miR-29b, let-7f and upregulation of miR-203 [69], miR-146, miR-584 [70]. upon exposure of oral pathogens to human gingival epithelial cells or fibroblasts, suggests

a key role of miRNAs in refining the host response to periodontal pathogens, by targeting IRAK1, SOCS3 or TRAF6 pathways. A study conducted comparing gingival biopsy samples derived from chronic periodontitis subjects, periimplantitis subjects and healthy subjects showed significant differential expression of miR-146a and miR-499 amongst these groups [71]. These findings collectively suggest the pivotal role of miRNAs in the immuno-modulation of periodontal inflammatory soft tissues and the underlying alveolar bone. miRNAs could contribute towards the healing of the periodontium by regulating the mRNAs and eventually, the pathways targeted. The knowledge gained by the miRNA interactions to the mainstream machinery at the level of DNA, mRNA and protein have expanded our scope for developing alternative therapeutic intervention strategies to treat periodontal disease.

Conclusion

MiRNAs are involved in the regulation of cell development, function, physiological and pathological activities in human, animals and plants. Role of natural compounds in regulating miRNA's has been illustrious in guiding EMT, metastasis and drug resistance. There is a need to bridge this existing gap by carrying out further studies between plant exogenous genetic material and the changes it may cause upon ingestion in humans.

It is very early to know the cross-kingdom miRNA effects; however, this new approach in herbal medicine could lead to number of applications in the pharmaceutical industry as it deals with potential biomarkers and drug-delivery systems. Thus by combining conventional therapeutics with medicinal plants could open new avenues. Thus, the paper seeks to answer two questions: What is the existing role of plant based medicines in the treatment of periodontal disease? Moreover, which plants hold potential for future treatment modalities against periodontal and gingival diseases and their interaction with miRNAs?

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