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Review article

Probiotics and metabolites regulate the oral and gut microbiome composition as host modulation agents in periodontitis: A narrative review

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ABSTRACT

Periodontitis is defined as an oral bacterial dysbiosis-induced persistent inflammation on dental supporting tissue resulting in periodontal tissue breakdown and alveolar bone destruction. The disease is initiated by the interaction between periodontopathogens and the host immune system. Its development and severity can be associated with several systemic diseases, such as cardiovascular disease (CVD), diabetes mellitus, and rheumatoid arthritis (RA). Moreover, the latest research has suggested that the oral and gut microbiome hypothesis lays the oral and systemic connection mechanism. Bacterial homeostasis and restoration in the oral cavity and intestine become therapeutics concepts. Concerning the treatment of periodontitis, a local inflammatory condition, prolonged systemic administration of antibiotics is no longer recommended due to bacterial resistance issues. Probiotics and several bioactive metabolites have been widely investigated to address the needs of host modulation therapy in periodontitis. Evidence suggests that the use of probiotics helps downregulate the inflammation process through the regulation of toll-like receptor 4 (TLR4) and the production of fatty acid, targeting reactive oxygen species (ROS). In brief, several herbals have anti-inflammatory properties by inhibiting pro-inflammatory cytokines and mediators, including mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB). Consistently, improvement of periodontal pocket depth (PPD) and gingival index (GI) was seen in a group given melatonin as an adjunct treatment. In all, this review will highlight host modulation agents regarding periodontitis therapy, plausible mechanisms on how probiotics and metabolites work on periodontal restoration, and their reported studies. Limitations given by published studies will be elaborated, while future directions will be proposed.

1. Introduction

Periodontitis is a highly prevalent chronic inflammatory disease of the periodontal tissue previously believed to be influenced by bacteria dysbiosis solely [1]. Pathogenic bacteria initiate the disease in the oral cavity. These gram-negative bacteria contain

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endotoxins, lipopolysaccharides (LPS), on the outer membrane and evoke the local immune response. When the bacterial LPS interacts with the gingival tissue, it initiates inflammation and tissue breakdown, progressing tooth mobility [2,3].

Over the years, researchers have been studying the potential correlation of periodontitis and or progression of several systemic diseases. Several systemic diseases such as cardiovascular disease [4], oral and colorectal cancer, gastrointestinal diseases, respiratory tract infection and pneumonia, adverse pregnancy outcomes, diabetes and insulin resistance, and Alzheimer's disease have been linked positively in relation to periodontitis [5–7].

In severe periodontitis patients, 10^8–10^{10} of the keystone periodontal pathogen *Porphyromonas gingivalis* can be swallowed each day, hence, interfering with the gut's microbiota [8,9]. There are two hypotheses regarding the periodontitis-systemic health mechanism, the first being bacteremia and upregulation of inflammation mediators originating from periodontal pockets and the second one being the impairment of the gut barrier function and modulation induced by dysbiotic oral bacteria resulting in endotoxemia and systemic inflammation [8].

At present, most clinicians prescribe systemic antibiotic treatment using the empirical guideline solely, without guidance from a microbiologic standpoint of the subgingival bacterial biofilm populations [10]. However, periodontal pathogens have varied resistance and susceptibility to the antibiotics of choice, increasing the likelihood of a clinical treatment failure [11]. This information suggested a new approach and strategy to managing periodontal diseases.

Host modulation therapy (HMT), a term developed almost three decades ago, is an adjunct treatment strategy that aims to promote periodontal regeneration and restore the balance of pro-inflammatory mediators, as seen in healthy individuals [12]. While the use of sub antimicrobial-dose doxycycline (SDD) has been approved as an adjunct to conventional periodontitis treatment, studies have shown that non steroid anti-inflammatory drugs (NSAIDs) and bisphosphonate as HMT have raised some concerns. Prolonged use of these synthetic agents might cause unwanted effects, including medication-related osteonecrosis of the jaw (MRONJ), rebound effects upon stopping the medication, gastrointestinal, renal, and lastly, hemostatic problems [13]. Due to the minimal side effects, the current trend of investigation and therapy has shifted to alternative materials, which leads to the discovery of probiotics and other natural agents which will now be discussed.

2. Periodontitis

Periodontitis is a disease with a multifactorial aetiology involving microorganisms and host responses. Biofilm bacteria on the tooth surface are the main aetiology, while the host response will determine the development of the disease along with other local factors such as plaque and calculus, genetic factors, environmental factors, patient system health, and lifestyle [14,15].

A microbial dysbiosis and a susceptible host that forms the inflammatory response are required for the transition to periodontitis. Dental plaque alone is not sufficient to cause periodontitis, the host's inflammatory response to a microbial challenge that can lead to the destruction of the periodontium [15]. Specific organisms that are prominent and involved in the aetiology of periodontitis are red bacterial complexes, including *P. gingivalis, Treponema denticola*, and *Tannerella forsythia* [15,16]. *P. gingivalis* is a gram-negative bacterium and assumed to interfere with host defence by altering the growth and development of the microbial community which further modify and give destructive effect in homeostatic conditions [15].

When pathogenic bacteria induce immune and inflammatory processes, the body produces leukocytes, fibroblasts, or other inflammatory cells to secrete substances that can protect tissues from infection, including metalloproteinases, cytokines, transglutaminases, prostaglandins, and proteolytic enzymes. The main cause of tissue damage is an imbalance between the levels of matrix metalloproteinases (MMPs) with their endogenous inhibitors. Furthermore, alveolar bone and tissue damage occurs through stimulation of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8, IL-12, IL-17, tumour necrosis factor (TNF)-α, and receptor activator of nuclear factor kappa B ligand (RANK-L) [17,18].

The goal of periodontitis treatment is to re-establish the homeostatic relationship between the periodontal tissues and the dental plaque polymicrobial community. Scaling and root planing (SRP) is the most effective and extensively used treatment for removing pathogenic biofilms [16,19]. Scaling and root planing has been known to improve clinical parameters such as clinical attachment level (CAL), bleeding on probing (BOP), and probing pocket depth (PPD) [19].

In conventional SRP, microorganisms in the dental biofilm can be eliminated incompletely. Cytokine levels were seen to decrease but remain higher than in healthy individuals [19]. Currently, adjunctive therapies, including local antibiotics or anti-inflammatory agents, are widely used to significantly improve the healing process [16,19]. Although the use of antibiotics can play a role in the treatment of periodontitis, their use is limited due to the development of antibiotic resistance. In recent years, target molecules that modulate microbial signalling mechanisms, host inflammatory substances, and bone immune responses have been widely researched [20]. Several studies in periodontitis treatment have focused on inflammatory pathways such as proinflammatory cytokines and complement, as well as tissue-destroying enzymes like MMPs [15,21]. Furthermore, antioxidant therapy can also be used to control the disease because the presence of reactive oxygen species (ROS) is associated with inflammatory conditions in periodontitis [22].

3. Oral and gut connection

Oral and gut are not only linked anatomically but also linked through the microbiomes that live in those organs [8,23]. While obligate anaerobic bacteria represent most of the microbial population in the gut, the oral cavity hosts the largest number of aerobic bacteria. The human gut hosts thousands of species of microorganisms including bacteria, archaea, and other eukaryotic microorganisms creating what's been referred as gut microbiome [24]. This large and diverse microbial community plays an important role that complements the activity of the mammalian digestive system. The gut microbiota contributes to human metabolism by producing

enzymes that are not encoded by the human genome, like breaking down polysaccharides, polyphenols, and the synthesis of vitamins [25]. In a normal environment, dental plaque biofilm in the oral cavity represents a major component of the oral microbiome, participating in the regulation of the host's metabolism [26].

The periodontal disease does not only affect the oral environment, causing tooth loss if leave untreated, but also affect the overall systemic conditions of the host [6,7,9]. There are two pathways that periodontal disease and systemic disease can be linked (Fig. 1.). First, the direct pathway in which the pathogenic bacteria from periodontal pockets can cause bacteremia that induces systemic inflammation [8,27]. *P.gingivalis* is an acid-resistant bacteria that can tolerate the low pH of the stomach, colonise in the gut, and disturb the balance of gut microbiota [28]. Oral and oropharyngeal microbiota can reach the gut through saliva ingestion, mastication, and drinking. On a daily basis, periodontal patients can ingest around 10^8–10^{10} CFU/mL *P.gingivalis*, the keystone bacteria in periodontitis, through saliva [8,9].

The second pathway is indirect, in which, the imbalance of oral microbiota leads to the imbalance of gut microbiota [8]. Meanwhile, the gut microbiota oversees many metabolic functions, including short-chain fatty acid production, amino acid synthesis, and the fermentation of indigestible substrates. Therefore, when the dysbiosis of the gut microbiota happens, it can induce the bacteremia condition causing allergies, diabetes, metabolic disorders, cancer, or even periodontitis [8,29]. Hence, from that process, it can be assumed that there is a reciprocal relationship between the gut microbiota and the oral microbiota.

Gut dysbiosis that occurs in the intestine due to an increase in periodontal pathogens will also cause the spread of bacteria to the connective tissue. Bacteria and their LPS components can act as toll-like receptor (TLR) ligands and will be recognized by neutrophils and macrophages in connective tissue through several receptors such as TLR2 and TLR4. This process can trigger the activation of pro-inflammatory cells such as IL-1β, IL-6, and TNF-α as well as release in ROS [30–32].

Inflammatory mediators such as cytokines can be transferred from one organ to another via the blood circulation [33]. This inflammatory mechanism is thought to be associated with oral inflammatory diseases, such as periodontitis, with systemic disease. Periodontitis is thought to contribute to the production of low levels of systemic inflammatory factors or low-grade inflammation (LGI) and conversely, LGI is also a risk factor for periodontitis [34,35].

Cytokines that are produced locally in periodontitis can move into the systemic circulation and change the inflammatory status so that it can eventually exacerbate existing diseases and even become risk factors for the development of systemic diseases, such as Alzheimer's disease, cardiovascular disease (CVD), rheumatoid arthritis, diabetes mellitus, and inflammatory bowel disease (IBD) [31, 34]. When compared with healthy controls, patients with severe periodontitis had increased levels of pro-inflammatory mediators such as (IL-1, IL-6, C-reactive protein (CRP), fibrinogen) and the number of neutrophils in the blood. In contrast, periodontal treatment can improve levels of markers of systemic inflammation [36].

In 2019, Iwauchi et al. studied the relationship between faecal microbiota and subgingival plaque microbiota in elderly patients. The study showed that there is a higher similarity in faecal and subgingival plaque microbiota found in elderly patients compared to those found in adult patients [9]. As such there is a higher prevalence of oral bacteria transitioning to the gut in the elderly than in adult patients. This could happen because of the declining function of the gastrointestinal tract due to ageing, making the oral bacteria easier to invade the gut and the systemic circulation [9].

Nowadays, there is more research focusing on systemic health improvement through gut microbiota regulation. One of the normal gut microbiotas, *Akkermansia muciniphila*, normally found in large numbers in the gut since the first year of the host's life. There are some considerations of *A. muciniphila* being a potential probiotic characteristic and a significant key in homeostatic conditions. *A. muciniphila* can adhere to the mucus layer, mainly protecting epithelial cells from microbial attacks [37–39]. However, *A. muciniph*ila will decrease through host ageing. A decreasing number of *A. muciniphila* will make the mucus layer thinner, which results in the microbial toxins being easier to disrupt the host [39]. *A. muciniphila* also contributes to preventing diabetes type 2,

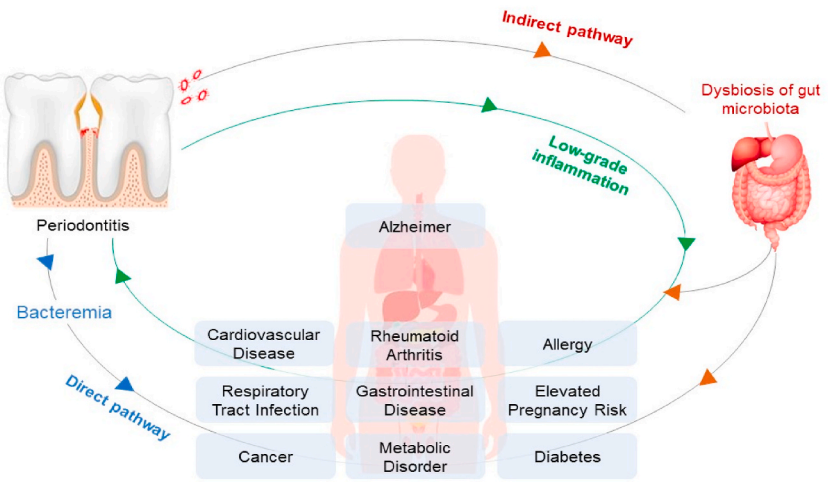

Fig. 1. The possible pathways that links periodontitis and systemic disease.

obesity, and other metabolic diseases as it can improve the glucose level and the metabolism of lipid [38,39]. Early data suggested that oral administration of *A. muciniphila* is safe to consume, but it still needed more studies to confirm [39]. Numbers of studies have investigated the efficacy of these bacteria.

4. Host modulation therapy

Not all individuals develop severe periodontitis, despite the bad oral hygiene. Bacteria is an essential key to periodontitis, but it is not sufficient to cause the disease alone. Inflammatory mediators have been recorded to play a key role in periodontal tissue damage, as it is a double-edged sword [12]. Host modulation therapy is a treatment concept that aims to modify the host's response towards the inflammatory process of a disease, reducing its damage (Fig. 2). Specifically, in periodontitis, host modulation therapy is intended to prevent tissue and bone damage by creating a more favourable environment for tissue repair, hence, reducing the host's susceptibility [40].

Several anti-inflammatory agents, both synthetic and naturally sourced are available and considered for use as an adjunct treatment along with conventional periodontal approaches. Doxycycline, a member of the tetracycline family, was identified to be superior in decreasing the pathological MMP level without interfering with the connective tissue's turnover rate. Therefore, SDD was introduced to act as a host modulation agent and has been the only agent approved by the United States Food and Drug Administration (FDA) for periodontitis treatment. However, SDD should be avoided to patients with a history of allergy to tetracyclines, pregnant mothers, and lastly young children as studies have recorded that tetracyclines can discolour developing teeth permanently. Another concern regarding the use of SDD is the potential antibiotic resistance because patients were given low doses of doxycycline 2 times a day for over 3 months [41]. These concerns have shifted the current trend into naturally sourced agents with minimum side effects. In this paper, the authors will discuss three metabolites as an option of HMT, namely, herbal, melatonin, and probiotics. Specifically, probiotics will be the focus topic in this paper.

4.1. Probiotics

The World Health Organization (WHO) defined probiotics as the bacteria that provides numerous benefits to the host when used in adequate proportion. Probiotics in dentistry come in many forms, including liquid, paste, and solid form [42,43]. There are a couple mechanisms where probiotics can prevent periodontal disease. First, probiotics act as an anti-inflammatory agent. In gingival areas where a large amount of *P. gingivalis* detected showed an increase in the level of inflammatory cytokines. Probiotics treatment with *lactobacilli* will reduce the level of inflammatory cytokines in gingival areas infected with *P. gingivalis* [43]. Second, probiotics can adhere in oral mucosa by colonising the epithelial cells and alter the pathogen bacteria. Third, probiotic's ability to produce substances such as bacteriocin, reuterin, and reutericyclin can suppress the growth in periopathogen [42,44]. Separately, probiotic strains also induce acidity from the production of lactic acid, which helped probiotic bacteria to grow and prevented pathogenic bacteria to develop [43]. Some of the most well researched species are *Lactobacillus* spp., *Bifidobacterium* spp., and *Saccharomyces* spp. [45]. These probiotics are also commonly found in the gastrointestinal tract.

The first species is *Bifidobacteria*, which can be found naturally in the oral cavity and intestinal lumen. *B. lactis* HN019 is a *Bifidobacterium* strain that is widely used and studied as a probiotic due to its good effect on modulating the immune system [46]. Administration of *B. lactis* HN019 in rats with periodontitis can reduce IL-1β levels, the ratio of RANKL-osteoprotegerin (OPG), and regulate the expression of TNF-α and IL-6. A recent study evaluated *B. lactis* HN019's effects toward periodontal parameters and reported its immunological and antibacterial properties by observing the BD-3, TLR4, and CD4 levels in gingival tissues [47]. The content of organic acids such as lactic acid produced by *Bifidobacterium* can disrupt the outer membrane of Gram-negative bacteria

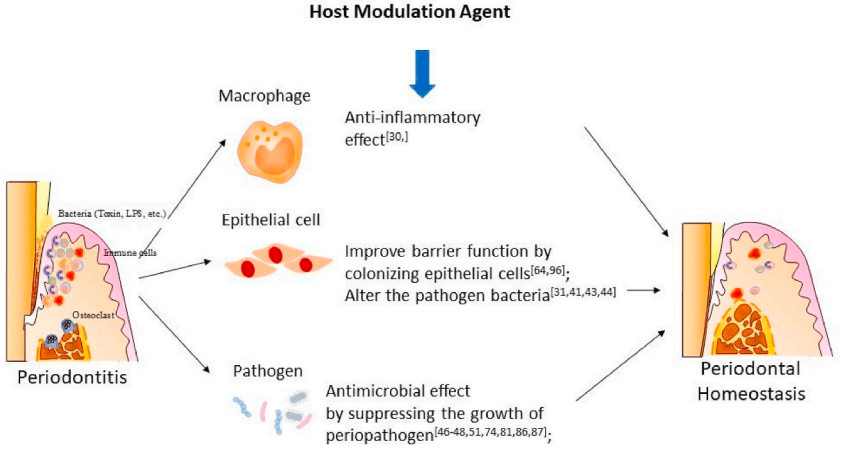

Fig. 2. Properties of host modulation agent in periodontal homeostasis.

[48]. *Bifidobacterium* also known to reduce the adhesion *P. gingivalis.* [47] (Fig. 3) These studies are thought to cause *B. lactis* and *B. infantis* to be antagonistic against periodontal pathogen and can be used as adjunctive agents in periodontal therapy [48].

Another note-worthy species is *Saccharomyces cerevisiae.* It is a yeast that has probiotic properties due to the beta glucans which consist in the cell wall. β-glucan is thought to have beneficial effects by modulating immunological parameters and affecting the microbiota. β-glucan can stimulate phagocytic activity and the production of inflammatory cytokines, thereby activating leukocytes (Fig. 3.). In addition, in a previous study β-glucan was found to increase the concentration of transforming growth factor (TGF)-β1 in the gingival crevicular fluid of patients with chronic periodontitis. This mechanism provides an anti-infective effect and increase its potential to accelerate periodontal healing [49]. Previous animal study also showed that *S. cerevisiae* as monotherapy or adjunctive therapy to SRP could be beneficial in controlling alveolar bone loss in periodontitis without adverse effect [43,49].

Minic et al. previous study pointed out that there is a significant reduction of BOP, Plaque Index (PI), and also PPD in the group of periodontitis patients that received SRP therapy combined with 5-days of applying local probiotics, compared to the group whom only received the SRP therapy [45]. In addition, previous systematic review reported that the combination of non-surgical periodontal therapy (NSPT) combined with probiotic preparation resulted in a better clinical outcome when compared to NSPT combined with placebo agent [13].

Lastly, *Lactobacillus* has been identified to produce metabolites such as 10-hydroxy-cis-12-octadecenoic (HYA) and 10-oxo-trans-11-octadecenoic acid (KetoC) through the polyunsaturated fatty acid process (PUFA) (Fig. 3.). Studies showed that KetoC continues to show promising results. In-vitro studies about KetoC confirmed its antioxidant properties by upregulating the nuclear erythroid 2-related factor 2-antioxidant response element (NRF2-ARE) pathway in HepG2 cells while countering oxidative stress in gingival epithelial cells through the G Protein coupled Receptor (GPR) 120-NRF2 ARE-MAPK pathway [50,51]. KetoC's hydrophobic nature and carbon-carbon double bond structure also play important role in its antibacterial properties as gram-negative bacteria are more susceptible to fatty acid due to its outer membrane causing KetoC to attach easily to the bacteria [50,52]. The action of ketoC depends on the presence of the free fatty acid receptor (FFAR) GPR120 in macrophages to further function in mitogen-activated protein kinase (MAPK) and inhibit NF-κB signalling in macrophages induced by bacterial LPS [53].

Apart from KetoC, HYA has been known to improve epithelial barrier function both in oral and gut by improving the expression of E-cadherin in the gingival tissue and regulating the GPR40-MEK-ERK respectively [54,55]. HYA modulates the inflammation process by decreasing the local inflammatory cytokines and reducing extracellular signal regulated kinase (ERK) phosphorylation and thus, suppressing alveolar bone loss. HYA also decr eases TNFR2 expression in colitis-induced mice which shares many similarities with human ulcerative colitis [56]. Ikeguchi et al. studied the effects of KetoC and HYA in the brain and found that KetoC and HYA inhibited LPS-induced nitric oxide (NO) production and suppressed the expression of inducible NO synthase in BV-2 cells, conforming their anti-inflammatory characteristics that is not only in the intestine but also in microglial cells in the brain [57]. HYA was also known for reducing The expression of tumor necrosis factor receptor type II (TNFR2) which can activate the NF-κB pathway [53,58]. In addition to that, previous studies found that ketoC and HYA can inhibit the production of cytokine IL-6, IL-1β, and TNF-α [53].

Several new species of *Streptococcus* have gained researchers' interest due to their ability to colonise, biocompatibility, and easy dose determination experimentally [59,60]. *Streptococcus* is a gram-positive bacterium that is included in the normal flora of the human oral cavity and also intestine [61]. *Streptococcus salivarius* was isolated from the saliva of healthy children [59]. In an *in vitro* study, *S. salivarius* strains K12 and M18 were reported to have the ability to inhibit the activity of periodontopathogens such as

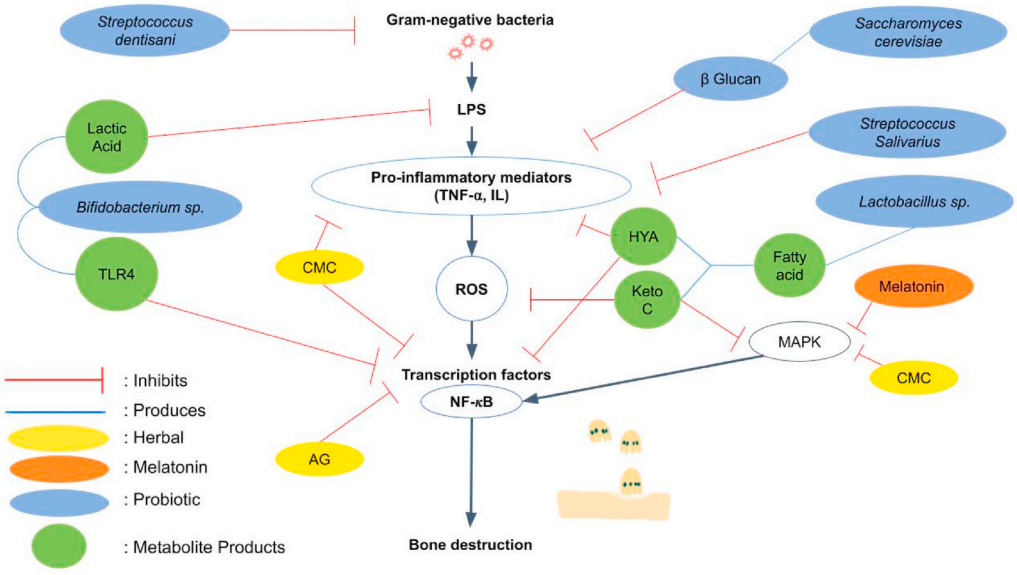

Fig. 3. Different host modulation agents and their role in suppressing alveolar bone destruction.

P. gingivalis, P. intermedia, F. nucleatum, and *Aggregatibacter actinomycetemcomitans.* Previous studies have also shown that *S. salivarius* is able to maintain immune homeostasis by targeting host cells. *S. salivarius* strains K12 and M18 were also able to inhibit the release of IL-6 and IL-8 triggered by *P. gingivalis, A. actinomycetemcomitans*, and *F. nucleatum.* [61] (Fig. 3.)

Another *streptococcus* species, *Streptococcus dentisani*, is a new bacterial species isolated from the oral cavity of healthy patients who have never had caries or periodontal disease [60,62]. These bacteria showed antibacterial activity against pathogenic bacteria such as *S. mutans, S. sobrinus, P. intermedia,* and *F. nucleatum* [60]. Another *in vitro* study by Esteban-Fernández et al. also showed the inhibitory action of *S. dentisani* against bacterial colonization of *P. gingivalis* and *F. nucleatum* on human gingival fibroblast-1 (HGF-1) (Fig. 3.). This is thought to occur due to the expression of bacteriocins that affect these pathogens. In addition, *S. dentisani* has anti-inflammatory properties, which can regulate the inflammatory response by reducing the production of pro-inflammatory cytokines triggered by exposure to *P. gingivalis* or *F. nucleatum* [62].

4.2. Herbal

Herbs and natural resources have been used in the medical field to treat various diseases for more than 3000 years, and the interest in using them in a periodontitis treatment keeps increasing [63,64]. The most important advantages of these resources are minimal side effects and lower costs compared to synthetic materials or medicine [63]. Different plant species showing anti-inflammatory effects and their potential to replace synthetic materials in periodontal treatment.

Curcumin, an Indian spice belonging to the ginger family, has been widely developed as a treatment for a variety of diseases including periodontitis [65,66]. Chemically modified curcumin (CMC) suggests beneficial effects in the reduction of inflammation [66]. Previous animal studies showed that CMC has been proven to reduce the activation of NF-κB, MAPK, MMPs, IL-1β, and also to inhibit alveolar bone loss [67–70]. (Fig. 3)

Andrographis paniculata (Burm F.) has been used in South Asian countries for inflammatory diseases for its active phytochemical compound called Andrographolide (AG). AG has been proposed as a natural adjunct to mechanical therapy in controlling inflammation and bone resorption in periodontal treatments. Research has shown that there is an AG's inhibitory effect on NF-κB and signal transducer and activator of transcription 3 (STAT3), i.e., the cells' transcription factors and signaling pathways that are involved in the production of inflammatory mediators [49]. (Fig. 3)

Lamiaceae family plants from the Mediterranean area are extensively used in the medical field due to their essential oils (EOs) components [64,71]. Thyme EOs in a cellular model has proven to be able to reduce IL-1β, TNF-α, and IL-6, while increasing anti-inflammatory cytokines such as IL-10. Lavender EOs, along with other EOs such as Terpineols, Linalool, Eucalyptol, based on in-vitro studies also known to have anti-inflammatory effects. Their effects are decreasing LPS-induced TNF-α and IL-6, as well as inhibiting the activation of NF-κB and MAPK [72,73].

Another variant is Aglycone baicalein, a major bioactive flavonoid extracted from *Scutellaria baicalensis* Georgi (Huang-qin in Chinese). Baicalein is known for providing good anti-inflammatory and antioxidant effects by reducing inflammatory mediators such as IL-1β, TNF-α, monocyte chemoattractant protein-1 (MCP-1), MMP-1, and MMP-2 on periodontal ligament cells stimulated by bacterial LPS and inhibit MAPK signaling activation by LPS. Apart from that, it is also presumed that Baicalein may function as an activator of Wnt signaling-a promoter of osteogenesis of inflamed periodontal ligament cells, by activating Wnt target proteins (LEF1, Cyclin D, and beta-catenin). This study concludes that Baicalein may be used to treat periodontal disease as a host response modulator [50].

Lastly, an Ayurvedic blend of toothpaste, Sudantha, is clinically proven to improve gingival and periodontal health due to its ability to inhibit the expression of the pro-inflammatory cytokine IL-8 and host inflammatory mediators (IL-1β and TNF-α) in a dose-dependent manner [51]. However, further studies are still needed to understand the recommendations for these herbal ingredients utilization in modulating the host immune-inflammatory response without interfering with the cell intrinsic host inflammatory surveillance.

4.3. Melatonin

Melatonin (N-acetyl-5- methoxytryptamine) is a hormone well known for its effect on the circadian rhythm and sleep quality. Other than that, melatonin also possesses potent antioxidant, anti-inflammatory and immunomodulatory, anti-tumoral, neuroprotective [52]. And lastly, osteopromotion and bone loss inhibition properties [53]. Melatonin is physiologically present in saliva and gingival crevicular fluid. Melatonin works as a powerful antioxidant by removing various free radicals mentioned as "scavenging action" and an anti-inflammatory agent by inhibiting nuclear transcription factors such as NF-κB and MAPK, making it a potential biomarker & therapy [54,55]. (Fig. 3) Several in-vitro studies have also been done to evaluate melatonin's ability as an antimicrobial agent. An animal study also confirmed melatonin's abilities to modulate osteoblastic-osteoclastic activities and reduce oxidative damage in irradiated periodontal tissues [56]. On top of that, human trials were conducted to evaluate melatonin's ability as a locally delivered adjunctive treatment and a possible host modulation therapy with oral administration [74].

5. Conclusion

While there are multiple etiological factors that cause periodontitis, bacteria dysbiosis remains the primary inducing factor. Not only the imbalance of oral microbiota but also the imbalance of gut microbiota influences periodontal tissue health. Furthermore, those microbiotas also impact the host's overall systemic condition. Researchers have further studied natural agents for HMT as an

adjunctive treatment, with probiotics being the most studied agent. In particular, the metabolites product of probiotics positively contributes to periodontal homeostasis. Future studies are required to investigate further metabolites products' role in periodontitis management and the long-term effect of probiotics.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

The data that has been used is confidential.

Declaration of interest's statement

The authors declare no competing interests

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