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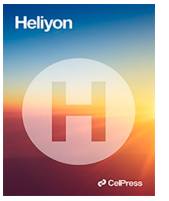

Review article

A literature review of bioactive substances for the treatment of periodontitis: *In vitro*, *in vivo* and clinical studies

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ABSTRACT

Periodontitis is a common chronic inflammatory disease of the supporting tissues of the tooth that involves a complex interaction of microorganisms and various cell lines around the infected site. To prevent and treat this disease, several options are available, such as scaling, root planning, antibiotic treatment, and dental surgeries, depending on the stage of the disease. However, these treatments can have various side effects, including additional inflammatory responses, chronic wounds, and the need for secondary surgery. Consequently, numerous studies have focused on developing new therapeutic agents for more effective periodontitis treatment. This review explores the latest trends in bioactive substances with therapeutic effects for periodontitis using various search engines. Therefore, this study aimed to suggest effective directions for therapeutic approaches. Additionally, we provide a summary of the current applications and underlying mechanisms of bioactive substances, which can serve as a reference for the development of periodontitis treatments.

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1. Introduction

Human gingival fibroblast (HGF), spindle-shaped cells, are the major cell constituents of the gingival connective tissue [1,2]. They consistently grow in a spindle-shaped form but appear to differentiate along a chondrogenic lineage rather than a fibrous connective tissue lineage [3]. HGF participates in the remodeling and maintenance of the structural integrity and tissue homeostasis of the gingival connective tissue and extracellular matrix (ECM), including collagen (COL), elastin, fibronectin, and proteoglycans, which have structural roles in the gingival connective tissue [4–6]. In particular, after periodontal surgeries or damage caused by periodontal diseases, they are responsible for gingival wound healing through the production of ECM [5]. Moreover, they play a critical role in the inflammatory response because of their ability to release pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) in response to lipopolysaccharides from *Porphyromonas gingivalis* (Pg-LPS) stimulation and high rate of proliferation [7–9]. Therefore, they can be used as an in vitro model for following up therapeutic effects and therapy research on gingivitis [9–11].

Periodontitis is a common chronic multifactorial inflammatory disease in the periodontal tissues and is one of the most prevalent chronic conditions in the world [12–14]. It usually occurs at the supporting structures of the teeth, such as the root cementum, gingiva, periodontal ligament, and alveolar bone [15]. It is induced by dental plaque bacteria and dysbiotic plaque biofilms, which are characterized by increased levels of subgingival pathogens, resulting in progressive destruction of tooth-supporting structures and alveolar bone loss [12,16–18]. Periodontitis is an important public health problem and is often called a silent disease because it has obvious signs and symptoms until it has progressed to its terminal stages [14]. *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* are the major pathogens that induce periodontitis [19]. Additionally, it is characterized by localized chronic inflammatory reactions with a raised serum pro-inflammatory state, as shown by pro-inflammatory cytokines, including TNF-α, interleukin (IL)-6, IL-10, and IL-17 [16,20].

Periodontitis is treated by nonsurgical and surgical methods, depending on the progression of the disease. In cases of non-advanced periodontitis, nonsurgical methods are usually used, including scaling, root planing, and topical or oral antibiotic treatment [21–23]. However, patients with advanced periodontitis require dental surgery, such as flap surgery, soft tissue grafting, and bone grafting [24–26]. Many researchers have developed new therapeutic approaches to develop more effective treatments for periodontitis [22, 26]. Previous studies have reported that antibacterial activity against periopathogens, anti-inflammatory activity, and antiosteoclastic activity can be used to treat periodontitis [27].

Therefore, the present study aimed to review the literature to identify therapeutic approaches for periodontitis through anti-inflammatory activity, as well as their modulatory effect on the host's immune and inflammatory responses (Fig. 1).

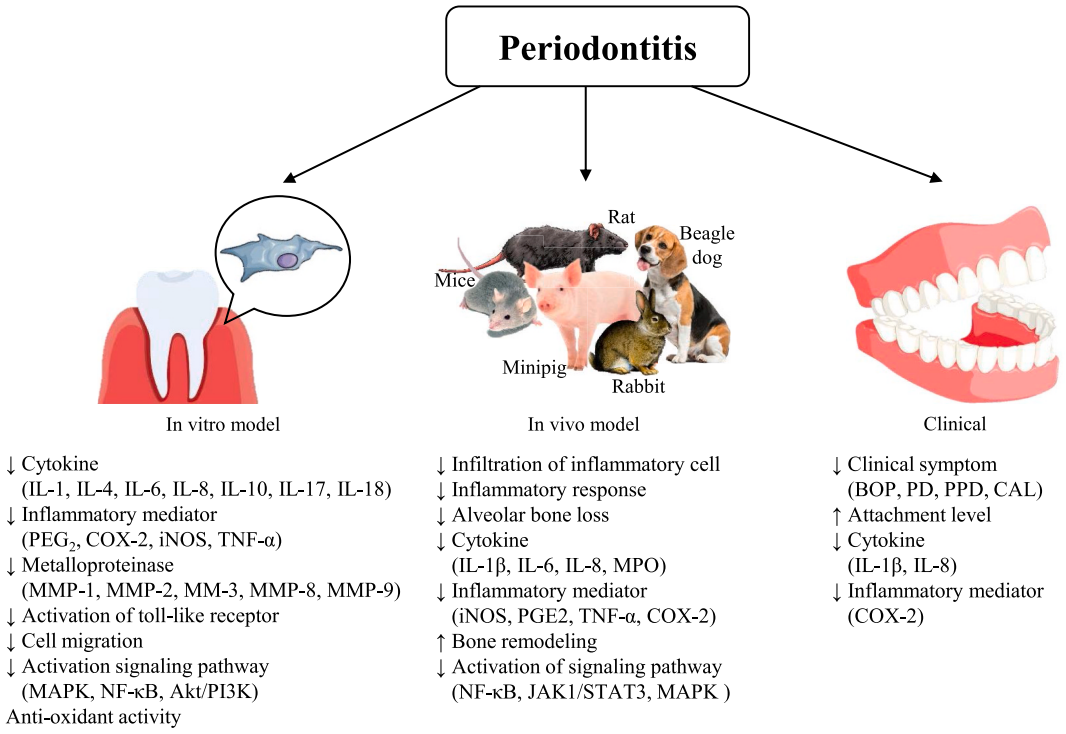

Fig. 1. Wide range of therapeutic effects of bioactive substance in periodontitis treatment.

2. Methods

2.1. Search strategy

A database search was conducted using Google Scholar, PubMed, and Web of Science (access date from January 2016 to December 2020). The search strategy terms were categorized into three groups: (periodontitis or periodontal disease), (human gingival fibroblast), (anti-inflammatory or anti-inflammation), and (In vitro or In vivo or Clinical). Search results from all relevant combinations of the above search terms were imported into the citation manager program, EndNote X7 software (Thomson Reuters, New York, USA), and all duplicates were automatically removed. The initial search results retrieved 955 articles. Of these, 852 articles were excluded from failing to meet the inclusion criteria, leaving 103 articles for discussion in this review.

2.2. Inclusion criteria

The effects were classified according to their anti-inflammatory effects. Studies reporting anti-inflammatory effects on HGF or tissues treated with exotoxins from periodontal pathogens were allocated to the anti-inflammatory group. This review includes in vitro studies, in vivo studies, and clinical trials that investigated anti-periodontitis activity via their anti-inflammatory effects. Only studies published in English from January 2016 were considered.

2.3. Exclusion criteria

Reviews and studies that were unrelated to periodontal pathogens and tissues were also excluded from this study. Additionally, reports investigating the anti-inflammatory effects along with routine pharmacological therapy, such as chlorhexidine mouthrinses or antibiotics, were excluded (Fig. 2).

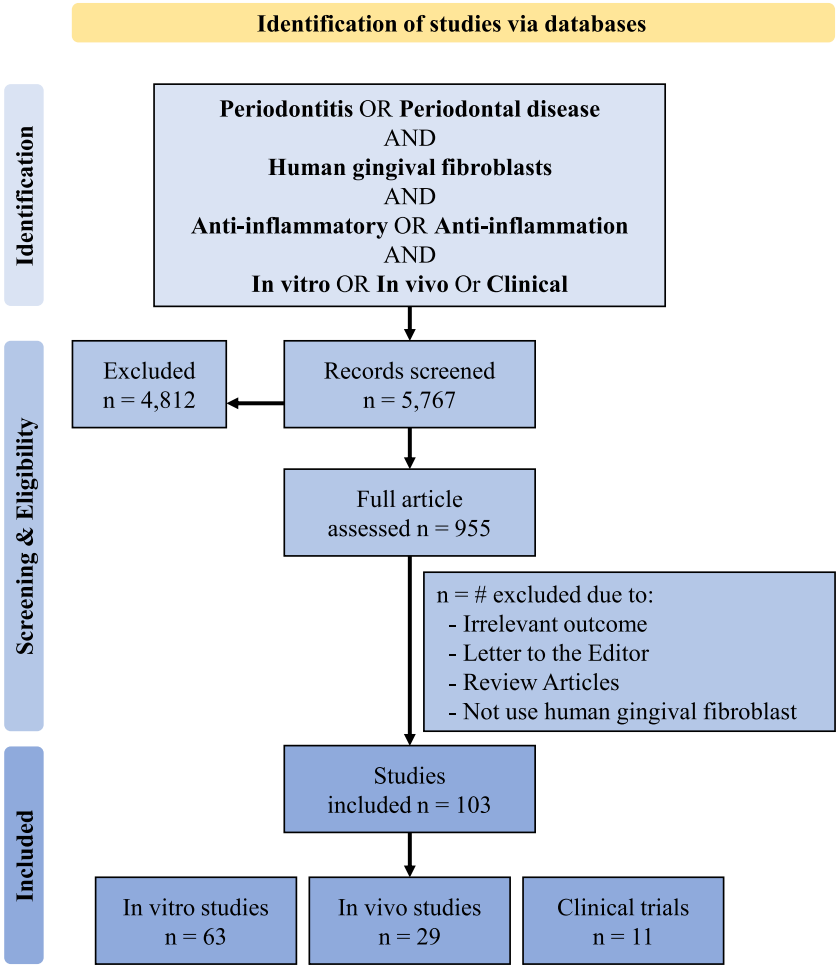

Fig. 2. Flow chart of the search strategy of this comprehensive review.

2.4. Data organization

The authors, publication year, type of study, sample, stimulator, and major outcomes of each study were recorded in a standard document and arranged by year. All articles were classified as in vitro studies, in vivo studies, or clinical studies.

3. Results

3.1. Publication outputs related to periodontitis treatment by year

We observed a steady increase in the number of studies related to periodontitis treatment published from 2016 to 2020. Intriguingly, the publication output was lowest in 2017 and 2018, with only 19 related studies during these years. However, the number of publications increased rapidly in 2019, indicating a rising interest the development of therapeutic approaches for periodontitis. These increasing trends in research output suggest a growing focus on periodontitis treatment.

3.2. Types of bioactive substances as therapeutic agents for periodontitis

We assessed 97 studies to identify the types of bioactive substances used for periodontitis (Fig. 3A). Our analysis showed that the most common type of bioactive substances for periodontitis was a single compound (38 studies), such as resveratrol, veratric acid, kaempferol, and vitamin D. Furthermore, only seven studies investigated the use of medicines, including Kampo medicines, metformin, doxycycline, HU-308, and simvastatin, to investigate other therapeutic effects beyond the original goal (Table 1). In 19 studies that used extracts as therapeutic agents for periodontitis, the most common types of extracts were flavonoid, essential oil, and propolis extracts, which are usually extracted from asterids, including *Ocimum gratissimum Garcinia mangostana*, and *Salvia sclarea* L. (7 studies) (Table 2). Additionally, one study investigated the therapeutic effect of extract derived from marine organisms for periodontitis [28].

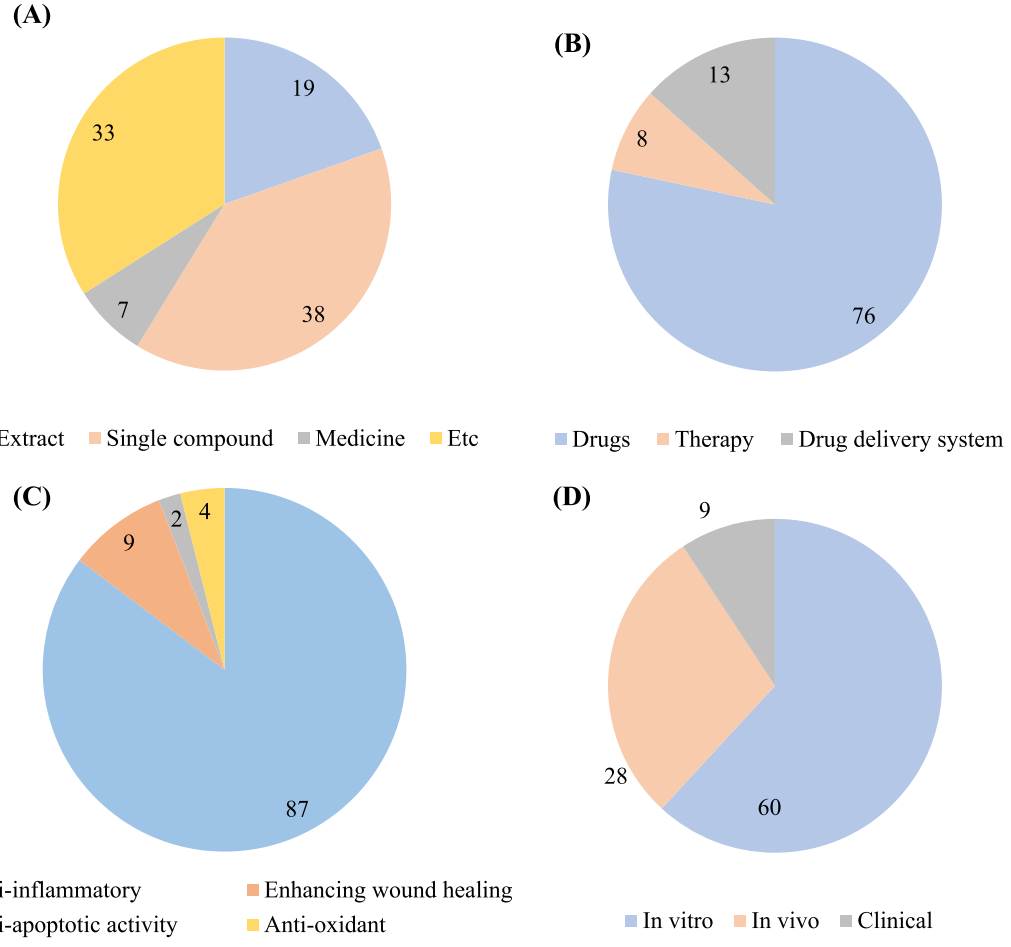

Fig. 3. Analysis of 101 articleson periodontitis treatment published between 2016 and 2020: (A) Bioactive substances used, (B), Forms of treatment application, (C) Mechanisms of therapeutic effects on periodontitis, and (D) Types of studies conducted.

Table 1
Information on single compounds as therapeutic agents for periodontitis.

Compounds	Extraction source	Ref
$1,25(OH)_2D_3$ and $_20(OH)D_3$	Synthesis	[29]
25-Hydroxyvitamin D3	Synthesis	[30]
6-Shogaol	Plants	[31]
Astiatic acid	Plants	[32]
Baicalin	Plants	[33]
CAPE	Plants	[34]
Capsazepine	Synthesis	[35]
Compounds Isolated from *Elaeagnus umbellata*	Plants	[36]
Curcumin	Synthesis	[37]
Cynaropicrin	Plants	[38]
DMOG	Plants	[39]
EGCG	Plants	[40,41]
Farrerol	Plants	[42]
Genistein	Plants	[43]
Glycyrrhizin	Plants	[44]
HMW-HA	Plants	[45]
Icariin	Plants	[46]
Isorhamnetin	Synthesis	[47]
Kaempferol	Plants	[48]
NAC	Synthesis	[49]
NBBA	Synthesis	[50]
Oridonin	Plants	[51]
Panduratin A	Plants	[52]
PHMG-P	Synthesis	[53]
Plantamajoside	Plants	[54]
Proanthocyanidins	Plants	[55]
Quercetin	Plants	[56]
Resveratrol	Plants	[57,58]
Silymarin	Plants	[58]
THSG	Plants	[59]
Tiludronic Acid	Plants	[60]
Tβ4 peptide	Human	[61]
UP446	Plants	[62]
Veratric Acid	Plants	[63]
Vitamin D	Plants	[29,64]
Y-27632	Synthesis	[27]
β-glucans	Yeast	[11]

Table 2
Information on extracts as therapeutic agents for periodontitis.

Extracts	Extraction source	Type of extraction source	Ref
Aqueous extract	*C. officinalis*	Asterids	[65]
Essential oils	*C. flexuosus*,	Commelinids	[66]
	R. officinalis	Asterids	
	T. zygis,	Asterids	
Essential oil	*O. gratissimum*	Asterids	[67]
Ethanol extract	*A. tegmentosum maxim*	Rosids	[68]
Ethanol extract	*C. officinalis*	Asterids	[69]
	R. officinalis	Asterids	
	Z. officinale	Commelinids	
Ethanol extract	*E. angustifolium*	Commelinids	[70]
Ethanol extract	*G. textorii*	Florideophyceae	[28]
Ethanol extract	Leaf of *P. miana*	Asterids	[71]
Ethanol extract	Skim milk	Foods	[72]
Ethanol extract	*S. sclarea* L.	Asterids	[73]
Extract	*C. sinensis*	Asterids	[74]
Extract	*G. mangostana* L.	Rosids	[75]
Extract	*T. sellowiana*	Asterids	[76]
High molecular weight non-dialyzable material	Cranberry juice	Asterids	[77]
Human placental extracts	Placental	Human	[78]
Methanol extract	Leaves of *L. inermis L.*	Rosids	[79]
Methanol extract	*P. lasiocarpa*	Rosids	[80]
	P. nigra	Rosids	
	P. ×berolinensis	Rosids	
Supercritical CO_2 extract	*C. xanthorrhiza*	Commelinids	[81,82]

3.3. Application form of bioactive substances for periodontitis treatment

As shown in Fig. 3B, to prevent or treat periodontitis, most studies applied bioactive substances as drugs (76 studies), followed by the use of drug delivery systems (13 studies) and combined therapies (8 studies).

3.4. Therapeutic effect of bioactive substance for periodontitis treatment

As illustrated in Fig. 3C, the majority of bioactive substances in 87 studies exhibited a preventive or therapeutic effect on periodontitis through their anti-inflammatory properties. Given that inflammation is a key factor in the pathogenesis of periodontitis, targeting the anti-inflammatory properties of bioactive substances is a primary approach for treating this disease. Other therapeutic approaches for this disease that have been analyzed included enhancing the wound healing process (9 studies), antioxidant activities (4 studies), and anti-apoptotic activities (2 studies). In particular, in clinical experiments, changes in clinical parameters such as attachment level (AL), probing depth (PD), bleeding on probing (BoP), and gingival index (GI) were observed and measured in most studies, except 5 studies [83–86].

3.5. Bioactive substance for periodontitis treatment

As mentioned above, the studies discussed in this manuscript will be classified into three parts: in vitro experiments, in vivo experiments, and clinical experiments. Most experiments (62 out of 101) were conducted using in vitro models, followed by in vivo models (28 studies), indicating that clinical experiments are rarely conducted (11 studies) (Fig. 3D). Therefore, this section provides more detailed information on the research content of bioactive substances for treating periodontitis based on several biological properties.

3.5.1. Characterization of periodontitis treatment based on in vitro studies

3.5.1.1. Extract-based treatments for periodontitis. The placenta serves as a reservoir of numerous bioactive compounds such as cytokines, growth factors, vitamins, and minerals [87,88]. In particular, human placental extracts reportedly have biological properties including anti-oxidative, anti-inflammatory, and wound healing activities [78]. Therefore, a study investigated the anti-inflammatory effects of human placental extracts provided by Melsmon Pharmaceutical Co., Ltd. on HGF stimulated with *Porphyromonas gingivalis* LPS (Pg-LPS) (100 ng/ml) [78]. Human placental extracts (1.5 mg/ml) decreased the secretion of IL-6 and IL-8 as well as the production of collagen type I (COL I), which is increased by Pg-LPS. These results suggest the potential of human placental extracts as a therapeutic agent for periodontitis.

Eriodictyon angustifolium is a plant of Yerba Santa that is used in traditional medicine to treat inflammatory disease. It contains a high content of flavonoids, including homoeriodictyol, sterubin, eriodictyol, isosakuranetin, and naringenin [89,90]. The anti-inflammatory activity of *E. angustifolium* crude extract (EE) and flavonoids derived from EE were assessed using HGF stimulated with 10 μg/ml Pg-LPS [70]. EE at 15 μg/ml attenuated the secretion of IL-6 but not IL-8. After confirming the potential of EE for inflammatory activity, they conducted fractionation and isolated eight single compounds from EE. In particular, eriodictyol and naringenin inhibited Pg-LPS-induced cytokine release, including IL-6, IL-8, and MCP-1. Based on these results, the authors confirmed their hypothesis that EE and erionic acids have potential as agents for inflammatory disease of the gingiva.

Ocimum gratissimum belongs to the family Lamiaceae and is used in traditional medicine to treat diverse illnesses such as cough, fever, infection, and abdominal pain in Africa [91,92]. Essential oils from *O. gratissimum* exhibit antibacterial effects against oral pathogens [67]. Therefore, a study investigated the inhibitory effect of essential oil from *O. gratissimum* on PGE_2 secretion in 300 pg/ml interleukin (IL)-1β-stimulated HGF [67].

Cranberry (*Vaccinium macrocarpon*) is rich in polyphenols, particularly proanthocyanidins, and possesses several pharmacological effects, such as anti-infective, anti-adhesion, antimicrobial, and anti-inflammatory effects [93,94]. Therefore, Tipton, D. A. et al. investigated the anti-inflammatory activity of high molecular weight non-dialyzable material derived from cranberry juice (NDM) in HGF stimulated by individual and combination treatment with Pg-LPS and glycated human serum albumin (G-HSA) [77]. In the G-HSA-treated group, 50 μg/ml NDM inhibited the production of IL-6 and MMP-3, similar to that in the non-treated group. In the G-HAS and Pg-LPS-treated group, 100 μg/ml NDM inhibited the production of MMP-3 and IL-6, similar to that in the non-treated group.

Curcuma xanthorrhiza is a medicinal plant that originates in Indonesia and contains several bioactive compounds, such as α-pinene, camphor, curcumin, and xanthorrhizol (XAN) [95]. XAN has anti-inflammatory activities against hippocampal cells and RAW 264.7 monocytes by suppressing mitogen-activated protein kinase (MAPK) activation [96]. Based on these facts, a study was conducted to investigate the effects of *C. xanthorrhiza* supercritical extract (CXS) and XAN on the expression of IL-1β, MMP-2, and MMP-8 by suppressing the activation of NF-κB and MAPK and phosphorylation of AP-1 on 1 μg/ml Pg-LPS-stimulated HGF [81]. The results showed that CXS and XAN have potential as therapeutic agents for treating periodontitis because of their anti-inflammatory effects.

Lactic acid bacteria-fermented milk products have numerous biological effects, including antioxidant, anti-inflammatory, and anticancer effects [72,97]. In particular, an ethanol extract of skim milk fermented with *Lactobacillus paracasei* subsp. *paracasei* NTU 101 (NTU101FSMEE) can prevent periodontal disease [98]. Therefore, Lui et al. investigated the anti-inflammatory properties of NTU101FSMEE [72]. They fractioned NTU1010FSMEE and identified a bioactive fraction containing a mixture of tyrosine and lactic

acid in a 3:1 ratio (3T1L). To confirm the anti-inflammatory activity of 3T1L, HGF stimulated with LPS (100 ng/ml) was treated with 3T1L. LPS treatment on inflammatory response-induced HGF, such as increased oxidative stress, cytokine levels (IL-6 and IL-8), and a decrease in total antioxidant activity. In contrast, 3T1L suppressed oxidative stress and cytokine levels and improved the total antioxidant activity of LPS-stimulated HGF [72]. Furthermore, the underlying mechanism was identified as suppressing the activation of MAPK and NF-κB using Western blot.

Garcinia mangostana L., known as mangosteen, contains mainly xanthone compounds and is used as a traditional medicine for several diseases [99,100]. Although many investigations of the biological activities of mangosteen have been conducted, it has not been fully investigated. Additionally, propolis is a natural substance derived from various plant sources, containing numerous bioactive compounds including flavonoids, cinnamic acid and its derivatives, and amino acids [101,102]. Several studies have reported various biological activities, including anti-inflammatory, antioxidant, antimicrobial, antitumor, and antioxidant activities [103,104]. Although mangosteen and propolis extracts individually have potential as an anti-inflammatory agent, no study reported whether a combination of mangosteen and propolis extract exhibits more effective anti-inflammatory activity than mangosteen and propolis extract alone. Therefore, a study investigated whether the combination of mangosteen and propolis shows a stronger anti-inflammatory effect on HGF stimulated with Pg-LPS (100 ng/ml) [75]. The experimental groups were set as nine groups with various mass ratios. All groups showed no cytotoxicity in the presence and absence of Pg-LPS. Among the groups, the 1:34 (mass ratio, mangosteen: propolis) group was highly effective as an anti-inflammatory agent by suppressing cytokine expression levels, such as IL-6, IL-8, and prostaglandin E_2 (PGE_2).

The potential of red algae ethanol extract as an anti-inflammatory agent for periodontitis has been widely studied [105–107]. However, the anti-inflammatory activity of *Gracilaria textorii* ethanol extract (GTEE) has not yet been reported. Therefore, Chungmu, Park, and Hyunseo, Yoon investigated whether GTEE can be used as a therapeutic agent for periodontitis through in vitro experiments. They induced the activities of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2)), and nitric oxide (NO) enzymes by treating HGF with 1 μg/ml Pg-LPS. However, GTEE was found to suppress LPS-induced NO enzyme activity, as well as the expression of iNOS and COX-2, by inhibiting the activation of NF-κB and AP-1, as well as the phosphorylation of Nrf-2 and NAD(P)H quinone oxidoreductase 1 [28].

Poplars (*Populus* spp.) comprise approximately 100 species and are commonly used in traditional medicine because of their bioactive compounds [80,108,109]. In particular, their leaf buds have been used to treat dermatitis in traditional medicine [110]. Based on previous studies, Loretta Pobłocka-Olech et al. evaluated and compared the anti-inflammatory effect of bud extracts from different species (*P. nigra*, *P.* ×*berolinensis*, and *P. lasiocarpa*) and flavonoids, which are mainly contained in poplars (pinocembrin and pinostrobin), for dermatitis treatment [80]. Inflammatory reactions were induced in HGF by treatment with Ag nanoparticles (3.5 μg/ml), which induced cytokine (IL-1β and IL-6) release and COX-2 protein expression. Flavonoids and bud extracts, with the exception of *P. lasiocarpa*, suppressed cytokine release and COX-2 protein expression. In particular, the bud extract of *P.* ×*berolinensis* showed the highest inhibitory effect by suppressing COX-2 protein expression, and cytokine release.

Acer tegmentosum maxim (ATM), also known as the East Asian stripe maple, contains various bioactive compounds, including flavonoids, lignans, phenolic compounds, steroidal glycosides, and coumarins, and exhibits antioxidant, anti-angiogenic, anti-inflammatory, anti-lipogenic, and anti-atopic activities [68,111–113]. Go-Eun Choi and Kyung-Yae Hyun investigated whether ATM ethanol extracts exhibited an anti-inflammatory effect for periodontitis treatment [68]. This study identified that ATM ethanol extracts have anti-inflammatory activities by suppressing not only the mRNA expression of TNF-α, IL-6, and macrophage inflammatory protein-1α but also the activities of malondialdehyde and iNOS on HGF stimulated with Pg-LPS.

3.5.1.2. Single compound-based treatments for periodontitis. Benzamide derivatives exhibit a broad spectrum of pharmacological activities [114]. Therefore, the potential of N-benzyl-4-bromobenzamide, as an anti-inflammatory agent was investigated using HGF stimulated by LPS (1 μg/ml) [50]. N-Benzyl-4-Bromobenzamide, and prednisolone were used as a positive control, suppressed the production of IL-6 and PGE_2 without cytotoxicity.

Resveratrol is a natural polyphenolic phytoalexin found in many plants and fruits and has numerous biological effects, including antioxidant, anti-inflammatory, and anticancer [115]. A study conducted in 2016 demonstrated the preventive activity of resveratrol on HGF stimulated by Pg-LPS [57]. Resveratrol decreased ROS production and protein expression of COX-2, MMP-2, MMP-9, and toll-like receptor (TLR4). Additionally, this compound inhibited the phosphorylation of c-Jun N-terminal kinases (JNK), p38, and Akt and suppressed the protein expression of HO-1 and Nrf.

Thymosin beta-4 (Tβ4) is a G-actin sequestering protein expressed in the embryonic heart and has diverse biological functions such as promoting angiogenesis, wound healing, inhibiting fibrosis, and regulating inflammatory response [116–119]. Therefore, S.-I., Lee et al. investigated the anti-inflammatory effect of Tβ4 in HGF stimulated with H_2O_2 [61]. Tβ4 inhibited H_2O_2-induced production of NO and PGE_2 by suppressing the expression of iNOS, COX-2, and osteoclastogenic cytokines. Moreover, Tβ4 regulated the inflammatory response by inhibiting the activation of ERK, JNK, and NF-κB.

Farrerol is a natural compound isolated from Rhododendron and possesses numerous biological effects, such as antioxidant, anti-inflammatory, antibacterial, and antitumor effects [120,121]. A previous study found that farrerol suppressed cytokine production (IL-6 and IL-8), similar to that in the untreated group, by inhibiting the activation of the PI3K/Akt/NF-κB signaling pathway in HGF stimulated with LPS [42].

Veratric acid is a derivative of vanillin and a simple benzoic acid found in vegetables and fruits that displays protective effects, including antibacterial, antihypertensive, antioxidant, anti-inflammatory, and antimicrobial activities [122]. A previous study investigated the effect of veratric acid (20, 40, and 80 μM) on the production of IL-6 and IL-8, as well as iNOS and COX-2 expression,

through suppression of the activation of the PI3K/Akt/NF-κB signaling pathway in HGF stimulated with Pg-LPS (1 μg/ml) [63].

2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (THSG) is a major bioactive component extracted from the root of *Polygonum mutiflorum* Thunb, a traditional Chinese herb medicine that possesses antioxidant, anti-aging, anti-inflammatory, antiatherosclerosis, and neuroprotective properties [123,124]. To investigate the therapeutic effect of THSG on periodontitis, Y.-T. Chin et al. performed quantitative real-time PCR and Western blot analysis of HGF stimulated with 1 μg/ml Pg-LPS [59]. Additionally, resveratrol was used as a positive control to compare the therapeutic efficiency. THSG reduced the expression of inflammation-related proteins (TNF-α, IL-1β, and IL-6) by suppressing the activation of AMP-activated protein kinase and NF-κB, as well as the phosphorylation of ERK on Pg-LPS-stimulated HGF. Furthermore, THSG exhibited higher effectiveness than resveratrol.

Polyhexanide phosphate is a major derivative of its salt, and is widely used as an antibacterial, antifungal, and antiviral additive in several applications [125–127]. Based on these facts, a study demonstrated that polyhexanide phosphate attenuated the periodontitis-related levels of PGE_2, IL-6, IL-8, and MMP-1in HGF stimulated with IL-1β (300 pg/ml) [53]. This result indicates that polyhexanide phosphate has therapeutic potential for periodontitis because of its anti-inflammatory and anti-microbial effects.

Asiatic acid (AA) is a pentacyclic triterpene isolated from various plants traditionally used for skin diseases and exhibits numerous biological activities, such as antioxidant, anti-inflammatory, anticancer, antihyperlipidemia, antifungal, and hepatoprotective activities [128,129]. Chunbo Hao et al. studied the anti-inflammatory activity of AA on Pg-LPS-induced HGF [32]. AA showed no cytotoxicity up to 100 μM in the presence and/or absence of 1 μg/ml LPS. The highest concentration of AA (100 μM) showed a strong inhibitory effect on the cytokine productions of PGE_2, NO, IL-6, and IL-8. Additionally, it was revealed that the anti-inflammatory activity of AA was mediated by inhibiting the activation of NF-κB pathway.

Dried tea leaves have high polyphenol content, including epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin-3-gallate, and epicatechin [130]. In particular, EGCG is the main constituent of crude green tea plant extract and exerts several biological effects, including anti-inflammatory, antioxidant, anti-apoptotic, and wound healing effects [131–133]. To investigate the therapeutic effect of EGCG on periodontitis, it was found that EGCG reduces the production of inflammatory cytokines, including IL-8 and IL-6, by suppressing the NF-κB pathway on HGF stimulated by LPS (1 μg/ml) [40]. Another study developed a 3D co-culture model of HGF and macrophages to evaluate the anti-inflammatory effect of green tea catechins and EGCG. EGCG and green tea catechins suppressed the expression of MMP-3, MMP-8, and MMP-9.

Govinda Bhattarai et al. investigated the preventive effect of genistein on periodontitis [43]. Genistein is a natural isoflavone usually found in soy and soy-based food products and possesses pharmacological activities such as anticancer, antioxidant, antiinflammatory, antiangiogenic, and anti-proliferative activities [134,135]. The study confirmed the anti-inflammatory effect of genistein on HGF stimulated by 5 μg/ml LPS from *Escherichia coli* (Ec-LPS) [43]. Genistein inhibited the expression of NOS2, COX-2, and TNF-α in inflammation-induced HGF. However, further studies are required to investigate the underlying mechanism of the anti-inflammatory effect of genistein.

Caffeic acid phenethyl ester (CAPE) is a physiologically active component of honeybee propolis and reportedly has several health benefits, including antioxidative, anti-inflammatory, and antimicrobial activities [136,137]. Li et al. demonstrated that CAPE decreased cytokine production of IL-6 and IL-8 and suppressed the expression of iNOS and COX-2. CAPE downregulates the activation of TLR4, MyD88, and NF-κB, as well as the phosphorylation of PI3K and Akt [34].

Kaempferol is a yellow bioactive flavonoid that is widely used in traditional medicine due to its numerous therapeutic activities, such as antioxidant, anti-inflammatory, antiobesity, antiaging, antiallergic, antitumor, antimicrobial, and antidiabetic activities [138–140]. Michelle and B. Michael investigated the anti-inflammatory effect of kaempferol on HGF stimulated with TNF-α (10 ng/ml) [48]. Kaempferol suppressed IL-8 secretion in HGF without cytotoxicity under 50 μM, and induced cell migration, which is an essential process of wound healing.

Among traditional Chinese medicines, glycyrrhizin (GL) is a natural oleanane-type triterpenoid saponin found only in the roots of *Glycyrrhiza glabra* (Liquorice) and exhibits hepatoprotective, anti-inflammatory, anti-oxidative, anti-microbial, anti-cancer, and antiviral activities [141–143]. Therefore, Na Zhang et al. investigated whether GL displays anti-inflammatory properties on HGF [44]. The results indicated an inhibitory effect of GL on IL-6 and IL-8 production, as well as iNOS and COX-2 expression, without cytotoxicity under 160 μg/ml on HGF stimulated by Pg-LPS. This anti-inflammatory activity is mediated by inhibition of NF-κB activation and activating LXRα.

Vitamin D is recognized as an essential nutrient for maintaining health, and it can be obtained from various dietary sources or synthesized in the skin [144]. Moreover, vitamin D is reported to contribute to the treatment of periodontal disease [29]. However, no studies have reported an association between vitamin D and its analogs and the inflammatory responses of HGF. Therefore, V. Nakashyan et al. investigated the regulatory effect of vitamin D and its analogs on HGF stimulated by IL-1β [29]. Vitamin D at 1 and 10 nM concentrations suppressed the production of IL-6 and IL-8 on HGF stimulated with IL-1β at 0.01 nM. However, the vitamin D analog did not show any effect. Furthermore, vitamin D mediated the inflammatory response by inhibiting NF-κB activation. One study developed an in vitro model of inflammation and hyperglycemia by treating G-HSA, which accumulates in periodontal tissues and leads to periodontitis in patients with diabetes mellitus. To mimic periodontitis in these patients, HGF was stimulated by combined exposure of IL-1β (0.01 nM), IL-17 (100 ng/ml), and G-HSA (125 μg/ml). Combined exposure strongly increased the IL-6 and IL-8 production. However, vitamin D significantly decreased the production of IL-6 and IL-8 [64]. These two studies suggest that vitamin D has potential as an anti-inflammatory agent for the prevention and treatment of periodontitis.

β-glucans derived from yeast have been widely used in functional ingredients and pharmaceutics industries due to their therapeutic effects, which include immunomodulatory, anti-inflammatory, and anti-allergy activities [145,146]. To explore the potential use of their immunomodulatory activity for the treatment of periodontitis, Viviam de Oliveira Silva et al. investigated the anti-inflammatory effect of β-glucan derived from *Saccharomyces cerevisiae* on HGF [11]. They developed a co-culture model using OBA-9 (human gingival

epithelial cells, top layer), HGF (bottom layer), and *A. actinomycetemcomitans* (1×10^6 cfu/ml basal chamber and insert) in a dual-chamber model to mimic the periodontium. This study showed that β-glucan inhibited the gene expression of IL-1α, IL-18, and prostaglandin-endoperoxide synthase-2 on co-cultured HGF.

Panduratin A (PA) is the major bioactive phytochemical isolated from *Boesenbergia pandurata*, commonly known as finger root [147]. This compound exhibits numerous bioactivities, including anti-obesity, anticancer, antioxidant, antibacterial, and anti-inflammatory activities, and inhibits the growth of periopathogens such as *P. gingivalis* [148,149]. Based on these findings, a study investigated the preventive effect of PA on periodontitis [27]. PA (1 μM) decreased the protein and mRNA expression of IL-1β through the inactivation of NF-κB and MAPK pathways on HGF stimulated with 1 μg/ml Ec-LPS.

Rho-kinase, a small monomeric guanosine triphosphatase Rho, plays an important role in different cellular functions, such as adhesion, smooth muscle contraction, and actin cytoskeleton organization, and it has been shown to induce inflammatory responses in several cell lines, including human epithelial cells, human endothelial cells, and mesangial cells [150,151]. However, the potential of Y-27632, a selective rho-kinase inhibitor, for periodontitis treatment has not yet been reported. Therefore, Wenyan Kang et al. demonstrated the anti-inflammatory effect of Y-27632 on periodontitis [52]. The results indicated that 40 μM Y-27632 suppressed the production and mRNA expression of IL-6 and IL-8, similar to the untreated group, by inhibiting the activation of TLR2 and TLR4 without cytotoxicity. The anti-inflammatory mechanisms was determined to be that Y-27632 inhibited the activation of NF-κB and the phosphorylation of p38 MAPK.

Isorhamnetin (Isor) is a natural flavonoid compound that is isolated from various plants and plant-derived foods and shows a wide spectrum of pharmacological effects, such as anti-inflammatory, anti-oxidative, antibacterial, and antivirus effects [152–154]. However, its preventive effect on periodontitis has rarely been investigated. Thus, a study conducted in 2018 suggested the potential of this compound for the treatment of periodontitis. Isor inhibited the production of inflammatory-related factors (PGE_2, NO, IL-6, and IL-8) by suppressing NF-κB activation and increasing Nrf2 and HO-1 expression in HGF stimulated with Pg-LPG (1 μg/ml) [47]. These results indicate the anti-inflammatory effect of Isor for the treatment of periodontitis.

Dimethyloxallyl glycine (DMOG) is a competitive inhibitor of the hypoxia-inducible factor prolyl hydroxylase and has been reported to reduce several inflammatory diseases, including inflammatory bowel disease and endotoxic shock [155,156]. Shang et al. confirmed that DMOG has potential as a therapeutic agent for periodontitis [157]. In their study, an in vitro model was developed using *Fusobacterium nucleatum* infection on HGF to mimic the initiation and progression of periodontitis. The results of this study demonstrated that DMOG attenuated the expression of IL-6, IL-8, TNF-α, IL-1β, TLR4, and MyD88 and inhibited the activation of MAPK, PI3K/Akt, and NF-κB signaling pathways.

Hyaluronic acid (HA) is a member of the family of natural glycosaminoglycans abundantly found in mammalian tissues [158]. It is composed of linear long chains of two alternating units of N-acetylglucosamine and D-acetylglucosamine and has a molecular weight (MW) range of 5–20,000 kDa [158–160]. HA is a key element in maintaining healthy periodontal tissue, because the periodontal matrix mainly contains HA [161]. Furthermore, high-MW HA (>103 kDa) (HMW-HA) exhibits anti-angiogenesis, anti-inflammatory, and wound healing effects compared with low-MW HA [162,163]. To treat periodontitis, MinshanChen et al. demonstrated the anti-inflammatory effect of HA with various MW (30, 300, and 1300 kDa) on HGF stimulated by Pg-LPS [45]. The 300 kDa and 1300 kDa HA inhibited cell migration, and only 1300 kDa HA strongly decreased the expression of IL-1β, IL-4, IL-6, IL-8, and IL-10 on HGF. The mechanism analysis showed that 1300 kDa HA suppressed the activation of NF-κB and MAPK signaling on HGF.

Resveratrol is a natural non-flavonoid polyphenolic phytoalexin compound with anti-oxidative, anti-inflammatory, and anticancer activities [164]. Silymarin belongs to the flavonolignans family and is a major component of milk thistle (*Silybum marianum*), and exhibits several pharmacological effects such as antioxidant, anti-inflammatory, anticancer, and immunomodulatory effects [165]. A combination therapy of resveratrol and silymarin was found to be more effective in reducing inflammation than a single therapy on HGF stimulated by histamine [58]. This combined therapy exhibited an inhibitory effect on the secretion of IL-6, IL-8, and TNF-α.

Cynara scolymus is used as a traditional medicine in Europe and contains a bioactive compound called cynaropicrin, which has anti-inflammatory, antibacterial, and anti-photoaging activities [166,167]. A previous study investigated the potential of *C. scolymus* extract and cynaropicrin for the treatment of periodontitis [38]. The extract and cynaropicrin downregulated mRNA expression and production of IL-6 and -8 without cytotoxicity at concentrations up to 500 μg/ml. In particular, the anti-inflammatory effect of cynaropicrin is mediated by the suppression of NF-kB activation.

Proanthocyanidins from *Pelargonium sidoides* DC root extract are flavonoids present in various plants as a defense against biotic and abiotic stressors [168]. Due to their anti-inflammatory activity, a study investigated their potential as a therapeutic agent for periodontitis [55]. The expression of IL-8 and PGE_2, caspase-3, and caspase-8 was decreased by proanthocyanidins on HGF stimulated by LPS.

Plantamajoside is a major ingredient isolated from *Plantago asiatica* and has been used in food and medicine for a long time [169]. Therefore, Fei Liu et al. investigated the anti-inflammatory effect of plantamajoside on HGF stimulated by Pg- LPS and its underlying mechanism [54]. The results indicated that plantamajoside reduced the production of PGE_2, NO, IL-6, and IL-8 without cytotoxicity in HGF. Furthermore, plantamajoside inhibited the activation of NF-κB and PI3K/Akt signaling.

6-Shogaol is a major biological compound found in ginger and has been shown to exhibit anti-inflammatory and anti-oxidant activities [170]. To investigate the potential of 6-shogaol as a therapeutic agent for periodontitis, a study was conducted to develop an in vitro periodontitis model using HGF stimulated by advanced glycation end-products (AGEs) or bovine serum albumin (BSA) [31]. The anti-inflammatory of 6-shogaol was evaluated in this in vitro periodontitis model. The results showed that 6-shogaol has anti-oxidant activity by reducing ROS activity and enhancing antioxidant enzyme production (HO-1 and NQO1). Furthermore, it showed a preventive effect on periodontitis by inhibiting the expression of the receptor for advanced glycation end products (RAGE), the production of IL-6 and ICAM-1 in AGEs-stimulated HGF.

Quercetin is a polyphenolic flavonoid compound found in many food resources and can treat periodontitis. A previous study demonstrated that quercetin suppressed the production of IL-1β, IL-6, IL-8, and TNF-α in HGF stimulated with Pg-LPS and reduced the expression of TLR4 and activation of NF-κB signaling [56].

Tianliang Yu et al. demonstrated that oridonin, a natural tetracycline diterpenoid, attenuated the cytokine production of PGE_2, NO, IL-6, and IL-8 by inhibiting NF-κB and PPARγ activation in HGF stimulated by Pg-LPS [51].

Elaeagnus umbellata is a berry that exhibits antioxidant and anti-inflammatory properties. A study isolated five new compounds and nine known compounds from *E. umbellate* and investigated their therapeutic potential for periodontitis [36]. Among the isolated compounds, 3-O-β-d-glucopyranosyl-(1 → 2)-β-d-galactopyranoside-7-O-α-l-rhamnopyranoside inhibited the LPS-induced expression of IL-6 and IL-8 in HGF stimulated with H_2O_2 (200 μM).

3.5.1.3. Medication-based treatments for periodontitis. Daiokanzoto (TJ-84) is a Kampo medicine consisting of rhubarb and licorice and is used as a drug in Japan [171]. Therefore, Fournier-Larente et al. investigated the therapeutic effect of TJ-84 on Pg-LPS-stimulated HGF [172]. These results indicated that TJ-84 inhibited the expression of major *P. gingivalis* virulence factors, including fimA and hagA, and IL-6 and CXCL 8. Moreover, Hangeshashinto, another Japanese Kampo medicine, suppressed PGE_2 production and COX-2 expression on IL-1β-stimulated HGF [173].

Shinbuto and Ninjinto are traditional Japanese Kampo medicines known for their anti-inflammatory properties [174,175]. A previous study investigated their potential as anti-inflammatory agents against on HGF stimulated by Pg-LPS [175]. Shinbuto and ninjinto inhibited the production and expression of PGE_2 and IL-6 while enhancing the expression of annexin 1. Notably, they induced cPLA expression.

In a 2017 study, metformin, a first-line antidiabetic medicine, was shown to inhibit cytokine production such as IL-1β, IL-6, and TNF-α through induction of ATF3 expression on Pg-LPS-stimulated HGF [176].

Ibuprofen (IBU) is a chiral non-steroidal anti-inflammatory drug that possesses anti-inflammatory and antipyretic properties [177]. Therefore, the study developed an electrospun polycaprolactone scaffold functionalized with IBU to control drug release and locally deliver the drug and investigated its therapeutic effect for periodontitis treatment through in vitro and in vivo experiments [178]. The scaffold with IBU inhibited proliferation and migration induced by Pg-LPS. Additionally, the scaffold suppressed the expression of extracellular matrix (ECM)-related molecules (fibronectin-1, COL IV, integrin α3β1, and laminin-5), as well as that of COX-2 and IL-8.

Atorvastatin is a therapeutic agent used for hypercholesterolemia treatment and shows other pharmacological activities, including antitumor and anti-inflammatory activities [179]. Chitosan, a natural polysaccharide derived from chitin by deacetylation, is used as a marine-derived antimicrobial agent and has biocompatibility and biodegradability [180]. A study developed an atorvastatin delivery system using chitosan. This delivery system inhibited pro-inflammatory cytokine expression (IL-1β, IL-6, IL-8, TGF-β1, and TGF-β2) on HGF stimulated by TNF-α [181].

Numerous studies have explored surface modification methods for dental implants to restore missing teeth at implanted sites. One such study modified the surface of titanium dental material using non-thermal atmospheric pressure plasma (NTAPP) to improve soft tissue integration around the implanted site. After surface modification, the dental material inhibited the release of IL-1β, IL-6, and IL-8 on HGF stimulated by Ec-LPS [182].

Triclosan is an antibacterial agent commonly used in oral hygiene products [183]. To combine the therapeutic effects of chitosan and triclosan, Pavez et al. developed nanoparticles composed of chitosan and triclosan and investigated their anti-inflammatory activity [184]. The results revealed that chitosan-triclosan particles suppressed cytokine expression (IL-1 and IL-6) without cytotoxicity and the JNK phosphorylation on HGF stimulated by IL-1β.

Doxycycline is a tetracycline antibiotic used for broad-spectrum activity [185]. Its therapeutic effect on periodontitis was investigated using HGF stimulated by a combination of *P. gingivalis* and adenosine triphosphate (ATP) [186]. Doxycycline attenuated inflammasome activation and IL-1β production in HGF.

3.5.1.4. Other therapies. Quercitrin, a naturally occurring yellow flavonoid, is widely found in flowers and has regenerative and anti-inflammatory effects on periodontal tissues [187,188]. Therefore, a study demonstrated that quercitrin-nanocoated titanium surfaces, which are biomaterials for the treatment of periodontal and peri-implant diseases, suppress COX-2 gene expression and PGE_2 release on HGF stimulated by IL-1β [189].

β-estradiol is a major endogenous human estrogen, and progesterone is a steroid hormone synthesized by the placenta, ovaries, and adrenal glands [190,191]. A study was conducted to investigate the effect of elevated levels of these two female sex hormones on periodontitis during pregnancy [9]. Pre-treatment of β-estradiol and progesterone inhibited the expression of MMP-1 and MMP-8 in HGF stimulated by Pg-LPS.

Mesenchymal stem cells (MSCs) secrete various molecules that have regenerative, anti-inflammatory, and anti-oxidative properties [192]. Based on this, a previous study investigated whether MSC-conditioned medium (MSC-CM) showed an anti-inflammatory effect on HGF stimulated with IL-6 (Group 1, 10 μg/L) or TNF-α (Group 2, 10 μg/mL) for the treatment of periodontitis. Following the placement of MSCs in hypoxic and ischemic conditions for 48 h in a serum-free medium, MSC-CM was obtained, centrifuged, and filtered for further experiments. The results indicated that MSC-CM inhibited the cytokine-induced expression of superoxide dismutase, malondialdehyde, TGF-β, keratinocyte growth factor, and caspase-3 [193].

MicroRNAs are small non-coding RNA molecules (containing 20–25 nucleotides) found in eukaryotes and are associated with RNA silencing, and post-transcriptional and translational regulation of gene expression [194]. In particular, miR-200c mediates the epithelial-mesenchymal transition, apoptosis, proliferation, and metastasis of various cancer cells. However, no study has reported its

anti-inflammatory effect [195]. Therefore, Adil Akkouch et al. demonstrated that miR-200c inhibits the inflammatory reaction on HGF stimulated by Pg-LPS [196]. The results indicated that miR-200c suppressed the secretion and expression of IL-6 and IL-8.

Basic fibroblast growth factor (bFGF), a member of the FGF superfamily, regulates cell growth and differentiation under physiological and pathological conditions [197]. Additionally, b-FGF is involved in angiogenesis, cell proliferation and differentiation, and the increase of extracellular matrix production, indicating its potential for wound healing activity [198]. In a study exploring the co-delivery of ibuprofen (IBU) and bFGF, a thermosensitive nanoparticle hydrogel was fabricated using a copolymer consisting of polyethylene glycol, ε-caprolactone, and 1,4,8-trioxa [4.6]spiro-9-undecanone. The potential for periodontitis treatment was then investigated. The results showed that IBU was stably released for 4 weeks from the hydrogel [199]. Furthermore, the fabricated hydrogel enhanced cell proliferation and adhesion and suppressed PGE_2 production without cytotoxicity on HGF simulated with Pg-LPS (1 μg/ml).

FPS-ZM1 is a specific inhibitor of RAGE, which is upregulated in various inflammatory diseases [200]. Therefore, Jialin Huang et al. confirmed that FPS-ZM1 has the potential for treating periodontitis through its inhibitory activity on the activation of RAGE [201]. These results indicated that treatment with FPS-ZM1 on HGF stimulated by Pg-LPS to mimic a periodontitis condition suppressed the protein expression of RAGE and HMGB1, as well as that of IL-6 on Pg-LPS-stimulated HGF. Additionally, FPS-ZM1 mediated its anti-inflammatory effect by inhibiting the activation of NF-κB signaling.

Two additional studies have demonstrated that leukocyte-platelet-rich fibrin which is a second-generation of biomaterials based on blood plasma, inhibits the release of TNF-α, IL-1β, and IL-6 [202,203].

Milk and dairy products contain several nutrients, including oleic acid, conjugated linoleic acid, vitamins, minerals, and bioactive compounds, and exhibit beneficial effects on the cardiovascular, nervous, gastrointestinal, and immune systems [204,205]. However, their anti-inflammatory effect on HGF for treating periodontitis has not yet been reported. This study was conducted to investigate their potential. Therefore, a study indicated that milk and dairy products showed inhibitory activity on the production of IL-1, IL-6, and IL-8 in HGF stimulated with both IL-1 and TNF-α [206].

Photodynamic therapy (PDT) produces highly reactive oxygen species (ROS) and singlet oxygen using LED light or laser at a specific wavelength and mainly uses indocyanine green (ICG), one of the main PDT dyes, to induce ROS production [207,208]. To gain a synergistic effect of ICG and antimicrobial PDT (aPDT), antimicrobial photodynamic therapy (aPDT) with ICG was conducted on HGF stimulated with biofilm-conditioned medium (BCM) of viable *Aggregatibacter actinomycetemcomitans*. The combined therapy decreased the production of IL-6, IL-8, CXCL10, TGF-β, and bFGF [208].

Adenosine triphosphate (ATP) is traditionally associated with cellular energy metabolism and is released after stress or injury during infection or inflammation [209]. For these reasons, CD73-dependent adenosine exhibits an inhibitory effect on CXCL8 secretion via the upregulation of HO-1 expression and AMP-activated protein kinase activation on HGF stimulated by IL-1β [209]. These results indicated that CD73-dependent adenosine has potential as a therapeutic agent for periodontitis.

3.5.2. Characterization of periodontitis treatment based on in vivo studies

3.5.2.1. Extract-based treatments for periodontitis. *Lawsonia inermis*, also known as henna, is a natural source of dye and has several biological effects, including antibacterial, antifungal, and anti-amoebiasis properties [210,211]. On the basis of these properties, Zubardiah Lies and Sudiono Janti hypothesized that the methanol extract from *L. inermis* L. leaves could eliminate gingivitis in the H_2O_2-mediated rat model. The results showed that methanol extract of *L. inermis* L. leaves suppressed inflammatory cell reduction and aided in epithelial connective tissue repair [79]. Therefore, the authors suggested that methanol extract from *L. inermis* L. leaves could be used as a therapeutic agent for periodontitis.

Salvia sclarea L. is known for its antibiotic, antimicrobial, and antioxidant properties and is used as an effectual agent for reducing gingival inflammation [212]. A previous study investigated the anti-inflammatory activity of an ethanolic extract of *S. sclarea* L. in a rat model of periodontitis [73]. Ethanolic extract of *S. sclarea* L. inhibited alveolar bone loss and inflammatory responses induced by injection of Ec-LPS into the interdental papilla.

Calendula officinalis, also known as marigold, is an edible plant that is grown across Europe and used in Bulgarian folk medicine as an anti-inflammatory, antipyretic, antitumorigenic, and cicatrizing remedy [213]. However, no study has reported the potential of *C. officinalis* for treating periodontitis. Therefore, a study was conducted to confirm that the aqueous extract of *C. officinalis* suppressed periodontitis progression using a periodontitis rat model stimulated by ligature [65]. Aqueous extract of *C. officinalis* inhibited alveolar bone loss and increased SirT1 mRNA expression. Therefore, the aqueous extract of *C. officinalis* can be used for the treatment of periodontitis.

A previous study has demonstrated that the ethanolic extract *of Tocoyena sellowiana*, whose bark is used as an anti-inflammatory agent, exhibits potential for treating periodontitis [76]. Anti-inflammatory activity is mediated by suppression of the expression of COX-2, IL-1β, MPO, and PEG_2.

The leaves of *Purple miana* have immunomodulatory effects that prevent tuberculosis infection [214]. Despite their biological activity, no studies have been reported on their potential for periodontitis treatment. Therefore, a study was conducted to investigate the effect of *P. miana* leaf extract (PMLE) on periodontitis in a rat model [71]. PMLE inhibited IL-10 mRNA expression in rats induced by *A. actinomycetemcomitans*.

Green tea offers several health benefits, such as anti-inflammatory, antiarthritic, antibacterial, antiangiogenic, antioxidative, antiviral, neuroprotective, and cholesterol-lowering effects [215]. However, few studies have reported the potential of green tea extract for periodontitis treatment. Therefore, a study investigated the preventive effect of green tea extract on periodontitis using a

ligation-induced periodontitis rat model [74]. These results indicated that green tea extract suppressed alveolar bone loss, and cytokine expression inducing IL-1β, IL-10, and TNF-α.

A study was conducted to investigate whether *Acer tegmentosum* maxim extracts exhibit a preventive effect on periodontitis through anti-inflammatory activity [68]. The results indicated that *A. tegmentosum* maxim extracts inhibited pathogenesis in gingival tissue and inflammatory cell infiltration in a Pg-LPS-induced periodontitis rat model.

3.5.2.2. Single compound-based treatments for periodontitis. A combination with resveratrol and silymarin has potential as a therapeutic agent for periodontitis through in vitro studies [58]. However, no study demonstrated the preventive effect of resveratrol alone through both in vitro and in vivo studies. Therefore, a study confirmed the preventive effect of resveratrol on periodontitis using a ligature/LPS-induced periodontitis rat model [57]. In vivo results indicated that alveolar bone loss occurred because of periodontitis and that inflammatory responses in gingival tissue were suppressed by resveratrol. This result demonstrated that resveratrol is a promising therapeutic agent for periodontitis.

THSG has been studied for its anti-inflammatory effect in treating periodontitis through both in vitro and in vivo studies. In vivo experiment have shown that THSG inhibited alveolar bone level loss and recovered the SirT1 mRNA expression in a ligature-induced periodontitis rat model [59].

Baicalin is a flavonoid compound extracted from *Scutellaria baicalensis* Georgi and has been used to treat several inflammatory diseases [216]. Moreover, a study confirmed whether baicalin can prevent periodontitis using a periodontitis rat model stimulated by *P. gingivalis* inoculation [33]. Baicalin inhibited periodontitis-induced alveolar bone loss and decreased the expression of HMGB1 and cytokines (TNF-α, IL-1β, and MPO) as well as the protein expression of TLR2 and TLR4. This modulatory effect on periodontitis is mediated by suppressing the activation of MyD88, p38 MAPK, and NF-κB.

Genistein inhibited periodontitis-induced alveolar bone loss and periodontal tissue degradation via anti-inflammatory activity in a mouse model stimulated with Ec-LPS and ligature. This result was supported by the inhibitory effect on the expression of COX-, TNF-α, and ICAM-1 [43]. Additionally, genistein inhibited mitochondrial stress and cellular ROS accumulation via autophagy induction.

Chunbo Hao et al. investigated the potential of Asiatic acid for periodontitis treatment using a periodontitis rat model stimulated with Pg-LPS [32]. Asiatic acid reduced the expression of IL-6 and IL-8.

Tiludronic acid is a non-nitrogen-containing bisphosphonate that inhibits inflammation and bone resorption [217]. Despite its biological activities, no study related to its potential for periodontitis treatment via anti-inflammatory effects has been reported. Therefore, a study investigated whether tiludronic acid inhibited the inflammatory response and prevented periodontitis in a ligation-periodontitis rat model [60]. Tiludronic acid not only suppressed periodontitis-induced alveolar bone loss and the expression of IL-1β, TNF-α, COX-2, and MMP-8.

Curcumin is a popular polyphenol compound that benefits inflammatory diseases, metabolic syndrome, and pain [218]. A previous study demonstrated that curcumin inhibited periodontitis-induced alveolar bone loss and inflammation in a ligation-induced periodontitis rat model [37].

In patients with type 2 diabetes mellitus, periodontitis is considered a complication [219]. 25-Hydroxyvitamin D3 is the main circulatory form of vitamin D3 in the body and is associated with improved bactericidal capacity and anti-inflammatory activity. Therefore, a previous study demonstrated the potential of 25-Hydroxyvitamin D3 for preventing diabetes mellitus-induced periodontitis in type 2 diabetes mellitus db/db mice [30]. The results showed that 25-Hydroxyvitamin D3 inhibited cytokine release, such as TNF-α, IFN-γ, and IL-6 by inhibiting JAK1/STAT3 signaling activation.

Icariin, the main bioactive compound of *Herba Epimedii*, is a prenylated flavonoid that provides numerous biological benefits, including the prevention of osteoporosis, reduction of sexual dysfunction, modulation of the immune system, and improvement of cardiovascular function [220]. A previous study revealed that icariin promoted bone regeneration through its anti-inflammatory activity in a minipig model of periodontitis induced by alveolar bone defects [46]. Furthermore, it was confirmed that its anti-inflammatory activity was demonstrated by suppressing the expression of IL-1β and IFN-γ.

Capsazepine, a pungent ingredient found in hot chili peppers and used as a therapeutic agent for inflammation and pain-related diseases, inhibited periodontitis-induced alveolar bone loss and cytokine levels such as TNF-α and PGE_2 in a mouse model of periodontitis stimulated with Ec-LPS [35,221].

UP446 is a well-defined mixture of *Scutellaria baicalensis* Georgi and *Acacia* rat model ability to downregulate the expression of proinflammatory cytokines, including IL-1β and TNF-α [222]. Therefore, a study investigated whether UP446 prevent periodontitis via its anti-inflammatory effect in a beagle dog model [62]. The results showed that UP446 decreased pocket depth, loss of attachment, and gum bleeding in Pg-LPS-induced periodontitis.

3.5.2.3. Medicine-based treatments for periodontitis. HU-308, a cannabinoid CB2 receptor agonist with a preventive effect on renal injury, inhibited iNOS activity and the concentration of TNF-α and PGE_2 in a periodontitis rat model stimulated with Ec-LPS [223,224].

Simvastatin (SIM), an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A, exhibits anti-atherosclerotic, anti-inflammatory, and immunomodulatory activities. Therefore, local delivery of SIM augmented the expression of anti-inflammatory cytokines, such as IL-10, IL-1 receptor-like 1, and bone anabolic genes (insulin-like growth factor, osteocrin, and fibroblast growth factor) in a rat model of ligature-induced periodontitis [225]. Their inhibitory activity is involved in the Wnt/β-catenin signaling pathway.

3.5.2.4. Other therapies. To investigate the synergistic effect of the scaffold and ibuprofen, a study was conducted using an electrospun polycaprolactone scaffold functionalized with ibuprofen through in vitro and in vivo experiments. In vivo results showed that the

scaffold inhibited bone destruction in a mouse model of periodontitis stimulated with a *P. gingivalis*-infected ligature [178].

Another study developed curcumin-loaded nanoparticles and investigated their potential for periodontitis treatment to overcome the limitations of the previous study [226]. Curcumin-loaded nanoparticles inhibited inflammatory bone resorption and inflammatory infiltration by suppressing the activation of MAPK and NF-κB signaling pathways in a rat model of periodontitis induced by Ec-LPS.

Among microRNAs, miR-200c showed an inhibitory effect on cytokine expression, such as IL-6 and IL-8, as well as periodontitis-induced alveolar bone loss in a periodontitis rat model stimulated with gingival flap [196].

Metronidazole (MTZ), a synthetic antibiotic derived from azomycin, has been approved by the FDA for treating several anaerobic bacterial infectious diseases [227]. To develop a delivery system, a study fabricated poly(vinyl alcohol) (PVA)-based hydrogel containing microcapsules composed of chitosan (CS)-decorated MTZ (CS@MTZ). The results indicated that CS@MTZ inhibited hyperkeratosis in the epithelial tissue in a periodontitis rat model stimulated by Pg-LPS [228].

Leukocyte-platelet-rich fibrin also showed an inhibitory effect on the progression of gingival ulcers, indicating similar results to those of in vitro experiments in the same study [202].

FomA is an immunogenic outer membrane protein of *Fusobacterium nucleatum*, that is associated with dental plaque formation, and Hgp 44 is the domain polypeptide of *P. gingivalis*. *Vibrio vulnificus* Fla B is an effective mucosal adjuvant and was employed to effectively deliver via mucosal immunization routes in this study. The study developed a divalent mucosal vaccine consisting of a mixture of FlaB-tFomA and Hgp44-FlaB fusion proteins and confirmed the preventive effect using a mouse model of periodontitis stimulated by *P. gingivalis* and oral infection of *F. nucleatum* [229]. Fusion proteins-based drug delivery system prevents periodontitis-induced alveolar bone loss.

Gingival mesenchymal stem cells (GMSCs) have several biological abilities, including immunomodulatory, anti-inflammatory, and self-renewal abilities [230]. A previous study isolated GMSCs from healthy volunteers and systemically injected GMSCs via the tail vein due to their biological abilities [231]. Transplant of GMSCs inhibited the loss of alveolar bone induced by periodontitis and enhanced formation of new alveolar bone. Moreover, previous studies have reported that the conditioned medium of periodontal ligament-derived mesenchymal stem cells (PDLSCs) enhanced periodontal tissue regeneration, but isolating PDLSCs is difficult and requires multiple periodontal membranes from extracted teeth [232,233]. To provide an alternative to PDLSCs, a study investigated whether the conditioned medium from GMSCs (GMSC-CM) exhibited an effect similar to that of the conditioned medium of periodontal ligament-derived mesenchymal stem cells [234]. GMSC-CM suppressed cytokine expression such as TNF-α and IL-1β in a periodontal defect-mediated rat model.

3.5.3. Characterization of periodontitis treatment based on clinical studies

3.5.3.1. Extract-based treatments for periodontitis. SRP with various therapeutic agents is an essential treatment for periodontitis [235]. Essential oils extracted from *Cymbopogon flexuosus* have been reported to possess pharmaceutical activities, including antimicrobial, anti-inflammatory, and antiseptic properties [236]. Due to their biological activities related to the treatment of periodontitis, a study investigated the therapeutic effect of a mouthrinse containing *C. flexuosus* essential oils following SRP in patients with chronic periodontitis [66]. This mouthrinse restored AL and PD, which is reduced by periodontitis, and decreased BoP and sulcus bleeding index (SBI).

Another study developed a polyherbal mouthwash containing extracts of *Zingiber officinale*, *Rosmarinus officinalis*, and *Calendula officinalis* [69]. *Z. officinale* is used as a traditional medicine due to its healing properties [237]. Extracts of *R. officinalis* possess anticancer effects [238]. Additionally, *C. officinalis* exhibits numerous activities, such as anti-inflammatory, antioxidant, antibacterial, antifungal, antiviral, antigenotoxic, and antitumor properties [239]. To obtain a synergic effect of these extracts, this study confirmed that polyherbal mouthwash containing these extracts inhibited a modified GI, gingival bleeding index, and modified Quigley-Hein scores from baseline in patients with gingivitis.

3.5.3.2. Single compound-based treatments for periodontitis. A study investigated whether N-acetylcysteine (NAC), the N-acetyl derivative of the natural amino acid L-cysteine having an antinflammatory effect, could prevent periodontitis [49,240]. The study found that NAC treatment for 3 months suppressed PD in patients with chronic periodontitis.

3.5.3.3. Other therapies. SRP with periodontal dressing, which contains colophony, zinc oxide, and magnesium oxide, exhibited anti-periodontitis action in patients with chronic periodontitis via a decrease in BOP, IL-8, and MMP-8 levels [83].

Platelet-rich plasma is a promising method for wound healing and tissue regeneration in many medical fields [241]. Therefore, a previous study was investigated whether injection of platelet-rich plasma into the periodontal pocket has a preventive effect on patients with chronic periodontitis [84]. Injection of platelet-rich plasma decreased the plaque index, GI, BoP, PPD, and relative AL as well as the number of lymphocytes at baseline, following 1 month of injection.

Previous studies have confirmed the potential of oral prophylaxis with antibiotic agents as an anti-infective treatment for periodontal diseases [242,243]. However, their anti-inflammatory effect has not been reported yet. Therefore, a study investigated the effect of oral prophylaxis, including tongue cleaning, on the levels of volatile sulfur compounds, organoleptic score, and tongue coating in patients with gingivitis [85]. It significantly decreased PD, GI, PI, Bop, and gingival crevicular fluid (GCF) volume after oral prophylaxis.

Ozone can be administered through various routes, such as water, oil, and inhalation, and it is considered an alternative agent for antiseptic and antimicrobial drugs in dentistry [244]. Thus, a study investigated the potential of ozonated gel for periodontitis

Table 3
Bioactive materials for periodontitis treatment through in vitro studies.

Publication Year	Sample	Type	Stimulator	Major outcomes	Ref
2016	Human placental extracts	Extract	Pg-LPS	↓ Secretion of IL-6 and IL-8	[78]
2016	*E. angustifolium* extract	Extract	Pg-LPS	↓ Release of IL-6 release (*E. angustifolium* extract) ↓ Release of IL-6, IL-8, and MCP-1 (eriodictyol and naringenin)	[70]
2016	Essential oil from *O. gratissimum*	Extract	IL-1β	↓ Secretion of PGE_2	[67]
2016	High molecular weight non-dialyzable material derived from cranberry juice	Extract	G-HSA & Pg-LPS	↓ Production of IL-6 and MMP-3	[77]
2016	NBBA	Single compound	LPS	↓ Production of IL-6 and PGE_2	[50]
2016	Resveratrol	Single compound	Pg-LPS	↓ Expression of COX-2, MMP-2/-9, and TLR4 ↓ Production of ROS ↓ Phosphorylation of Akt, JNK, and p38 ↑ Expression of HO-1 and Nrf	[57]
2016	Tβ4 peptide	Single compound	H_2O_2	↓ Production of NO and PGE_2 ↓ Expression of COX-2, iNOS and osteoclastogenic cytokines ↓ Phosphorylation of ERK, JNK ↓ Activation of NF-κB	[61]
2016	Farrerol	Single compound	Pg-LPS	↓ Production of IL-6 and IL-8 ↓ Activation of PI3K/Akt/NF-κB signaling pathway	[42]
2016	Veratric Acid	Single compound	Pg-LPS	↓ Production of IL-6 and IL-8 ↓ Expression of COX-2 and iNOS ↓ Activation of PI3K/Akt/NF-κB signaling pathway	[63]
2016	THSG	Single compound	Pg-LPS	↓ Expression of IL-1***β***, IL-6, and TNF-***α*** ↑ Activation of AMPK ↓ Activation of NF-κB ↑ Phosphorylation of ERK	[59]
2016	TJ-84	Medicine	Pg-LPS	↓ Expression of major *P. gingivalis* virulence factors ↓ Secretion of IL-6 and CXCL8	[172]
2016	Hangeshashinto	Medicine	IL-1β	↓ Production of PGE_2 ↓ Expression of COX-2	[173]
2016	Quercitrin-nanocoated titanium surfaces	–	IL-1β	↓ Production of PGE_2 ↓ Expression of COX-2	[189]
2017	PHMG-P	Single compound	IL-1β	↓ IL-1β-induced PGE_2, IL-6, IL-8, and MMP-1 levels	[53]
2017	Astatic acid	Single compound	Pg-LPS	↓ Production of IL-6, IL-8, NO, and PGE_2 ↓ Activation of NF-κB ↑ Expression of PPAR-γ	[32]
2017	EGCG	Single compound	Pg-LPS	↓ Expression of IL-6 and IL-8 ↓ Activation of MAPK, NF-κB, and PI3K pathways	[40]
2017	Genistein	Single compound	Ec-LPS	↓ Expression of COX-2, ICAM-1, and TNF-α	[43]
2017	Caffeic acid phenethyl ester	Single compound	Pg-LPS	↓ Production of COX-2, IL-6, IL-8, and iNOS ↓ Activation of MyD88, NF-κB, and TLR ↓ Phosphorylation of Akt and PI3K	[34]
2017	Green tea catechins & EGCG	Single compound	Aa LPS by the 3D co-culture model	↓ Expression of MMP-3, MMP-8, and MMP-9	[41]
2017	Kaempferol	Single compound	TNF-α	↓ Secretion of IL-8	[48]
2017	Glycyrrhizin	Single compound	Pg-LPS	↓ Production of IL-6 and IL-8 ↓ Expression of iNOS, COX-2 ↓ Activation of NF-κB pathway ↑ Activation of LXRα	[44]

(*continued on next page*)

Table 3 (*continued*)

Publication Year	Sample	Type	Stimulator	Major outcomes	Ref
2017	Vitamin D & Vitamin D analog	Single compound	IL-1β	↓ Production of IL-6 and IL-8 (Vitamin D) ↓ Activation of AP-1 and NF-κB	[29]
2017	β-glucans	Single compound	Co-culture with *A. ctinomycetemcomitans* strain	↓ Expression of IL-1α and IL-18	[11]
2017	Shinbuto & Ninjinto	Medicine	Pg-LPS	↓ Production of IL-6 and PGE_2 ↓ Expression of cPLA2 (Shinbuto) ↑ Expression of annexin1, COX-2, and ERK (Shinbuto & Ninjinto)	[175]
2017	Metformin	Medicine	Pg-LPS	↓ Production of IL-1β, IL-6, and TNF-α ↑ Expression of ATF3	[176]
2017	β-estradiol & progesterone	–	Pg-LPS	↓ Expression of MMP-1 and MMP-8	[9]
2017	MSC conditional medium	–	IL-6 or TNF-α	↓ Expression of caspase-3, KGF, MDA, SOD, and TGF-β	[193]
2018	*C. xanthorrhiza* supercritical extract & Xanthorrhizol	Extract	Pg-LPS	↓ Expression of IL-1β, MMP-2, and MMP-8 ↓ Activation of AP-1, MAPK, and NF-κB	[81]
2018	Panduratin A	Single compound	Ec-LPS	↓ Expression of IL-1β, MMP-2, and MMP-8 ↓ Activation of AP-1, MAPK, and NF-κB	[52]
2018	Y-27632	Single compound	Pg-LPS	↓ Protein expression of IL-6 and IL-8 ↓ mRNA expression of IL-6, IL-8, TLR2, and TLR4 ↓ Activation of MAPK and NF-κB	[27]
2018	Isorhamnetin	Single compound	Pg-LPS	↓ Release of IL-6, IL-8, NO, and PGE_2 ↓ Activation of NF-κB ↑ Expression of HO-1 and Nrf2	[47]
2018	Dimethyloxallyl glycine	Single compound	LPS	↓ Expression of IL-1β, IL-6, IL-8, MyD88, TLR4, and TNF-α ↓ Activation of MAPK, NF-κB, and PI3K/Akt	[39]
2018	Electrospun polycaprolactone scaffold functionalized with ibuprofen	-	Pg-LPS	↓ Expression of COX-2 and IL-8	[178]
2018	Chitosan based system for local delivery of atorvastatin	–	TNF-α	↓ Release of IL-1β, IL-6, IL-8, TGF-β1, and TGF-β2	[181]
2018	NTAPP	–	Ec-LPS	↓ Release of IL-1β, IL-6, and IL-8	[182]
2018	Chitosan-triclosan particles	–	IL-1β	↓ Expression of fibronectin, IL-1β, and IL-6	[185]
2019	A mixture of tyrosine and lactic acid	Extract	LPS	↓ Secretion of IL-1β, IL-6, IL-8, IL-17, NO, and TNF-α ↓ Secretion of MMP-9 in culture su ↑ Secretion of TIMP-1 ↓ Production of ROS ↓ Activation of MAPK and NF-κB	[72]
2019	*Garcinia mangostana* L. & propolis extracts	Extract	Pg-LPS	↓ Production of PGE_2	[75]
2019	*G. textorii* ethanol extract	Extract	Pg-LPS	↓ Protein expression of COX-2 and iNOS ↓ Enzyme activity of NOS ↓ Activation of AP-1 and NF-κB ↑ Protein expression of NQO1 and Nrf-2	[28]
2019	Buds from different species of *Populus*	Extract	AgNPs	↓ Release of IL-1β and IL-6 ↓ Expression of COX-2	[80]
2019	High molecular weight hyaluronic acid	Single compound	Pg-LPS	↓ Expression of IL-1β, IL-4, IL-6, IL-8, and IL-10 ↑ Cell migration ↓ Activation of MAPK and NF-κB	[45]
2019	Vitamin D	Single compound	The combinations IL-1β, IL-17, G-HSA, and HSA	↓ Production of IL-6 and IL-8	[64]
2019	Combination of resveratrol and silymarin	Single compound	Histamine	↓ Secretion of IL-6, IL-8, and TNF-α	[58]
2019	Cynaropicrin from *Cynara scolymus* L.	Single compound	Pg-LPS	↓ Production of IL-6 and IL-8 ↓ Activation of NF-κB	[38]

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Table 3 (*continued*)

Publication Year	Sample	Type	Stimulator	Major outcomes	Ref
2019	Proanthocyanidins from *Pelargonium sidoides* DC Root Extract	Single compound	LPS	↓ Expression of caspase-3 and caspase-8 ↓ Expression of IL-8 and PGE_2	[55]
2019	Plantamajoside	Single compound	Pg-LPS	↓ Production of IL-6, IL-8, NO, and PGE_2 ↓ Activation of NF-κB and PI3K/Akt	[54]
2019	6-Shogaol	Single compound	AGEs or BSA	↓ Activity of ROS ↓ Expression of HO-1 and NQO1 ↓ Expression of ICAM-1, IL-6, and RAGE ↓ Activation of MAPK and NF-κB	[31]
2019	Quercetin	Single compound	Pg-LPS	↓ Production and mRNA level of IL-1β, IL-6, IL-8, and TNF-α ↓ Expression of TLR4 ↓ Activation of NF-κB	[56]
2019	Oridonin	Single compound	Pg-LPS	↓ Production of IL-6, IL-8, NO, and PGE_2 ↓ Activation of NF-κB and PPARγ	[51]
2019	Doxycycline	Medicine	Pg-LPS with ATP	↓ Activation of inflammasome ↓ Production of IL-1β	[186]
2019	miR-200c oligonucleotides	–	Pg-LPS	↓ Secretion and expression of IL-6 and IL-8	[196]
2019	Thermosensitive nanoparticle hydrogel	–	Pg-LPS	↓ Production of PGE_2	[202]
2019	FPS-ZM1, 250–750 nM	–	Pg-LPS	↓ Expression of HMGB1, IL-6, and RAGE ↓ Activation of NF-κB	[206]
2019	Leukocyte-platelet rich fibrin	–	Pg-LPS	↓ Release of IL-1β, IL-6, and TNF-α	[202]
2019	Milk and dairy products	–	IL-1 and TNF-α	↓ Production of IL-1, IL-6, and IL-8	[206]
2019	Indocyanine green with aPDT	–	BCM of viable *A. actinomycetemcomitans*	↓ Production of CXCL10, bFGF, IL-6, IL-8, and TGF-β	[208]
2019	CD73-dependent adenosine	–	IL-1β	↓ Secretion of CXCL8 ↑ Expression of HO-1 ↑ Activation of pAMPK	[209]
2019	DMOG	–	Infection of *Fusobacterium nucleatum*	↓ Expression of IL-1β, IL-6, IL-8, and TNF-α	[157]
2020	*Acer tegmentosum* maxim extracts	Extract	Pg-LPS	↓ Activity of MDA and iNOS ↓ mRNA expression of IL-6, MIP-1α, and TNF-α	[68]
2020	Compounds isolated from *Elaeagnus umbellata*	Single compound	LPS	↓ Expression of IL-6 and IL-8	[36]

treatment and compared its therapeutic efficacy with that of chlorhexidine, which is the most widely used adjunctive antiseptic [86]. The results showed that the ozonated gel reduced the concentration of gingivitis-induced IL-1β and the volume of GCF. Moreover, it was found to be more effective for periodontal treatment than gel containing chlorhexidine.

Boric acid, an antimicrobial agent with anti-inflammatory and antioxidant properties, is used as an alternative medicine for the treatment of chronic periodontitis [245]. Mechanical periodontal therapy is also a common treatment for periodontal infections by directly removing biofilm and calculus from the root surfaces [246]. To achieve a dual therapeutic effect with these treatments, a study conducted mechanical periodontal therapy with boric acid irrigation [247]. It showed a significant inhibitory effect on the plaque index, GI, and PPD.

This review provides a summary of the contents of related studies (Tables 3–5).

4. Conclusion

This review investigated the potential of bioactive substances as therapeutic agents for periodontitis. A total of 97 studies were analyzed and summarized. Analysis of the published years shows that the highest number of articles on bioactive substances related to periodontitis was published in 2019. However, we expect that the number of studies on the therapeutic potential of bioactive substances for periodontitis will likely increase after 2020. As described in Fig. 3A, bioactive substances for periodontitis are primarily used as single compounds with anti-inflammatory properties, mainly extracted from plants such as rhododendron, *Polygonum multiflorum* Thunb, *Centella asiatica* (L.) Urban, and *Boesenbergia pandurata* Roxb. Furthermore, extracts from asteroids are the main source of therapeutic agents for periodontitis. Although numerous investigations have been conducted to develop therapies for periodontitis, several limitations and weaknesses remain regarding the extraction source, application, and underlying mechanism.

First, most investigations conducted on therapeutic agents for periodontitis have focused on extracts or single compounds derived from terrestrial biological resources, except one study [28]. However, marine biological resources exhibit significant pharmacological

Table 4
Bioactive materials for periodontitis treatment through in vivo studies.

Publication Year	Sample	Type	Stimulator	Model	Animal	Major outcomes	Ref
2016	*Lawsonia inermis* L. leaves methanol extracts	Extract	H_2O_2	Periodontitis	Rat	↓ The number of inflammatory cell in gingival tissue ↑ Recovery of epithelial connective tissue junction	[79]
2016	Resveratrol	Single compound	Pg-LPS	Periodontitis	Rat	↓ Alveolar bone loss (ABL) ↓ Inflammatory responses	[57]
2016	THSG	Single compound	Ligature	Periodontitis	Rat	↓ Alveolar bone level lost ↑ mRNA expression of SirT1	[59]
2016	Baicalin	Single compound	*P. gingivalis* inoculation	Periodontitis	Rat	↓ Alveolar bone loss ↓ Expression of HMGB1, IL-1β, MPO, TLR2, TLR4, and TNF-α ↓ Activation of MAPK, MyD88, and NF-κB	[33]
2016	HU-308	Medicine	Ec-LPS	Periodontitis	Rat	↓ Activity of iNOS ↓ Content of PGE_2 and TNF-α ↓ Salivary secretory response to pilocarpine	[223]
2017	*Salvia sclarea* L. ethanolic extract	Extract	Ec-LPS	Periodontitis	Rat	↓ Gingival tissue lesion ↓ Alveolar bone loss ↓ Inflammatory responses	[73]
2017	Genistein	Single compound	Ec-LPS & Ligature	Periodontitis	Mouse	↓ Alveolar bone loss and periodontal tissue degradation ↓ Level of COX-2, ICAM-1, and TNF-α ↓ Mitochondrial stress and cellular ROS accumulation ↑ Autophagy	[43]
2017	Astiatic acid	Single compound	Pg-LPS	Periodontitis	Rat	↓ Expression of IL-6 and IL-8	[32]
2018	Aqueous flower extract of *Calendula officinalis*	Extract	Ligation	Periodontitis	Rat	↓ Level of bone loss, neutrophilia, BALP, and leukocyte infiltration ↓ Concentration of TNF-α and IL-1β ↑ Activity of MPO and BALP ↓ Alveolar process and cementum ↓ Inflammatory cell infiltration ↓ Gingival level of IL-1β and TNF-α ↓ Leukocytosis and neutrophilia	[67]
2018	*Tocoyena sellowiana* extract	Extract	Ligation	Periodontitis	Rat	↓ Alveolar bone loss ↓ MPO activity ↓ Secretion of IL-1β and PEG_2 ↓ Expression of COX-2	[76]
2018	*Curcuma xanthorrhiza* Supercritical Extract	Extract	Ec-LPS	Periodontitis	Rat	↓ Collapse of gingival tissue ↓ Expression of IL-1β, MMPs, and NF-κB ↓ Expression of NFATc1, TRAP, and cathepsin K ↑ Expression of ALP and collagen type I alpha ↑ Bone remodeling	[82]
2018	Tiludronic Acid	Single compound	Ligation	Periodontitis	Rat	↓ Alveolar bone loss ↓ Expression of COX-2, IL-1β, MMP-8, and TNF-α	[60]
2018	Curcumin	Single compound	Ligation	Periodontitis	Rat	↓ Alveolar bone loss ↓ Inflammation	[37]
2018	25-Hydroxyvitamin D_3	Single compound	Oral inoculation of *P. gingivalis*	Type 2 diabetes mellitus	Mouce	↓ Release of IFN-γ, IL-6, and TNF-α ↓ Expression of JAK1/STAT3 signaling proteins	[30]
2018	Icariin	Single compound	Alveolar bone defect	Periodontitis	Minipig	↑ Bone regeneration ↓ Expression of IFN-γ and IL-1β	[46]
2018	Electrospun polycaprolactone scaffold	–	*P. gingivalis*-infected ligation	Periodontitis	Mouse	↓ Bone destruction	[178]

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Table 4 (*continued*)

Publication Year	Sample	Type	Stimulator	Model	Animal	Major outcomes	Ref
	functionalized with ibuprofen						
2018	Curcumin-loaded nanoparticle	–	Ec-LPS	Periodontitis	Rat	↓ Inflammatory bone resorption and inflammatory infiltrate ↓ Activation of MAPK and NF-κB	[226]
2019	PMLE	Extract	*A.actinomycetemcomitans*		Rat	↓ Expression of IL-10	[71]
2019	Green tea extract	Extract	Ligation	Periodontitis	Rat	↓ Alveolar bone loss ↓ Expression of IL-1β, IL-10, and TNF-α	[74]
2019	Capsazepine	Single compound	Ec-LPS	Periodontitis	Mouse	↓ Alveolar bone loss ↓ Level of TNF-α and PGE_2	[35]
2019	UP446	Single compound	Pg-LPS	Periodontitis	Beagle dog	↓ Pocket depth, loss of attachment, and gum bleeding	[62]
2019	miR-200c oligonucleotides	–	Pg-LPS	Periodontitis	Rat	↓ Expression of IL-6 and IL-8 ↓ Alveolar bone loss	[196]
2019	Chitosan (CS) decorated metronidazole (MTZ) microcapsules (CS@MTZ)	–	Gingival flap	Periodontitis	Rat	↓ Hyperkeratosis in the epithelial tissue	[228]
2019	Local delivery of simvastatin (SIM)	Medicine	Ligature	Periodontitis	Rat	↑ Expression of Anti-inflammatory (IL-10 and IL-1 receptor-like 1) and bone anabolic (insulin-like growth factor, osteocrin, fibroblast growth factor, and Wnt/β-catenin) genes	[225]
2019	Leukocyte-platelet rich fibrin	–	Incision at inflamed site	Oral mucositis	Rabbit	↓ Progress of gingival ulcer	[202]
2019	Divalent mucosal vaccine consisting of a mixture of FlaB-tFomA and Hgp44-FlaB fusion proteins	–	Oral infection of *F. nucleatum* and *P. gingivalis*	Periodontitis	Mouse	↓ Alveolar bone loss	[229]
2019	Systematically transplanted gingival mesenchymal stem cells	–	Ligation	Periodontitis	Mouse	↓ Alveolar bone loss ↑ Formation of new alveolar bone	[231]
2020	*Acer tegmentosum* maxim extracts	Extract	Pg-LPS	Periodontitis	Rat	↓ Pathogenesis in the gingival tissue ↓ Inflammatory cell infiltration	[68]
2020	Conditioned medium	–	Periodontal defect	Periodontitis	Rat	↓ Expression levels of TNF-α and IL-1β in the GMSC-CM and PDLSC-CM	[234]

properties, including antibacterial, antibiofilm, antimicrobial, antioxidant, and anti-inflammatory properties, which can be beneficial in preventing and treating periodontitis. Second, in terms of the modes of bioactive substances for periodontitis, most studies have focused on direct treatment in vitro and in vivo models, rather than using drug delivery systems. Regarding the underlying mechanism of bioactive substances for periodontitis, of the 101 studies conducted, only 28 studies investigated their effects on signaling pathways. These studies primarily focused on MAPK and NF-κB pathways, whereas the involvement of HO-1, STAT3, and AP-1 signaling pathways was not extensively explored. Despite the limitations of bioactive substances for periodontitis, there has been a recent surge in attention to developing more effective drugs for this disease.

Collectively, additional research is needed not only to further investigate additional bioactive substances from marine biological resources, such as starfish, algae, jellyfish, and unstudied marine organisms, but also to confirm other signaling pathways related to anti-periodontitis properties in in vitro and in vivo models. Additionally, there is a need to combine biomedical engineering with bioactive substances to enhance their delivery efficacy. This can be achieved through the development of hydrogels, three-dimensional scaffolds, nanofibers, and films to effectively deliver bioactive substances for the treatment of periodontitis.

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Data availability statement

Data will be made available on request.

Table 5
Bioactive materials for periodontitis treatment through clinical trials.

Publication Year	Sample	Type	Patient	Major outcomes	Ref
2016	Mouthrinse containing essential oils following SRP	Extract	Chronic periodontitis (n = 46, Both)	↑ Attachment level (AL) ↓BOP, SBI, and PD	[66]
2016	Polyherbal mouthwash containing *Zingiber officinale*, *Rosmarinus officinalis* and *Calendula officinalis* extracts	Extract	Gingivitis (n = 60, Both)	↓ MGI, GBI, and MQH scores from baseline	[66]
2016	SRP with periodontal dressing	–	Chronic periodontitis (n = 28, Both)	↓ BOP ↓ Level of IL-8 and MMP-8	[83]
2017	NAC	Single compound	Chronic periodontitis (n = 28, Both)	↓ Probing depth at 3 months	[49]
2018	Platelet-rich plasma injection	–	Chronic periodontitis (n = 20, Both)	↓ PI, GI, BOP, PPD, and RAL following 1 month of treatment ↓ Lymphocyte count at baseline after 1 month of treatment	[84]
2019	Oral prophylaxis including tongue cleaning	–	Gingivitis (n = 36, Both)	↑ VSC levels, organoleptic and tongue coating score ↓ GCF levels of IL-1β and IL-8	[85]
2019	Ozonated gel	–	Plaque-induced gingivitis (n = 50, Male)	↓ Concentration of IL-1β ↓ GCF volume	[86]
2019	Boric acid 0.75% irrigation with mechanical periodontal therapy	–	Localized chronic periodontitis (n = 40, Both)	↓ PI, GI, and PPD	[247]

CRediT authorship contribution statement

Tae-Hee Kim: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Seong-Yeong Heo:** Writing – review & editing, Investigation, Conceptualization. **Pathum Chandika:** Writing – review & editing, Methodology, Investigation. **Young-Mog Kim:** Writing – review & editing, Visualization, Supervision. **Hyun-Woo Kim:** Writing – review & editing, Visualization, Supervision. **Hyun Wook Kang:** Writing – review & editing, Visualization, Supervision. **Jae-Young Je:** Writing – review & editing, Investigation, Conceptualization. **Zhong-Ji Qian:** Writing – review & editing, Methodology. **Namwon Kim:** Writing – review & editing, Methodology. **Won-Kyo Jung:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

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Abbreviations

Aa LPS *Aggregatibacter actinomycetemcomitans* LPS
Activator protein-1 AP-1
AGEs Advanced glycation end-products
AgNPs Ag nanoparticles
ALP Alkaline phosphate
AMPK AMP-activated protein kinase
aPDT Antimicrobial photodynamic therapy
ATF Activating transcription factor
ATP Adenosin triphosphate
BALP bone-specific alkaline phosphatase
BCM Biofilm-conditioned medium
bFGF Basic fibroblast growth factor
BOP bleeding on probing
BSA Bovine serum albumin
CAL Clinical attachment level
COX Cyclooxygenase
cPLA2 Cytosolic phospholipase A2
CXCL C-X-C motif chemokine
DMOG Dimethyloxallyl glycine

Ec-LPS	*Escherichia coli* LPS
EGCG	Epigallocatechin-3-gallate
ERK	Extracellular signal-regulated kinase
GBI	Gingival bleeding index
GCF	Gingival crevicular fluid
G-HSA	Glycated human serum albumin
GI	Gingival index
GR	Gingival recession
HMGB	High mobility group box
HO-1	Heme Oxygenase-1
IBU	Ibuprofen
ICAM-1	Intercellular adhesion molecule
IFN-γ	Interferon gamma
IL	Interleukin
iNOS	Inducible nitric oxide synthase
JNK	c-Jun N-terminal kinases
KGF	Keratinocyte growth facto
LXRα	liver X receptors
MDA	Malondialdehyde
MGI	Modified gingival index
MIP-1α	Macrophage Inflammatory Protein-1 Alpha
MMP	Matrix metalloproteinase
MPO	Myeloperoxidase
MQH	modified Quigley-Hein
MSC	Mesenchymal stem cell
NAC	N-acetylcysteine
NBBA	N-Benzyl-4-Bromobenzamide
NFATc1	Nuclear factor of activated T-cells c1
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
NO	Nitric oxide
NOS	Nitric oxide synthase
NQO1	NAD(P)H Quinone Dehydrogenase 1
NTAPP	Non-thermal atmospheric pressure plasma treated titanium surface
Pg-LPS	*Porphyromonas gingivalis* LPS
PGE_2	Prostaglandin E_2
PHMG-P	Polyhexamethylene guanidine phosphate
PI	Plaque index
PI3K	Phosphoinositide 3-kinase
PMLE	Purple miana leaf extract
PPAR-γ	Peroxisome proliferator-activated receptor γ
PPD	Probing pocket depth
RAGE	Receptor for advanced glycation endproducts
RAL	relative attachment level
ROS	Reactive oxygen species
SirT1	Sirtuin 1
SOD	Superoxide dismutase
SRP	Scaling and root planning
TGF-β	Transforming growth factor-β
THSG	2,3,5,4-Tetrahydroxystilbene-2-O-β-glucoside
TIMP	tissue inhibitors of metalloproteinases
TJ-84	Daiokanzoto
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
TRAP	Tartrate-resistant acid phosphatase
Tβ4 peptide	Thymosin β-4

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