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REVIEW ARTICLE

# Potential targets of phytochemical immunomodulatory therapy in periodontitis immunopathogenesis: A narrative review

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**KEYWORDS**

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**Abstract** *Introduction:* Periodontitis is one of the most prevalent diseases occurring worldwide, and is caused by an imbalance of host immunological defenses and microbiome profile which occurs in the oral cavity. This imbalance leads to irregularity and uncontrolled activities of immune cells, resulting in over-reactivity of periodontopathogens and tissue destruction. To alleviate periodontitis, exact targeting of specific events involving particular cells could be a potential application of immunomodulatory agents. Phytochemical drug development targeting specific immunopathogenesis events could be a promising complementary, alternative approach to periodontal therapy.

*Objectives:* This review aimed to explore various events involving a variety of cells in the immunopathogenesis of periodontitis in order to determine potential specific immunomodulation targets for future development of effective phytochemical drugs.

*Results:* Immunopathogenesis of periodontitis contributes significantly to the disease onset and resolution. Various events occur during the disease development, which involve a variety of immune cells and mediators. Among these, neutrophils, cytokines and lymphocytes, especially Th17 cells, were reported to be the most relevant components in the disease pathogenesis. These components affect the initial responses to periodontopathogens, inhibit oxidative stress formation, control inter-

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cellular communication to enhance inflammation, and promote effector cells' migration to induce alveolar bone resorption. Several phytochemical drugs were developed to cure periodontitis, however, the development of phytochemical immunomodulatory drugs to target specific events has not been realized.

*Conclusion:* This review concluded that development of phytochemical immunomodulatory drugs to target particular events generated by neutrophils, pro-inflammatory cytokines and lymphocytes has tremendous potential to regulate and modulate the immunopathogenesis of periodontitis.



**Contents**



## 1. Introduction

Bacterial accumulation in oral biofilms, causes chronic inflammation of periodontal tissue and ultimately tissue breakdown, is the cause of periodontitis. Periodontitis is characterized by gingival inflammation, which progresses to periodontal pocket formation, alveolar bone destruction and ultimately tooth mobility (Huang and Gibson, 2014; Listl et al., 2015). Most people have mild periodontitis or gingivitis, and about 47% of those cases progress to more severe forms, with around 8.9% reaching advanced stage (Listl et al., 2015; Zidar et al., 2021). Worldwide, 11% of people have severe periodontitis, making it the sixth most common disease.

Several factors contribute to the pathogenesis of periodontitis, which is primarily caused by dysbiosis and pathogenic transformation caused by altered polymicrobial interactions (Könönen et al., 2019; Sell et al., 2017). *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* were among red complex bacteria involved in this interaction, but interactions with *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum* were also noted (Hema et al., 2018). Polymicrobial interactions that trigger periodontitis involve around 700 species (Gao et al., 2020). However, regulation failures and uncontrolled immune response to biofilms are what ultimately lead to the destruction of periodontal tissue (Huang and Gibson, 2014).

*P. gingivalis* dampens immune response, thereby preventing effective bactericidal activity (González et al., 2018; Hajishengallis, 2015; Makkawi et al., 2017). Bacteria thrive in settings where there is chronic hyperinflammation and failure to eradicate infections results in tissue breakdown and inflammation (González et al., 2018; Zidar et al., 2021). This bacterial proliferation further aggravates host's inflammatory responses to become increasingly ineffective, unregulated, and destructive (Makkawi et al., 2017; Sell et al., 2017; Yang et al., 2021). Disease progression is influenced by immune cells, cytokines, chemokines, and mediators. Main components of periodontitis pathogenesis involve neutrophils, macrophages, T and B lymphocytes, also cytokines (Yang et al., 2021).

Plants contain phytoconstituents that could be applied as bioactive agents to alleviate periodontal diseases (Kerdar et al., 2019; Vo et al., 2020). They interact as ligands to specific cells or cytokines to modulate immune responses (Yende et al., 2021). Development of immunomodulatory agents targeting precise processes would be a promising adjuvant and alternative therapy for periodontitis and its inflammation. This review aimed to identify potential targets in the immunopathogenesis of periodontal disease that could be effective targets to be modulated by immunomodulatory phytochemicals to relieve destructive immune responses.

## 2. Immunopathogenesis of periodontitis

Periodontitis is caused by complicated interplays between immune system and periodontopathogens that is affected by genetic, systemic, and environmental variables (Fig. 1). A key risk factor for periodontitis is the presence of biofilms, but if inflammatory response to this threat is efficient, the disease cannot develop. As depicted in Fig. 2, periodontal tissue deterioration and persistent inflammation result from unregulated inflammation (Gao et al., 2020; González

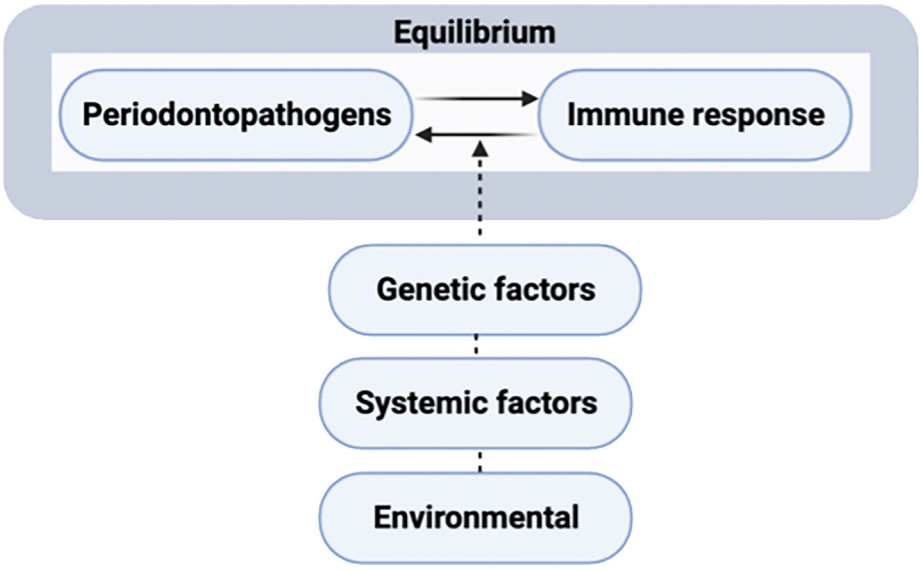


**Fig. 1 Interaction of etiology and risk factors involved in periodontal disease.** Periodontitis occurs because imbalance between virulence factors of periodontopathogen bacteria and host immune response towards it. Various risk factors could affect this interaction, such as genetic factors and overall systemic health of the patient, and also various environmental factors occurs in the oral cavity, such as oral hygiene.

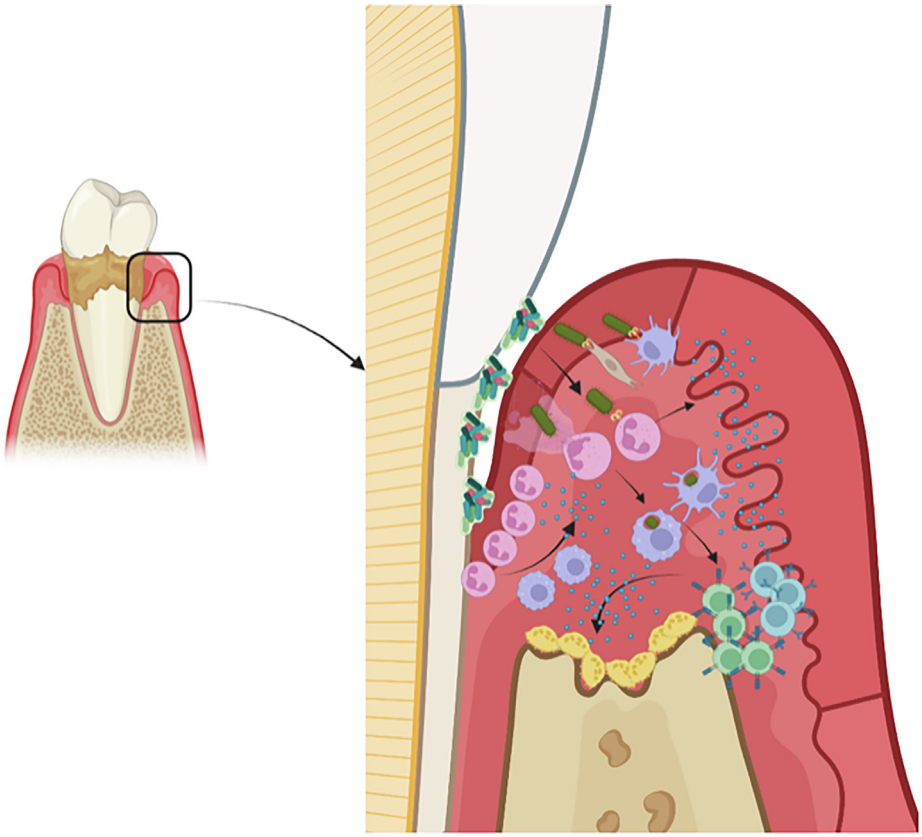

**Fig. 2 Immunopathogenesis of periodontitis involves diverse cells and events leading to periodontal breakdown.** Periodontitis is triggered by biofilm deposit in the oral cavity, especially inside the gingival sulcus. These bacteria could induce initial response by various cells, especially neutrophils and resident macrophages to eliminate the bacteria. These cells then triggers various inflammatory mediators production, especially pro-inflammatory cytokines and mediators. These could further lead to activation of effector cells and osteoclast maturation to initiate and maintain osteoclastic activities in order to break the periodontal tissue down.

et al., 2018; Hajishengallis, 2015; Hema et al., 2018; Könönen et al., 2019).

Innate immune system recognizes microorganisms and their by-products via pattern recognition receptors (PRRs). PRRs are found on inflammatory and periodontal cells, including epithelial cells, fibroblasts, dendritic cells (DCs), and osteoblasts. PRRs identify bacterial pattern-associated molecular patterns (PAMPs), including CpG DNA, lipopolysaccharides and peptidoglycans (Song et al., 2017; Wallet et al., 2018). Chronic periodontitis displayed considerably higher levels of Toll-like receptors (TLRs), such as TLR2 and TLR4, than controls (Makkawi et al., 2017). *Campylobacter rectus, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia* and *Bacteroides forsythus* are also capable of releasing highly immunogenic GroEl or HSP60 homologues (Yamazaki et al., 2002). Additionally, periodontal tissues contain cells that secrete damage-associated molecular patterns (DAMPs), including S100, HMGB, and neutrophil extracellular traps (NET), which cause immune responses (Zhu et al., 2022).

Neutrophils are recruited via junctional epithelium (JE) in response to chemotaxis signals. Lysozyme and collagenase-containing granules in neutrophils are employed to destroy pathogens. Additionally, neutrophils create reactive oxygen species (ROS), bactericidal proteins, and accomplish phagocytosis (Sell et al., 2017). However, hyperactive neutrophils make these processes potentially tissue-damaging (Hajishengallis, 2020). Macrophages also create significant amounts of cytokines and chemokines, such as tumor necrosis factor (TNF) and interleukins (ILs) including IL-1, IL-10, and IL-8. Both macrophages and neutrophils secrete chemokines, which draw cells to the site of injury. Additionally, macrophages could develop into osteoclasts to destruct bone (Huang and Gibson, 2014; Ono et al., 2020; Pan et al., 2019).

DCs act as antigen-presenting cells (APCs) to present PAMPs to immature T cells. In response to antigen, T helper (Th) cells such as Th1, Th2, Th17, follicular helper (Tfh), and regulatory T (Tregs) cells clonally develop and multiply (Sell et al., 2017). Patients with periodontitis have up to 9x increased levels of IL-17 produced by Th-17 in their gingival crevicular fluid (GCF), alveolar bone, and gingiva. Osteoblasts, epithelial, endothelium, fibroblasts, chondrocytes, keratinocytes, and macrophages all have IL-17 receptors, and Th17 cells typically gather on oral mucosal tissues. These cells produce antimicrobial peptides and recruit neutrophils to protect periodontal tissue, leading to becoming overly activated and causing neutrophils migration which cause tissue injury. Additionally, IL-17 and IL-1 collaboratively trigger CCL-20, which further enhances Th17 and IL-17 (Bunte and Beikler, 2019; Huang et al., 2021; Sell et al., 2017).

Receptor activator of nuclear factor kappa-B ligand (RANKLs) are controlled by inflammation (Sell et al., 2017). Monocytes are induced by RANKL to differentiate into osteoclasts. Both osteoclasts and osteoclast precursors possess nuclear factor kappa-B ligand receptor (RANK). RANK-RANKL binding causes osteoclasts activation and bone resorption. Osteoprogreterin (OPG), its antagonist, reduces RANKL activity by competitively inhibit RANK-RANKL binding (Ono et al., 2020). Persistence of pro-inflammatory effector cells induces tissue injury and bone resorption through adaptive and innate immune systems' cellular and molecular components (Quach et al., 2022; Sell et al., 2017; Yang et al., 2021).

## 3. Immunomodulation of periodontitis

Balance between pro-inflammatory and anti-inflammatory responses is needed for homeostasis, inflammation resolution, control of osteolysis and promotion of bone deposition (Issaranggun Na Ayuthaya et al., 2018; Quach et al., 2022; Vo et al., 2020; Yang et al., 2021). Immunomodulation in periodontitis can be targeted at specific crucial events in the pathogenesis. In case of innate or adaptive immune responses, neutrophils, macrophages, monocytes, and T lymphocytes are among the diverse cells that might be targeted in immunomodulation (Table 1) (Huang and Gibson, 2014; Könönen et al., 2019; Pan et al., 2019; Quach et al., 2022; Sell et al., 2017; Zidar et al., 2021).

### *3.1. Immunomodulation of neutrophils*

Neutrophils are the tissue's initial line of defense against infections, therefore maintaining their balance is crucial. Periodontitis is generally characterized by significant neutrophil infiltration with dysfunctional phagocytosis that influence other immune cells (Hajishengallis, 2020; Quach et al., 2022). This makes neutrophils potential target to control inflammatory responses.

Neutrophil recruitment, migration, and infiltration are accelerated in patients with periodontitis, while phagocytic activity is significantly diminished (Hajishengallis, 2020; Metzemaekers et al., 2020; Sell et al., 2017; Yang et al., 2021). This is caused by an increase in several mediators, including ROS, GM-CSF, miRNA, NLRP12, and inflammasomes. TNF-α, IL-8, neutrophil elastase, histidine decarboxylase, eosinophil cationic protein and histamine are examples of pro-inflammatory mediators whose synthesis increases while IL-10, an anti-inflammatory mediator, is reduced. Periodontopathogens and its by-products such as leukotoxins have impacts on these alterations (Quach et al., 2022; Scott and Krauss, 2012; Sell et al., 2017; Yang et al., 2021).

ROS overproduction is one of primary damaging actions of neutrophils in periodontitis. PAMPs overstimulation in neutrophils results in production of $O_2$ by NADPH oxidase that enters phagosomes and extracellular matrix, where it is transformed to radical and non-radical derivatives such as OH, HOCl, $H_2O_2$ and $_1O2$ (Scott and Krauss, 2012; Wang et al., 2017; Yang et al., 2021). ROS directly harm tissues by forming metabolites from lipid peroxidase, causing DNA damage and protein degradation (Scott and Krauss, 2012; Wang et al., 2017).

ROS-induced oxidative stress harms cells and molecules at molecular level. ROS also activates matrix metalloproteinases (MMPs), which are crucial in extracellular matrix breakdown. Primary proteases involved in pathophysiology and destruction of periodontium are MMP-2, MMP-8, MMP-9, and MMP-13 (Scott and Krauss, 2012). Active MMPs trigger signaling molecules such as growth factors, transcription factors, cytokines, and chemokines, leading to accelerated osteoclastogenesis (Könönen et al., 2019). Nrf2, which is involved in antioxidant genes and detoxifying enzymes transcription, is likewise inhibited by ROS in neutrophils (Liao et al., 2021).

Neutrophils's roles in periodontitis make neutrophils an important potential immunomodulatory target. Oxidative stress occurs when antioxidants cannot neutralize increased

**Table 1** Summary of immunomodulatory target in periodontitis immunopathogenesis.

| Target cells or biomolecules | Events modulated | Immunomodulating therapy | References |
|---|---|---|---|
| Neutrophils | Immune cells chemotaxis and phagocytosis initiation<br>Oxidative stress and MMPs control | Polyphenols, resveratrol, quercetin, NAC, ascorbic acid | (Hajishengallis, 2020; Scott and Krauss, 2012; Yang et al., 2021) |
| Cytokines | Initial response against pathogens<br>Immune cells signalling, chemotaxis, activity, proliferation and differentiation<br>Inflammation<br>Osteoclast maturation | b-carotene, benzydamine, *trans*-cinnamic aldehyde, calcitonin gene-related peptide | (Chung et al., 2018; Pan et al., 2019; Ramadan et al., 2020; Son et al., 2020; Yang et al., 2021; Zague et al., 2018; Zhou et al., 2018) |
| T cells | Adaptive immunity<br>Cytokines and RANKL production<br>Inflammatory status<br>Immune cells regulation and activation<br>Tissue protective and destructive cellular and molecular balance | Curcumin, calcitriol, *Astragalus membranaceus,* vitamin D | (Bi et al., 2020, 2019; Figueredo et al., 2019; Meghil et al., 2019; Okui et al., 2014; Yang et al., 2021; Zhang and Deng, 2019) |
| B cells | Humoral immune response and pathogens-specific antibody production<br>Autoantibodies production to collagen, fibronectin and laminin<br>RANKL production<br>Bacterial clearance<br>Cytokines production | PDLSCs | (Demoersman et al., 2018; Figueredo et al., 2019; Kawai et al., 2006; Liu et al., 2013) |
| Dendritic cells | Antigen presentation<br>Inflammation regulation<br>Cytokines release and innate immunity alteration<br>Th1, Th2, Th17, Treg and B cells regulation<br>Source of osteoclast precursors | PRMT5 inhibitor, systemic antibody | (Mi et al., 2021; Rajendran et al., 2019; Song et al., 2018; Wilensky et al., 2014) |
| Macrophages | Antigen presentation<br>Phagocytosis<br>Inflammatory cytokines, chemokines and mediator release<br>Phenotypes polarization balance<br>Osteoclastic differentiation | Resveratrol, proanthocyanidins, metformin | (Sell et al., 2017; Yang et al., 2021) |

Abbreviations: MMPs = matrix metalloproteinases; NAC = N-acetylcysteine; RANKL = receptor activator of nuclear factor kappa-B ligand; PDLSCs = periodontal ligament stem cells; Th1 = T helper 1 cells; Th2 = T helper 2 cells; Th17 = T helper 17 cells; Treg = T regulatory cells; PRMT5 = protein arginine methyltransferase 5.

ROS production (Wang et al., 2017). Antioxidants, such as superoxide dismutase (SOD) and catalase (CAT), decrease along with increased periodontal pockets in patient's saliva (Vo et al., 2020). Gingival activity of SOD, CAT, and GPx was increased in periodontitis patients who smoked. Moreover, healthy patients had significant levels of these antioxidants in their saliva and plasma (Hajishengallis, 2020; Wang et al., 2017). This difference shows tremendous potential of antioxidant therapy to immunomodulate neutrophil response to pathogens.

Polyphenols, ascorbic acid and resveratrol are antioxidant agents that protect tissues from deterioration and damage by ameliorating inflammation and oxidative stress. These agents activate Nrf/ARE to inhibit nuclear factor kappa B (NF-kB) and further activate Bcl-2, thus reducing transcription of inflammatory cytokines and apoptotic signals (Liao et al., 2021; Vo et al., 2020; Yang et al., 2021). Immunomodulation could also be done directly by inhibiting neutrophil production by increasing developmental endothelial locus-1 (DEL-1) and pentraxin-3 (PTX3). DEL-1 can interact with integrins vβ2 and vβ3 to inhibit neutrophil migration. The same mechanism is also carried out by PTX3 which binds to P-selectin for neutrophil recruitment regulation (Yang et al., 2021).

### *3.2. Immunomodulation of lymphocytes and cytokines*

Periodontitis patient generally have pocket epithelium with accumulation of T cells and macrophages, and lamina propria rich in plasma cells and B cells (Figueredo et al., 2019). The gingiva show a lower CD4+/CD8 + ratio than in the blood, although several components of both subsets were significantly increased (Kayar et al., 2020; Quach et al., 2022). However, dominance of $CD4^+$ over $CD8^+$ in gingiva of periodontitis patients was also reported (Figueredo et al., 2019). This finding suggests involvement of humoral and cellular also cytotoxic responses of lymphocytes in periodontitis immunopathogenesis.

There are conflicting and diverse hypotheses about actual mechanisms and functions of T and B lymphocytes in periodontitis. Periodontitis is primarily characterized by B cells, while gingivitis is more frequently associated with an increase in T cells, indicating that progressing lesions are Th2-mediated while chronic and stable lesions are Th1-mediated (Quach et al., 2022). APCs release Th1-specific cytokine IL-12 to promote Th1 differentiation by activating STAT4 and T-bet and to create IFN-γ for the pathogens' eradication (Sell et al., 2017). Although Th1 cytokine responses contribute

to inflammation, they also offer protection against tissue damage. Levels of IL-12 in gingival crevicular fluid (GCF) of patients with chronic periodontitis were similar to normal individuals. Moreover, an increase in pocket depth was found to had no association with IFN-γ and IL-12. Accordingly, Th1 response, mediated by cytokines IFN-γ and IL-12, promotes *P. gingivalis* control and elimination, reduces bone resorption, and protects against periodontal progression (Issaranggun Na Ayuthaya et al., 2018).

Th2 responses are primarily regulated by IL-4, which is generated by $CD4^+$ and B cells, and stimulates STAT6 and GATA3 to regulate B cell growth. IL-5, IL-4 and IL-13 are frequently released by activated Th2 cells to mediate humoral responses (Sell et al., 2017). IL-4 cytokines are decreased in chronic periodontitis and become raised post-therapy (Behfarnia et al., 2010; Pan et al., 2019). Nevertheless, Th2 cells stimulate inflammatory response of B cells and broad infiltration of plasma cells and B cells, which are common in severely developing periodontitis (Quach et al., 2022). It is believed that precise targeting of regulating the pathogenesis of periodontitis and determining disease development involve immunomodulation of the harmony between Th1/Th2 cells.

Activation of Th1, Th2, and Th17 produces aggravating cytokines including IL-1, IL-25, and IL-17, which also activates DCs, neutrophils, and B cells (Sell et al., 2017). Bone resorption results from increased RANKL production caused by T and B cell activation (Ono et al., 2020; Sell et al., 2017). Tfh cell activation of B cells result in antibodies against pathogens, but also form autoantibodies against collagen, fibronectin, and laminin, which cause tissue injury (Figueredo et al., 2019). Failure to control immune response and inflammation is another effect of the decline in Tregs that contributes to persistent inflammation. This demonstrates diverse therapeutic potentials that can be produced when immunomodulating T and B lymphocyte cells. Immunomodulation of Th1/Treg cells can improve immune response's protective properties, whereas Th2/Th17 cells and B cells act as destroyers (Figueredo et al., 2019; Quach et al., 2022; Yang et al., 2021).

Periodontitis pathogenesis is significantly influenced by cytokines, since they connect each tissue cells to various immune cells (Behfarnia et al., 2010; Pan et al., 2019). Cytokine gene polymorphisms are linked to increased risk and severity of periodontitis, suggesting that cytokine dysregulation accelerates periodontitis (Kozak et al., 2020; Pan et al., 2019). This shows that immunomodulation has capacity to regulate and prevent exaggerated reactivity to periodontopathogens by directly targeting the cytokine interaction system.

First released cytokines after microbiome invasion are IL-1, TNF-α and IL-6 (González et al., 2018; Könönen et al., 2019; Makkawi et al., 2017). Each pro-inflammatory cytokines affects lymphocytes and tissue damage in many ways. They cause APCs to release cytokines linked to differentiation of a particular subset of lymphocytes (Pan et al., 2019). These cytokines stimulate particular signaling pathways, as well as maturation and differentiation of particular effector cells, and each cell secretes particular cytokines as third-stage cytokines release (Könönen et al., 2019; Pan et al., 2019; Ramadan et al., 2020; Sell et al., 2017). Majority of these cytokines' functions are related to mucosal barrier immunomodulation, pathogen control, osteoclast induction or suppression, and exaggerated immune response inhibition (Pan et al., 2019; Ramadan et al., 2020).

### *3.3. Immunomodulation of Th17 cells*

Th17 cells and IL-17 cytokines are thought to be the most effective immunomodulating agents in periodontitis (Bunte and Beikler, 2019; Huang et al., 2021). These cells are activated by IL-23 via ROR activation, with the cytokine implicated in increasing cell pathogenicity. Induction of IL-23R and TGF-3, as well as IL-10 repression, result in cell pathogenicity (Sell et al., 2017). IL-1-stimulated periodontal ligament fibroblasts and myeloid APCs that have been exposed to *P. gingivalis* secrete IL-23. In chronic periodontitis, the level of IL-23 of GCF was correlated with attachment loss (Bunte and Beikler, 2019; Pan et al., 2019).

IL-17A, IL-17F, I-21, IL-26 and IL-22 are secreted by Th17 cells, and periodontitis has greater Th17 numbers than gingivitis. Members of IL-17 group, IL-17A and IL-17F function as mucosal and surface barrier immunosurveillance and chronic inflammation progression, respectively (Bunte and Beikler, 2019; Pan et al., 2019). IL-17 play key role in oral immunity and microbiota was essential for immunomodulation of oral tissues. Three properties of IL-17 that are related to its activity include neutrophil recruitment, antimicrobial factors secretion, and protective effect of local mucosal barriers (Bunte and Beikler, 2019; Huang et al., 2021; Ramadan et al., 2020).

Although IL-17 has been shown to have protective functions, it has also been linked to periodontitis pathogenesis. Subjects with high levels of IL-17 had severe periodontal bone destruction (Behfarnia et al., 2010). IL-17 was discovered in GCF in chronic periodontitis patients and was found to be related to disease severity (Sadeghi et al., 2018). Furthermore, IL-17 and dysbiosis can interact and influence one another, increasing pathogenicity of microbiome and immune responses (González et al., 2018; Hajishengallis, 2015). Th17 cells in periodontal tissue are malleable and can change into Th2 under effect of IL-4, and Th2 can change into Th1 under influence of IL-12 and APCs. This illustrates the importance of Th17/Treg control (Bunte and Beikler, 2019). Immunomodulation with IL-35 was found to dampen Th17 lymphocytes and enhance Tregs in patients with periodontitis, resulting in a lower rate of bone resorption (Cafferata et al., 2020). As a result, IL-17 is essential for maintaining local tissue homeostasis as well as development of periodontitis. Immune plasticity in oral cavity is controlled by the equilibrium between IL and 17 and its antagonist factors, which includes DEL-1, to ascertain axis of the role of IL-23 and IL-17 in disease etiology (Bunte and Beikler, 2019; Quach et al., 2022; Yang et al., 2021). This points to the importance of IL-17 as an immunomodulation target in periodontitis immunopathogenesis.

## 4. Current and future applications of phytochemical research in periodontitis

Natural products are promising to be used because they can evade various drawbacks attributed to chemicals or synthetic drugs, especially cytotoxicity (Shukla et al., 2014). Plants have large number of phytoconstituents that could act as bioactive

agents and natural immunomodulatory drugs to interact with various cells or molecules (Behl et al., 2021; Vo et al., 2020).

Several findings indicated that variety of plants have immunomodulatory and anti-inflammatory properties (di Sotto et al., 2020; Shukla et al., 2014). These activities are exerted by phytochemicals such as glycoproteins, saponins, alkaloids, phenolics, terpenoids, polysaccharides and fatty acids contained inside (di Sotto et al., 2020). Resveratrol may reduce IL-8, TNF- α, IFN- γ, and IL-1, and increase IL-10, while *Camellia sinensis' epigallocatechin-3-gallate* inhibits ROS production and cytokine signaling (Jantan et al., 2015).

Utilization of phytochemicals in periodontal disease therapy has been emerging in recent decades. *Scrophularia striata* mouthwash was found to alleviates periodontitis symptoms through its antimicrobial, anti-inflammation and anti-oxidant activities (Kerdar et al., 2019). Indonesia's Indian jujube could inhibit *P. gingivalis* growth (Pratiwi et al., 2022). Papaya seed extract could reduce osteoclasts count in a periodontitis rat model (Pusporini et al., 2019). *Piper marginatum* Jacq. and *Ilex guayusa* have antibacterial activities against various periodontopathogens (Gamboa et al., 2018), while roselle flower petal extract was found to inhibit biofilm formation (Sebastian and Widyarman, 2021). It can be inferred that current studies have mostly uncovered the potential antimicrobial and anti-inflammatory applications, and rarely the actual mechanisms involved in immunomodulatory agency.

Despite effectivity of phytochemicals to inhibit periodontitis, its precise immunomodulatory molecular mechanisms and pathways affected are unidentified. Research on herbal medicine as periodontal therapy has mostly involved in vitro (Gamboa et al., 2018; Panjaitan et al., 2022; Pratiwi et al., 2022; Sebastian and Widyarman, 2021) or in vivo models at the tissue level (Pusporini et al., 2019), while observations on the molecular level are yet to be done. These studies also used pure extracts (Gamboa et al., 2018; Panjaitan et al., 2022; Pratiwi et al., 2022; Pusporini et al., 2019; Sebastian and Widyarman, 2021), and only did exploration on the phytoconstituents (Gamboa et al., 2018; Panjaitan et al., 2022; Pratiwi et al., 2022; Sebastian and Widyarman, 2021), without analyzing each phytochemical to see bioactivity of each on periodontitis. Molecular interactions between each phytochemical with their yet unidentified cellular interactions need to be closely observed to uncover tremendous potential of these phytochemicals.

Phytochemicals interact with biomolecules by acting as ligand between various cells and biomolecules, whether to inhibit or to induce molecular events (Malik et al., 2021; Shin et al., 2020). They interact with cells and cytokines with specific binding efficacy for each of biomolecules and phytochemicals (Bhattacharya et al., 2021). Phytochemicals could inhibit IL-6 by binding to its receptors in patients with COVID-19 to dampen inflammatory storms (Malik et al., 2021). They also affect inflammatory pathways through binding with TLR4 to inhibit its downstream events. Phytochemicals such as resveratrol, curcumin and ellagic acid were also found to enhance Nrf2 and inhibit NF-kB, AP-1, IRF5, TNF-α, IL-6, IL-1β, IL-2COX-1 (Saleh et al., 2021). These findings show that potential immunomodulation of periodontitis could also be done using a variety of these phytochemicals to regulate the balance between Treg, Th17, Th1 and Th2, along with their cytokines.

Specific phytochemicals might have a specific affinity to particular targets, thus thorough examination is needed on their binding capacity to targets that play roles in periodontitis pathogenesis. In silico studies are particularly promising to explore phytochemicals and their binding capacity. Molecular docking models are often used to predict the interactions of specific biomolecules (Pinzi and Rastelli, 2019). This approach can model phytochemicals to represent molecular events in periodontal therapy to examine binding affinity, and predict potential application of immunomodulatory therapy to specific events (França et al., 2022).

## 5. Conclusions

Periodontitis immunopathogenesis provides potential targets to be modulated in order to control destructive immune responses. These targets involve various cells, and their control would create potential effective immunomodulatory agent. Interactions of phytochemicals with immune system could potentially alter immunological events, thus leading to modulation of immune responses to periodontopathogens. Future research, especially in molecular docking, is needed to discover the ideal interactions and targets between phytochemicals and targets in periodontitis immunopathogenesis.

## Authors contribution

AS collected, analyzed and interpreted the data, and wrote the original manuscript. ALJ constructed the study design and supervised the manuscript writing. All authors have read and approved the final manuscript to be published.

## CRediT authorship contribution statement

**Andari Sarasati:** Investigation, Resources, Formal analysis, Data curation, Visualization, Writing – original draft. **Alma Linggar Jonarta:** Conceptualization, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

Behfarnia, P., Birang, R., Andalib, A.R., Asadi, S., 2010. Comparative evaluation of IFNγ, IL4 and IL17 cytokines in healthy gingiva and moderate to advanced chronic periodontitis. Dent. Res. J. 7, 45–50.

Behl, T., Kumar, K., Brisc, C., Rus, M., Nistor-Cseppento, D.C., Bustea, C., Aron, R.A.C., Pantis, C., Zengin, G., Sehgal, A., Kaur, R., Kumar, A., Arora, S., Setia, D., Chandel, D., Bungau, S., 2021. Exploring the multifocal role of phytochemicals as immunomodulators. Biomed. Pharmacother. 133, 1–18.

Bhattacharya, S., Majumdar, S., Paul, N., 2021. Efficacy of phytochemicals as immunomodulators in managing COVID-19: a comprehensive view. Virusdisease 32.

Bi, C.S., Wang, J., Qu, H.L., Li, X., Tian, B.M., Ge, S., Chen, F.M., 2019. Calcitriol suppresses lipopolysaccharide-induced alveolar bone damage in rats by regulating T helper cell subset polarization. J. Periodont. Res. 54, 612–623.

Bi, C.S., Li, X., Qu, H.L., Sun, L.J., An, Y., Hong, Y.L., Tian, B.M., Chen, F.M., 2020. Calcitriol inhibits osteoclastogenesis in an inflammatory environment by changing the proportion and function of T helper cell subsets (Th2/Th17). Cell Prolif. 53, 1–12.

Bunte, K., Beikler, T., 2019. Th17 cells and the IL-23/IL-17 axis in the pathogenesis of periodontitis and immune-mediated inflammatory diseases. Int. J. Mol. Sci. 20, 1–24.

Cafferata, E.A., Terraza-Aguirre, C., Barrera, R., Faúndez, N., González, N., Rojas, C., Melgar-Rodríguez, S., Hernández, M., Carvajal, P., Cortez, C., González, F.E., Covarrubias, C., Vernal, R., 2020. Interleukin-35 inhibits alveolar bone resorption by modulating the Th17/Treg imbalance during periodontitis. J. Clin. Periodontol. 47, 676–688.

Chung, J., Kim, S., Lee, H.A., Park, M.H., Kim, S., Song, Y.R., Na, H.S., 2018. Trans-cinnamic aldehyde inhibits Aggregatibacter actinomycetemcomitans-induced inflammation in THP-1–derived macrophages via autophagy activation. J. Periodontol. 89, 1262–1271.

Demoersman, J., Pochard, P., Framery, C., Simon, Q., Boisramé, S., Soueidan, A., Pers, J.O., 2018. B cell subset distribution is altered in patients with severe periodontitis. PLoS One 13, 1–14.

di Sotto, A., Vitalone, A., di Giacomo, S., 2020. Plant-derived nutraceuticals and immune system modulation: An evidence-based overview. Vaccines 8, 1–34.

Figueredo, C.M., Lira-Junior, R., Love, R.M., 2019. T and B cells in periodontal disease: New functions in a complex scenario. Int. J. Mol. Sci. 20, 1–13.

França, A.L. de Q., Chaves, H. v., Freire, J.M. de O., de Sousa, L.H. T., Pimenta, A.T.A., Lima, M.A.S., de Oliveira, B.R., de Mattos, M.C., Pinto, V. de P.T., Portela, A.M.L.R., Pereira, K.M.A., Costa, J.J. do N., Goes, P., Jorge, R.J.B., Silveira, J.A. de M., Braz, H.L.B., de Moraes, M.E.A., Bezerra, M.M., 2022. Molecular docking study and antireabsorptive activity of a semi-synthetic coumarin derivative from Platymiscium floribundum in the ligature-induced periodontitis in rats: the involvement of heme oxygenase-1. Clin Oral Investig. 26, 1701–1711.

Gamboa, F., Muñoz, C.C., Numpaque, G., Sequeda-Castañeda, L.G., Gutierrez, S.J., Tellez, N., 2018. Antimicrobial activity of piper marginatum jacq and ilex guayusa loes on microorganisms associated with periodontal disease. Int. J. Microbiol. 2018, 1–9.

Gao, L., Kang, M., Zhang, M.J., Reza Sailani, M., Kuraji, R., Martinez, A., Ye, C., Kamarajan, P., Le, C., Zhan, L., Rangé, H., Ho, S.P., Kapila, Y.L., 2020. Polymicrobial periodontal disease triggers a wide radius of effect and unique virome. npj Biofilms Microbiomes 6, 1–13.

González, J.F., Hahn, M.M., Gunn, J.S., 2018. Chronic biofilm-based infections: Skewing of the immune response. Pathog Dis. 76, 1–7.

Hajishengallis, G., 2015. Periodontitis: From microbial immune subversion to systemic inflammation. Nat. Rev. Immunol. 15, 30–44.

Hajishengallis, G., 2020. New developments in neutrophil biology and periodontitis. Periodontol. 2000 (82), 78–92.

Huang, N., Dong, H., Luo, Y., Shao, B., 2021. Th17 cells in periodontitis and its regulation by A20. Front. Immunol. 12, 1–18.

Huang, N., Gibson, F.C., 2014. Immuno-pathogenesis of periodontal disease: Current and emerging paradigms. Curr. Oral Health Rep. 1, 124–132.

Issaranggun Na Ayuthaya, B., Everts, V., Pavasant, P., 2018. The immunopathogenic and immunomodulatory effects of interleukin-12 in periodontal disease. Eur J Oral Sci. 126, 75–83.

Jantan, I., Ahmad, W., Bukhari, S.N.A., 2015. Plant-derived immunomodulators: An insight on their preclinical evaluation and clinical trials. Front. Plant Sci. 6, 1–18.

Kawai, T., Matsuyama, T., Hosokawa, Y., Makihira, S., Seki, M., Karimbux, N.Y., Goncalves, R.B., Valverde, P., Dibart, S., Li, Y. P., Miranda, L.A., Ernst, C.W.O., Izumi, Y., Taubman, M.A., 2006. B and T lymphocytes are the primary sources of RANKL in the bone resorptive lesion of periodontal disease. Am. J. Pathol. 169, 987–998.

Kayar, N.A., Çelik, İ., Alptekin, N.Ö., 2020. Immune responses in women with periodontitis and preterm low birth weight: Levels of CD4 + and CD8 + T cells in gingival granulation tissue. Arch. Oral Biol. 109, 1–7.

Kerdar, T., Rabienejad, N., Alikhani, Y., Moradkhani, S., Dastan, D., 2019. Clinical, in vitro and phytochemical, studies of Scrophularia striata mouthwash on chronic periodontitis disease. J. Ethnopharmacol. 239, 1–7.

Könönen, E., Gursoy, M., Gursoy, U.K., 2019. Periodontitis: A multifaceted disease of tooth-supporting tissues. J. Clin. Med. 8, 1–12.

Kozak, M., Dabrowska-Zamojcin, E., Mazurek-Mochol, M., Pawlik, A., 2020. Cytokines and their genetic polymorphisms related to periodontal disease. J. Clin. Med. 9, 1–20.

Liao, M.T., Wu, C.C., Wu, S.F.V., Lee, M.C., Hu, W.C., Tsai, K.W., Yang, C.H., Lu, C.L., Chiu, S.K., Lu, K.C., 2021. Resveratrol as an adjunctive therapy for excessive oxidative stress in aging covid-19 patients. Antioxidants 10, 1–33.

Listl, S., Galloway, J., Mossey, P.A., Marcenes, W., 2015. Global economic impact of dental diseases. J. Dent. Res. 94, 1355–1361.

Liu, O., Xu, J., Ding, G., Liu, D., Fan, Z., Zhang, C., Chen, W., Ding, Y., Tang, Z., Wang, S., 2013. Periodontal ligament stem cells regulate B lymphocyte function via programmed cell death protein 1. Stem Cells 31, 1371–1382.

Makkawi, H., Hoch, S., Burns, E., Hosur, K., Hajishengallis, G., Kirschning, C.J., Nussbaum, G., 2017. Porphyromonas gingivalis stimulates TLR2-PI3K signaling to escape immune clearance and induce bone resorption independently of MyD88. Front. Cell. Infect. Microbiol. 7, 1–12.

Malik, A., Naz, A., Ahmad, S., Hafeez, M., Awan, F.M., Jafar, T.H., Zahid, A., Ikram, A., Rauff, B., Hassan, M., 2021. Inhibitory potential of phytochemicals on interleukin-6-mediated T-cell reduction in COVID-19 patients: A computational approach. Bioinf. Biol. Insights 15, 1–9.

Meghil, M.M., Hutchens, L., Raed, A., Multani, N.A., Rajendran, M., Zhu, H., Looney, S., Elashiry, M., Arce, R.M., Peacock, M.E., Dong, Y., Cutler, C.W., 2019. The influence of vitamin D supplementation on local and systemic inflammatory markers in periodontitis patients: A pilot study. Oral Dis. 25, 1403–1413.

Metzemaekers, M., Gouwy, M., Proost, P., 2020. Neutrophil chemoattractant receptors in health and disease: double-edged swords. Cell. Mol. Immunol. 17, 433–450.

Mi, W., Qiao, S., Zhang, X., Wu, D., Zhou, L., Lai, H., 2021. PRMT5 inhibition modulates murine dendritic cells activation by inhibiting the metabolism switch: a new therapeutic target in periodontitis. Ann Transl Med. 9, 755–755.

Okui, T., Aoki-Nonaka, Y., Nakajima, T., Yamazaki, K., 2014. The role of distinct T cell subsets in periodontitis—Studies from humans and rodent models. Curr. Oral Health Rep. 1, 114–123.

Ono, T., Hayashi, M., Sasaki, F., Nakashima, T., 2020. RANKL biology: Bone metabolism, the immune system, and beyond. Inflamm. Regen. 40, 1–16.

P, H., R, S., B, S. begum, Dimple, N., Na, V.K.B., KS, S., 2018. Microbiological Profile of Chronic and Aggressive Periodontitis-A Review. J Sci Dent. 8, 41–46.

Pan, W., Wang, Q., Chen, Q., 2019. The cytokine network involved in the host immune response to periodontitis. Int. J. Oral Sci. 11, 1–13.

Panjaitan, C.C., Widyarman, A.S., Amtha, R., Astoeti, T.E., 2022. Antimicrobial and antibiofilm activity of cinnamon (Cinnamomum burmanii) extract on periodontal pathogens-An in vitro study. Eur. J. Dent. 16, 938–946.

Pinzi, L., Rastelli, G., 2019. Molecular docking: Shifting paradigms in drug discovery. Int. J. Mol. Sci. 20, 1–23.

Pratiwi, G.Y., Mandalas, H.Y., Sugiaman, V.K., 2022. The effect of Indian jujube leaves extract in inhibiting the growth of Porphyromonas gingivalis. Padjadjaran J. Dent. 34, 57.

Pusporini, R., Basori, A., Krismariono, A., 2019. Anti-inflammatory role of papaya seed extracts in inhibiting osteoclastogenesis of rats with periodontitis. Majalah Kedokteran Gigi Indonesia 4, 95–101.

Quach, S.S., Zhu, A., Lee, R.S.B., Seymour, G.J., 2022. Immunomodulation—What to modulate and why? Potential immune targets. Front. Dent. Med. 3, 1–15.

Rajendran, M., Looney, S., Singh, N., Elashiry, M., Meghil, M.M., El-Awady, A.R., Tawfik, O., Susin, C., Arce, R.M., Cutler, C.W., 2019. Systemic antibiotic therapy reduces circulating inflammatory dendritic cells and Treg–Th17 plasticity in periodontitis. J. Immunol. 202, 2690–2699.

Ramadan, D.E., Hariyani, N., Indrawati, R., Ridwan, R.D., Diyatri, I., 2020. Cytokines and chemokines in periodontitis. Eur. J. Dent. 14, 483–495.

Sadeghi, R., Sattari, M., Dehghan, F., Akbari, S., 2018. Interleukin-17 and interleukin-23 levels in gingival crevicular fluid of patients with chronic and aggressive periodontitis. Cent. Eur. J. Immunol. 43, 76–80.

Saleh, H.A., Yousef, M.H., Abdelnaser, A., 2021. The anti-inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF-κB-mediated inflammation. Front. Immunol. 12, 1–29.

Scott, D.A., Krauss, J.L., 2012. Neutrophils in periodontal inflammation. Front. Oral Biol. 15, 56–83.

Sebastian, J., Widyarman, A.S., 2021. Roselle flower petals extract inhibits periodontal pathogenic biofilms. J. Dentomaxillofac. Sci. 6, 102–105.

Sell, A.M., Alencar, J.B. de, Visentainer, J.E.L., Silva, C. de O. e, 2017. Immunopathogenesis of Chronic Periodontitis, in: Periodontitis - A Useful Reference. InTech, pp. 143–161.

Shin, S.A., Joo, B.J., Lee, J.S., Ryu, G., Han, M., Kim, W.Y., Park, H. H., Lee, J.H., Lee, C.S., 2020. Phytochemicals as anti-inflammatory agents in animal models of prevalent inflammatory diseases. Molecules 25, 1–27.

Shukla, S., Bajpai, V.K., Kim, M., 2014. Plants as potential sources of natural immunomodulators. Rev. Environ. Sci. Biotechnol. 13, 17–33.

Son, H.S., Lee, J., Lee, H.I., Kim, N., Jo, Y.J., Lee, G.R., Hong, S.E., Kwon, M., Kim, N.Y., Kim, H.J., Park, J.H., Lee, S.Y., Jeong, W., 2020. Benzydamine inhibits osteoclast differentiation and bone resorption via down-regulation of interleukin-1β expression. Acta Pharm. Sin. B 10, 462–474.

Song, L., Dong, G., Guo, L., Graves, D.T., 2018. The function of dendritic cells in modulating the host response. Mol. Oral Microbiol. 33, 13–21.

Song, B., Zhang, Y.L., Chen, L.J., Zhou, T., Huang, W.K., Zhou, X., Shao, L.Q., 2017. The role of toll-like receptors in periodontitis. Oral Dis. 23, 168–180.

Vo, T.T.T., Chu, P.M., Tuan, V.P., Te, J.S.L., Lee, I.T., 2020. The promising role of antioxidant phytochemicals in the prevention and treatment of periodontal disease via the inhibition of oxidative stress pathways: Updated insights. Antioxidants 9, 1–28.

Wallet, S.M., Puri, V., Gibson, F.C., 2018. Linkage of infection to adverse systemic complications: Periodontal disease, toll-like receptors, and other pattern recognition systems. Vaccines 6, 1–27.

Wang, Y., Andrukhov, O., Rausch-Fan, X., 2017. Oxidative stress and antioxidant system in periodontitis. Front. Physiol. 8, 1–13.

Wilensky, A., Segev, H., Mizraji, G., Shaul, Y., Capucha, T., Shacham, M., Hovav, A.H., 2014. Dendritic cells and their role in periodontal disease. Oral Dis. 20, 119–126.

Yamazaki, K., Ohsawa, Y., Tabeta, K., Ito, H., Ueki, K., Oda, T., Yoshie, H., Seymour, G.J., 2002. Accumulation of human heat shock protein 60-reactive T cells in the gingival tissues of periodontitis patients. Infect. Immun. 70, 2492–2501.

Yang, B., Pang, X., Li, Z., Chen, Z., Wang, Y., 2021. Immunomodulation in the treatment of periodontitis: Progress and perspectives. Front. Immunol. 12, 1–20.

Yende, S.R., Shah, S.K., Arora, S.K., Moharir, K.S., Lohiya, G.K., 2021. In silico prediction of phytoconstituents from Ehretia laevis targeting TNF-α in arthritis. Digital Chinese Med. 4, 180–190.

Zague, V., do Amaral, J.B., Rezende Teixeira, P., de Oliveira Niero, E. L., Lauand, C., Machado-Santelli, G.M., 2018. Collagen peptides modulate the metabolism of extracellular matrix by human dermal fibroblasts derived from sun-protected and sun-exposed body sites. Cell Biol Int. 42, 95–104.

Zhang, L., Deng, S., 2019. Effects of astragaloside IV on inflammation and immunity in rats with experimental periodontitis. Braz. Oral Res. 33, 1–8.

Zhou, Y., Zhang, H., Zhang, G., He, Y., Zhang, P., Sun, Z., Gao, Y., Tan, Y., 2018. Calcitonin gene-related peptide reduces Porphyromonas gingivalis LPS-induced TNF-α release and apoptosis in osteoblasts. Mol. Med. Rep. 17, 3246–3254.

Zhu, X., Huang, H., Zhao, L., 2022. PAMPs and DAMPs as the bridge between periodontitis and atherosclerosis: The POTENTIAL THERAPEUTIC TARGETS. Front. Cell Dev. Biol. 10, 1–12.

Zidar, A., Kristl, J., Kocbek, P., Zupančič, Š., 2021. Treatment challenges and delivery systems in immunomodulation and probiotic therapies for periodontitis. Expert Opin. Drug Deliv. 18, 1229–1244.