SCIENTIFIC Publishing Limited

Trends in Immunotherapy

https://ojs.ukscip.com/index.php/ti

Review

Targeting TLR2/TLR4 Pathways in Periodontitis: Molecular Insights and Emerging Aptamer-Based Therapeutic Strategies

Muhammad Aiman Bin Azizul [1], Yun Han Ng [1], Nydia Lynn Yong Shu Thiin [1], Nur Alia Binti Othman [2] and Fong Fong Liew [1,3,*]

[1] Faculty of Dentistry, MAHSA University, Jalan SP 2, Bandar Saujana Putra, Jenjarom 42610, Malaysia; bdds20106328@mahsastudent.edu.my (M.A.B.A.); bdds20106014@mahsastudent.edu.my (Y.H.N.); bdds20106207@mahsastudent.edu.my (N.L.Y.S.T.)

[2] Research Management Centre, MAHSA University, Jalan SP 2, Bandar Saujana Putra, Jenjarom 42610, Malaysia; nurlia.o@mahsa.edu.my

[3] Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur 50603, Malaysia

[*] Correspondence: ffliew@um.edu.my

Received: 18 May 2026; **Revised:** 8 June 2026; **Accepted:** 4 August 2026; **Published:** 20 August 2026

Abstract: Periodontitis is a chronic inflammatory disease of the gingival and periodontal tissues, primarily initiated by bacterial accumulation and driven by an excessive host immune response. This persistent inflammatory condition promotes periodontal tissue degradation through the activation of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) signalling pathways, leading to the production of pro-inflammatory mediators, including interleukin-6, interleukin-8 and tumour necrosis factor-alpha. These mediators alter the local inflammatory microenvironment, perpetuate immune activation and contribute to progressive periodontal tissue destruction. This review summarises the roles of TLR2- and TLR4-associated genes, proteins and microRNAs in the pathogenesis of periodontitis, based on reported research findings, STRING protein–protein interaction network analysis, GO/Reactome enrichment analysis and profiling. The study also explores the potential roles of antibodies and aptamers in suppressing inflammation and promoting wound healing. Although antibodies exhibit high target specificity, their complex manufacturing processes, higher costs and potential immunogenicity may limit their clinical applicability compared with aptamers. Aptamers, in contrast, are relatively stable, cost-effective and generally non-immunogenic, making them promising molecular tools for targeted therapeutic intervention. Based on the reviewed findings, aptamers may be further explored as potential therapeutic agents for regulating intracellular signalling pathways associated with TLR2- and TLR4-mediated inflammation. Overall, this review highlights the relationship between molecular mechanisms and therapeutic innovation in periodontitis, particularly through TLR2- and TLR4-associated pathways. It also emphasises the relevance of molecular network analysis, computer-assisted simulation technologies and precision medicine approaches in advancing therapeutic strategies for chronic inflammatory disorders.

Keywords: Periodontitis; Inflammation; TLR2; TLR4; Antibody; Aptamer

1. Introduction

The periodontium, which includes the gums, periodontal ligament and alveolar bone, can deteriorate as a result of periodontitis (PD), a chronic inflammatory disease [1,2]. It is a risk factor for conditions affecting multiple organ systems, highlighting the importance of integrating oral health into medical care and professional training [3,4]. This illness results from an abnormal inflammatory response to microbial build-up, leading to ongoing tissue destruction and bone resorption. In the initial phase of the disease, bacteria form biofilms on the gums, also referred to as dental plaque, which may lead to gingivitis. Without early treatment, inflammation spreads deeper into the tissues that hold the teeth in place and progresses to periodontitis [5,6]. The immune response becomes persistent and uncontrolled due to prolonged exposure to pathogens. It is essential to determine the involvement of macrophages in periodontitis and the possibility of using biomaterials to regulate the polarisation of macrophages as a new treatment option for periodontal regeneration while addressing the associated challenges and opportunities [7].

Toll-like receptors (TLRs) are important mediators expressed on the cell surface, particularly TLR2 and TLR4. These receptors stimulate the signalling pathways of NF-κB and MAPK signalling pathways by detecting and responding to structural microbial components, including lipopolysaccharides (LPS) and bacterial lipoproteins, which in turn encourage the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α) [8,9]. While TLR activation is necessary to eliminate pathogens, continuous and excessive activation can lead to uncontrolled inflammation and progressive destruction of periodontal tissue. This allows the cell to adapt its response depending on the nature of the threat it faces by utilising different MyD88-dependent and TRIF-dependent pathways. Because of this dynamic and flexible system, the immune response can be accurately regulated. However, overactivation of these mechanisms makes them difficult to suppress [10,11].

A complete understanding of the downstream gene, protein and microRNA (miRNA) networks that coordinate these pathways is still lacking, even though evidence regarding the relationship between TLR2/TLR4 signalling and periodontal inflammation is quite extensive [12]. Furthermore, more precise, dependable and cost-effective treatment platforms that can specifically regulate TLR-mediated inflammation are needed, although several immunomodulatory strategies have been examined [13].

The objective of this paper is to identify and analyse the TLR2- and TLR4-related genes, proteins and miRNAs that contribute to periodontitis. Additionally, the regulatory processes leading to chronic inflammation were assessed, and the effectiveness of antibodies and aptamers as therapeutic and diagnostic agents was compared. By utilising molecular network analysis with novel biomolecule strategies, the present work fills a major gap in periodontal therapy. The current study lays the groundwork for future computer simulations and precision medicine approaches that may also be important for other chronic inflammatory diseases.

2. Protein and Genes Associated with TLR2/4 Signalling Pathway

A literature review was conducted using PubMed and Google Scholar to identify relevant studies published between 2014 and 2024. The main search terms included "TLR2", "TLR4" and "*P. gingivalis*". The search was performed according to predefined inclusion and exclusion criteria. Studies were included if they examined TLR2 and/or TLR4 activation and downstream gene or protein expression related to periodontitis. Eligible studies included *in vitro* and *in vivo* investigations involving experimental induction or modulation of TLR2/TLR4 signalling in cellular or animal models. Studies without mechanistic analysis, clinical studies lacking cellular or molecular components and review articles were excluded.

The study selection process is summarised in the PRISMA flow diagram. A total of 934 records were identified from PubMed and Google Scholar. After duplicate removal, 922 records were screened by title and abstract. Of these, 866 records were excluded because they did not meet the inclusion criteria. The remaining 56 full-text articles were assessed for eligibility. Eleven full-text articles were excluded because they lacked cell–molecular mechanisms, investigated alternative pathways, or focused on proteins and genes without examining their involvement in TLR2/TLR4-mediated signalling, as shown in **Figure 1**. Three reviewers independently assessed each included study. Any disagreements were resolved through discussion and consensus among the reviewers. The PRISMA 2020 checklist (**Supplementary Materials**) was also completed to support transparent reporting of the

study selection process.

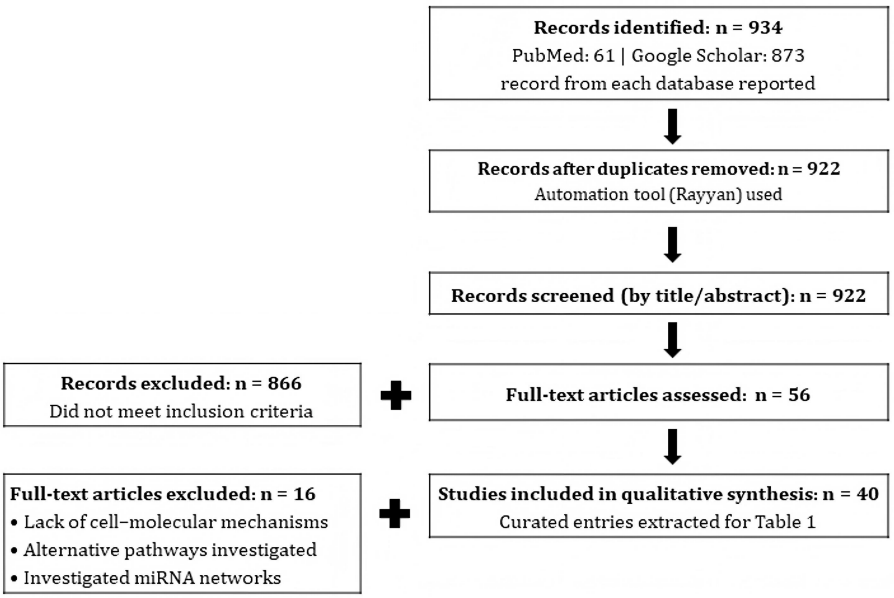


Figure 1. PRISMA flow diagram. A total of 934 records were identified from PubMed and Google Scholar between 2014 and 2024.

Protein and gene information from research articles was extracted from eligible studies, including TLR2 or TLR4 activation, receptor expression, downstream genes and proteins and the absence or suppression of specific molecules. Experimental details such as cell source, bacterial strain, stimulation duration and diagnostic methods, including qPCR, Western blotting, ELISA and RNA sequencing, were reviewed. The identified TLR2- and TLR4-associated genes and proteins were then standardised according to official gene symbols before downstream computational analysis.

Protein–protein interaction analysis was conducted using the STRING database (https://string-db.org/). The organism was set to *Homo sapiens* and the interaction network was constructed using a medium confidence interaction score threshold of 0.400. The network type was designated as a full STRING network. Active interaction sources included experiments, curated databases, co-expression, gene neighbourhood, gene fusion, gene co-occurrence, text mining and protein homology. Disconnected nodes were retained to preserve all reported targets. Functional enrichment analysis was performed in STRING using Gene Ontology categories, including biological process, molecular function and cellular component, together with Reactome pathway enrichment. Enriched terms were considered significant when the false discovery rate (FDR) was less than 0.05.

This section discusses the genes and proteins involved in TLR2- and TLR4-mediated periodontitis, with emphasis on their inflammatory mechanisms and potential relevance as therapeutic targets. In this context, activation of TLR2 and TLR4 initiates several downstream signalling cascades, including the NF-κB, MAPK and PI3K/Akt pathways [14–16]. This signalling leads to an increase in TNF-α, IL-1β, IL-6 and IL-8, which, through the RANKL–RANK–OPG pathway, lead to tissue damage and bone loss [17,18].

Beyond causing inflammation, TLR signalling modulates cellular immune cell differentiation, blood vessel formation and tolerance to repeated exposures to bacteria, through the MyD88- and TRIF-dependent pathways and IRAK-M, Lyn kinase and IRF3 regulators [14,19–22]. TLR2 and TLR4 are vital in disease progression and are effective therapeutic targets; examples of new therapeutic modalities, such as aptamers, are currently being considered as stable and cost-effective alternatives to antibodies for therapeutic intervention [23–25].

Recent studies, as illustrated in **Table 1**, further emphasise the complex effects of *P. gingivalis* on both local and systemic immunity. TLR4-dependent signalling enhances bone loss through elevated RANKL expression, whereas ligature-induced bone resorption occurs independently of TLR2/TLR4 [26]. Extracellular vesicles from periodontal pathogens also promote osteoclastogenesis by increasing osteoclast markers such as TRAP and cathepsin K [27].

P. gingivalis LPS and RagB protein activate TLR2/TLR4 and downstream NF-κB/MAPK pathways, inducing strong cytokine responses (IL-1β, IL-6, IL-8, TNF-α and VEGF) that drive tissue destruction and angiogenesis [19,28–30]. Repeated stimulation, however, can induce immune tolerance in macrophages, reducing pro-inflammatory cytokine production [21]. In addition to direct inflammatory bone loss, bone-cell safety and bone remodelling responses should also be considered during therapeutic development, as some drugs may affect bone cells, bone density and fracture risk [31]. At the osteocyte level, disruption of β2-spectrin (Sptbn1), a cytoskeleton-associated protein, has been shown to increase osteocyte membrane fragility and promote larger, slower-repairing plasma membrane disruptions under mechanical stress. These changes reduce osteocyte survival, mildly alter calcium signalling and impair bone adaptation to loading in mice [32].

Table 1. Overview of TLR2/TLR4-driven immune mechanisms in periodontal disease.

No.	Protein	Gene	Function	Ref.
1	• RANKL	• *TNFSF11* • *Il1b* • *Il10* • *Tnf*	TLR4 contributes to bone loss induced by *P. gingivalis* infection but not to ligature-induced bone loss, indicating different mechanisms. *P. gingivalis* infection increases RANKL expression, promoting osteoclast-mediated resorption. Differences in IL-1β, TNF-α and IL-10 between models reflect distinct immune profiles.	Lin et al. [26]
2	• TLR2 • TLR4 • TNF-α • IL-1β • IL-10	Not reported	Repeated *P. gingivalis* exposure induces macrophage immune tolerance, lowering TNF-α and IL-1β. This may regulate excessive periodontal inflammation.	Lu et al. [21]
3	• TLR2 • TLR4 • MCP-1 • TNF-α • IL-6 • NF-κB (ACP-1 activity) • SEAP • MD-2 • CD14	Without direct gene expression measurement	This paper shows that ultrapure *P. gingivalis* LPS activates inflammatory signalling through TLR4, not TLR2. The study also found a clear species difference: human TLR4 and human whole-blood cells responded strongly to *P. gingivalis* LPS, whereas mouse TLR4, mouse cell lines and mice showed only weak cytokine responses. The main cytokines assessed were TNF-α, IL-6 and MCP-1, and their secretion was much lower in mouse models than in human cells.	Nativel et al. [15]
4	• VEGF-A • IL-6 • p-FAK (Y397) • FAK	Not reported	*Porphyromonas endodontalis* and *P. gingivalis* LPS mediate angiogenesis in endothelial cells through TLR2 and TLR4. Cell migration and tube formation in response to *P. endodontalis* LPS, which is a strong agonist of both receptors. VEGF-A synthesis is also independent of TLR2 or TLR4 via these LPS, which raises IL-6 production by TLR2/TLR4, also indicating a dual mode of angiogenic activation and the importance of TLR-mediated and non-TLR2-TLR4 pathways in vascular responses in relation to periodontitis and apical periodontitis.	Fernández et al. [19]
5	• IL-17A • IFN-γ • TNF-α • IL-1β • IL-6 • IL-23 • IL-10 • IL-12p70 • TLR2 • TLR4 • CD40 • CD54 (ICAM-1) • CD86 • HKA-DR/MHC class II	Not reported	*P. gingivalis* and *A. actinomycetemcomitans* are able to activate human $CD14^+$ monocytes through TLR2 and TLR4 and induce high levels of IL-1β, IL-6 and TNF-α. These cytokines promote the differentiation and expansion of Th17 by the activation of RORγt and STAT3, which leads to the production of high levels of IL-17. This Th17 development induced by monocytes describes one of the major pathways by which periodontal pathogens are associated with increased inflammation and progression of periodontitis.	Cheng et al. [33]
6	• TNF-α • IL-6 • IL-1β • G-CSF • IL-1Ra • IP-10 • KC • MIP-1α • MIP-1β • MIP-2 • RANTES • SICAM-1 • CD25 • SEAP • TRAP	Not reported	*P. gingivalis* extracellular vesicles can promote inflammatory bone loss by stimulating osteoclast differentiation mainly through TLR2 activation. Their lipoproteins and LPS appear to be the major components responsible for this effect.	Kim et al. [27]

Table 1. *Cont.*

No.	Protein	Gene	Function	Ref.
7	• IL-10 • CD5 • CD93 • IgM	• *IL10* • *CD5* • *CD93* • *IGHM*	*P. gingivalis* LPS enhances the development of regulatory B cells (Bregs) which secrete IL-10 through TLR2 and TLR4 pathways. Upon stimulation, TLR2/TLR4 signalling via MyD88 and TRIF adaptors activates NF-κB and IRF3, regulating key transcription factors (BCL6, BLIMP-1, PAX5) to drive B cell differentiation (involving markers like CD19 and CD138). In particular, it is demonstrated that, upon stimulation with Pg-LPS, $CD5^+$ / IgM^+ / $CD93^-$ B cells are the predominant subpopulation, which enhances IL-10 production, which is tied to the presence of TLR2 and TLR4.	Liu et al. [20]
8	Not applicable	• *TLR2* • *TLR4* • *IL6* • *IL10* • *IL18*	*P. gingivalis* LPS produces a strong but time-dependent inflammatory response in human dental pulp stem cells, mainly through TLR4. Its effect is more inflammatory during the first 24 hours, but prolonged exposure may promote anti-inflammatory regulation through increased IL-10 and reduced TLR4 and IL-18 expression.	Mojtahedi et al. [34]
9	• Ki-67 • AKT	• *TNF* • *TGF-β* • *MMP2* • *MMP9* • *IL1β* • *IL6* • *IL10* • *TET1* • *TET2* • *TET3* • *DNMT1* • *DNMT3A* • *DNMT3B*	Brain microvascular endothelial cells respond to LPS of *P. gingivalis* through the TLR2 and TLR4 receptors. This activates NF-κB and MAPK signalling and drastically upregulates IL-6 and CCL2. These results suggest that periodontal LPS may be involved in neuroinflammation and blood–brain barrier dysfunction.	Sato et al. [35]
10	• OPN • CD90 • CD166 • CD39 • CD44 • CD73 • CD105 • CD146 • PDGFR • SSEA-4 • STRO-1 • NG2 • CD34 • CD45 • CD14 • IL-6 • IL-8 • OCN • ALP	• *TLR2* • *TLR3* • *TLR4* • *CCL2* • *CXCL1* • *CCL5* • *IDO1* • *CXCL10* • *CXCL12* • *TGFB1* • *LAP* • *HIF1A* • *HGF* • *IGFBP4* • *TNFRSF11B* • *MMP3* • *TIMP1* • *IGFBP4* • *SPP1* • *COL1A1* • *RUNX2* • *BMP2* • *IL6* • *CXCL8* • *BGLAP*	Gingival mesenchymal stromal cells (GMSCs) derived from periodontitis-affected gingiva (P-GMSCs) show higher basal and *P. gingivalis*-induced expression of TLR2 and pro-inflammatory cytokines/chemokines (IL-6, IL-8, MCP-1, GRO-α and RANTES) compared with healthy GMSCs. These P-GMSCs also have reduced immunosuppressive capacity, suggesting that chronic inflammation reprograms their immunomodulatory behaviour.	Bekić et al. [36]
11	• FGF23 • ACE2 • Podoplanin • Mac-1 • VCAM-1 • E-selectin (CD62E)	Not reported	*P. gingivalis* LPS administration in diabetic mice increases expression of leukocyte adhesion molecules, FGF23 and ACE2 in the kidney, suggesting that Pg-LPS contributes to renal inflammation and may exacerbate diabetic nephropathy.	Kajiwara et al. [37]
12	• p-p38 • pPKC • IκB-β • IL-6 • IL-8 • F2R • F2RL1	• *CXCL8* • *IL6* • *PAR1* • *PAR2* • *TLR2* • *TLR4*	*P. gingivalis* activates TLR2/TLR4 and PAR-1/PAR-2 in gingival fibroblasts, driving NF-κB/MAPK signalling and cytokine production (IL-6, IL-8 and TNF-α). Coordinated TLR–PAR signalling contributes to tissue destruction in periodontitis.	Palm et al. [28]

Table 1. *Cont.*

No.	Protein	Gene	Function	Ref.
13	• TLR2 • TLR4 • MyD88 • TRIF • TRAM • MAL • SARM • SOCS-1 • TNF-α	• *TLR2* • *TLR4* • *MYD88* • *TICAM1* • *TICAM2* • *TIRAP* • *SARM* • *TNF* • *IL6*	*P. gingivalis* activates two types of signalling pathways through TLR2/TLR4: MyD88-dependent and TRIF-dependent. This double signalling triggers specific TIR-domain adaptors, such as TIRAP and TRAM, which subsequently activate downstream IRAKs, NF-κB and MAPKs. This cascade leads to swift and delayed inflammatory cytokine responses, which demonstrate intricate interactions involving the innate immune system in periodontal inflammation.	Bugueno et al. [14]
14	• IL-8 • IL-6 • IFN-γ • TNF-α • IL-12p70 • IL-10 • STAT4 • p-STAT4 • p-p65 • TLR2 • TLR4 • NF-κB p65	• *IL1A* • *IL1B* • *IL6* • *IL8* • *CCL2* • *CCL20* • *IL12B* • *TNF* • *STAT4*	TLR2/TLR4 is triggered by the RagB protein of *P. gingivalis* leading to IL-12 and downstream STAT4 activation, resulting in the amplification of NF-κB/MAPK-driven cytokine production. RagB is therefore a strong periodontal inflammatory agent.	Hutcherson et al. [29]
15	• NF-κB • IL-6 • IL-8	• *IL6* • *IL8*	*P. gingivalis* has an impact on respiratory epithelial cells. The interaction between the pathogen and TLR2 stimulates NF-kB and MAPK signalling cascades leading to the production of pro-inflammatory cytokines, including IL-1b, IL-6 and TNF-α. It is an indication that *P. gingivalis* is involved in respiratory tract inflammation.	Watanabe et al. [30]
16	• LOX-1 • RANK • FDPS • TRAP	• *OLR1* • *TNFRSF11A* • *MYD88*	TLR2 activation increases LOX-1 expression and primes osteoclast precursors, enhancing RANKL-induced differentiation through NF-κB/MAPK/TRAF6 signalling. This TLR2–LOX-1 axis links periodontal inflammation to osteoclast overactivation.	Ohgi et al. [38]
17	• TLR2 • TLR4 • FcγRIIB • FcγRIII • TRAP (ACP5) • CD68 • CD80 • CD163 • CD206	• *ACP5* • *CTSK* • *CCL17* • *CCL22* • *CXCL10* • *CXCL11* • *FCGR2B* • *FCGR3* • *FCER1G* • *FCRG* • *KLF4* • *MRC1* • *NFATC1* • *TNFRSF11A* • *TLR1* • *TLR2* • *TLR4*	Opsonised *P. gingivalis* triggers Fcγ receptors and then regulates TLR2/TLR4 and NF-κB signalling. This crosstalk not only causes an increase in the production of pro-inflammatory cytokines (such as IL-1β, IL-6 and TNF-α), but also changes the balance of the RANK-RANKL-OPG axis with a marked increase in OPG production. Thus, antibody opsonisation appears to protect from periodontal bone loss by decreasing the osteoclastogenesis induced by RANKL.	Pandruvada et al. [18]
18	• TLR2 • TLR4 • TNF-α • HMGB1 • MyD88 • MPO • p38 MAPK • p-p38 MAPK • NF- κB p65 • P-NF-κB p65 • IL-1β	• *TLR2* • *TLR4* • *TNF*	*P. gingivalis*–induced periodontitis activates the TLR2/TLR4–MyD88–p38 MAPK–NF-κB inflammatory pathway, leading to increased inflammatory mediators, gingival inflammation and alveolar bone loss. Baicalin suppresses TLR2/TLR4 expression and downstream inflammatory signalling, demonstrating therapeutic potential for reducing periodontitis-associated inflammation.	Sun et al. [39]
19	• TLR2 • TLR4 • IL-8 • IL-10	No direct gene-expression measurements	*Lactobacillus rhamnosus* restores TLR2/TLR4–mediated NF-κB signalling to reverse the *P. gingivalis*–mediated suppression of CXCL8 (IL-8) expression. This restoration also restores equilibrium in the release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) with the recruitment of neutrophils and periodontal defense by CXCL8, thus offering the basis for the use of probiotics in these areas.	Mendi et al. [40]
20	• TRAP • TNF-α • ALP	• *TLR2* • *TLR4* • *TNF* • *NFATC1* • *ACP5* • *RUNX2* • *ALPL* • *SPARC*	Chronic TLR2/TLR4 activation reduces RANKL and enhances OPG expression, suppressing osteoclastogenesis without affecting osteogenesis markers (RUNX2, ALP). Persistent TLR signalling may thus limit bone loss while sparing regeneration.	Karlis et al. [41]

Table 1. *Cont.*

No.	Protein	Gene	Function	Ref.
21	• IL-2 • IL-10 • IL-12 • IL-13 • IFN-ɣ • CD11c • MHC Class II • CD80 • CD86 • CD40	Not reported	*P. gingivalis* LPS promotes dendritic-cell maturation and antigen presentation, but it tends to drive a Th2-biased immune response through TLR2. In contrast, *E. coli* LPS promotes a stronger Th1-biased response mainly through TLR4.	Su et al. [42]
22	• TNF-α • VEGF • MCP-1	• *TNF* • *VEGFA* • *CCL2*	*P. gingivalis* LPS activated human mast cells to increase the gene expression and protein release of TNF, VEGF and MCP-1 without causing significant degranulation. TNF production was mainly mediated through TLR2, whereas VEGF production involved both TLR2 and TLR4; MCP-1 release appeared independent of these receptors.	Palaska et al. [43]
23	• TLR2 • TLR4 • CD14 • IL-1β • IL-6 • NF-$_{\kappa}$B p65 • p- NF-$_{\kappa}$B p65 • p-STAT3 • STAT3 • TNF-α • IL-17A • IL-23	• *TLR2* • *TLR4* • *CD14* • *IL1B* • *IL6* • *NFKB* • *STAT3* • *TNF* • *IL17A* • *IL23A*	*P. gingivalis* LPS activates TLR2/4-mediated NF-κB and STAT3 signalling in microglial cells, leading to increased inflammatory cytokine production. However, its inflammatory activity is weaker than that of *E. coli* LPS, mainly because of structural differences in lipid A.	Qiu et al. [22]
24	• CD14 • TLR2 • TLR4 • TNF-α	Not reported	*P. gingivalis* gingipains, particularly Kgp and RgpA, selectively reduced CD14 surface protein expression on macrophages without altering TLR2 or TLR4 expression. This reduction in CD14 weakened macrophage TNF-α production and phagocytosis following exposure to live *P. gingivalis*. The study suggests that gingipain-mediated CD14 cleavage helps *P. gingivalis* evade innate immune clearance and promote persistent periodontal infection.	Wilensky et al. [44]
25	• TNF-α • IL-1α • IL-1β • IL-6 • Il-10 • Il-12p40 • IL-12p70 • CD40 • CD86 • CD206 • KC • RANTES • Eotaxin • MCP-1 • MIP-1α	• *Nos2* • *Arg1* • *Chil3*	Although *P. gingivalis* LPS weakly stimulates M1/M2 macrophages, it still induces low-grade inflammatory cytokines including TNF-α, facilitating chronic inflammation without triggering strong immune clearance.	Holden et al. [45]
26	• TSP-1	• *THBS1*	*P. gingivalis* elevates thrombospondin-1 (TSP-1) in THP-1 cells, suggesting a role in ECM remodelling and inflammatory modulation during periodontal disease.	Gokyu et al. [46]
27	• OMV proteins • TLR2 • TLR4 • TLR7 • TLR8 • TLR9 • NOD1 • NOD2	Not reported	Outer membrane vesicles from different periodontal pathogens differentially activate pattern-recognition receptors, particularly TLR2 and TLR4, demonstrating species-specific immune modulation and distinct virulence strategies. *P. gingivalis* OMVs also moderately activated TLR7, TLR8 and TLR9. This study primarily assessed the functional activation of these receptors rather than changes in their gene or protein expression.	Cecil et al. [47]
28	• TLR2 • TLR4 • TNF-α • IL-8	Not reported	Subgingival plaque activated both TLR2 and TLR4, but TLR4 was functionally more important. The TLR4 inhibitor markedly suppressed plaque-induced TNF-α and IL-8 production, whereas the TLR2 inhibitor had little effect.	Ziauddin et al. [48]
29	• IL-6 • IL-8 • MCP-1	• *IL6* • *CXCL8* • *CCL2* • *TLR2* • *TLR4*	Pretreatment with low-dose *P. gingivalis* LPS generally did not reduce inflammatory mediator production, indicating that the periodontal ligament cells did not develop endotoxin tolerance. Stimulation with *P. gingivalis* LPS, *E. coli* LPS and Pam3CSK4 increased IL6, CXCL8 and CCL2 gene expression and increased the corresponding IL-6, IL-8 and MCP-1 proteins.	Blufstein et al. [49]

Table 1. *Cont.*

No.	Protein	Gene	Function	Ref.
30	• IL-8 • TNF- α • IL-1β	• *TLR2* • *TLR4*	Probiotic co-infection generally restored or increased TLR2 transcription and reduced the *P. gingivalis*-induced increase in TLR4 transcription. *P. gingivalis* increased the production of IL-1β and TNF-α proteins.	Albuquerque-Souza et al. [50]
31	• BSP • IL-8 • ERK1/2 • p38 MAPK • JNK	• *IBSP* • *CXCL8* • *TLR2* • *TLR4*	*P. gingivalis* LPS regulates BSP and IL-8 production via TLR2/4 and MAPK signalling in periodontal ligament fibroblasts. This may contribute to periodontitis pathogenesis.	Zhang and Li [51]
32	• Type I collagen • Podoplanin • SGLT2	• *SLCA2*	*P. gingivalis* LPS-induced diabetic nephropathy leads to overexpression of SGLT2 in the kidney. The findings suggest that periodontitis-associated *P. gingivalis* LPS may aggravate both diabetes and diabetic kidney disease by promoting abnormal renal SGLT2 expression.	Kajiwara and Sawa [52]
33	• IL-1 β • IL-6 • MCP-1 • p38 MAPK • ERK • JNK • IκBα	• *IL1B* • *IL6* • *CCL2* • *TLR2* • *TLR4*	Genomic DNA from *Lactiplantibacillus plantarum* suppresses *P. gingivalis* LPS-induced inflammation. This occurs via inhibition of TLR, MAPK and NF-κB signalling.	Choi et al. [53]
34	• IL-33 • TLR2	• *IL33*	The increase in IL-33 mRNA and intracellular protein was markedly reduced in TLR2-deficient cells, showing that the response was TLR2-dependent.	Tada et al. [54]
35	• TNF • IL-1β • IL-10 • IL-12p40 • IL-8 • TLR2 • TLR4 • mTOR • AKT	Not reported	*P. gingivalis* OMVs induce TNF tolerance via TLR4 and mTOR pathways. This contributes to immune evasion.	Waller et al. [55]
36	• ANGPTL2 • IL-1β • IL-8 • TNF-α • TLR2 • TLR4 • Integrin α5β1 • LILRB2	• *ANGPTL2* • *IL1B* • *CXCL8* • *TNF*	*P. gingivalis* LPS increased ANGPTL2 expression and secretion in human gingival epithelial cells through TLR2- and TLR4-mediated signalling. ANGPTL2 then activated integrin α5β1, increasing IL-1β, IL-8 and TNF-α production, whereas ANGPTL2 knockdown or integrin α5β1 blockade reduced this inflammatory response. The study identifies an LPS–ANGPTL2–integrin α5β1 inflammatory pathway that may prolong chronic inflammation and contribute to periodontal tissue destruction.	Ohno et al. [56]
37	• Insulin • AKT	• *IL1B* • *TNF* • *IL6* • *TLR2* • *TLR4* • *Ins1* • *Ins2*	Bacterial supernatants enhance glucose-dependent insulin secretion via PI3K/AKT signalling in pancreatic β-cells. Bacterial supernatants, especially those from *P. gingivalis* and *T. denticola*, upregulated IL1B, TNF, IL6, TLR2, TLR4, Ins1 and Ins2 gene expression. This suggests potential interactions between oral and metabolic health.	Ramenzoni et al. [57]
38	• TGF-β1 • SLPI • IL-6 • IL-8	• *TLR2* • *TLR4* • *F2RL1* • *F2R* • *SLPI* • *TGFB1* • *IL6* • *CXCL8*	*P. gingivalis* stimulates cytokine expression in gingival fibroblasts via TLRs and PARs. This suggests a role in periodontal inflammation.	Palm et al. [58]
39	• TLR2 • IL-8	• *TLR2* • *TLR4* • *CXCL8*	*P. gingivalis* and its LPS increased TLR2 gene and protein expression, TLR4 gene expression, IL8 gene and IL-8 protein production in human gingival epithelial cells. Irsogladine maleate suppressed these responses, while TLR2 knockdown confirmed that TLR2 partially regulates IL-8 induction.	Savitri et al. [59]
40	• TLR2 • TLR4 • MMP-9 • MMP-2 • TNF-α • IL-6 • IL-1β	Not reported	A novel sulfated polysaccharide reduces inflammatory mediator production in *P. gingivalis* LPS-stimulated monocytes/macrophages. This suggests a potential therapeutic approach for periodontitis. MMP-2 was not significantly detected.	Gu et al. [60]

TLR2/TLR4 activation also shapes adaptive immunity. In B cells, MyD88 and TRIF signalling regulates transcription factors such as BCL6, BLIMP-1, PAX5 and alters cytokine output, including IL-6 and IFN-β [20,34]. In monocytes, TLR-driven signalling enhances Th17 differentiation via RORγt and STAT3 [33], while gingival fibroblasts and inflamed gingiva-derived MSCs mount exaggerated cytokine responses following TLR activation [36]. Systemically, *P. gingivalis* contributes to respiratory inflammation, diabetic nephropathy and neuroinflammation through TLR2/TLR4-mediated activation of endothelial cells and modulation of ICAM-1, VCAM-1, FGF23, ACE2, IL-6 and CCL2 [30,35,37].

P. gingivalis has been shown to use immune-evasion strategies. While TLR2 responses induced by *E. coli* LPS are stronger compared to *P. gingivalis* LPS, there are muted responses that reduce the activation of dendritic cells [42, 61]. Additionally, gingipains cleave CD14 and OMV sphingolipids that induce TNF-α tolerance via the TLR4-mTOR pathway [21, 42]. Beyond these immune-evasion mechanisms, current osteocyte biology indicates that periodontal bone loss should not be interpreted solely through osteoclast activation or the RANKL–OPG axis. Osteocytes are now recognised as central regulators of alveolar bone homeostasis because they produce RANKL, OPG and sclerostin, thereby controlling both osteoclastogenesis and osteoblast-mediated bone formation [62, 63]. This osteocyte-level mechanism is particularly relevant because osteocytes form an extensive lacuno-canalicular network that senses mechanical loading, coordinates mineral homeostasis and communicates with osteoblasts and osteoclasts. Chronic TLR-driven inflammation may disturb this network through cytokine-mediated stress, osteocyte apoptosis, altered mechanosensing and dysregulated release of RANKL and sclerostin. Recent evidence also suggests that osteocyte-intrinsic MyD88 signalling can directly regulate inflammatory osteolysis, indicating that osteocytes may act as active innate immune-responsive cells during bacterial bone infection [64,65]. Thus, incorporating osteocyte biology provides a more complete model of periodontal bone destruction, linking bacterial recognition, TLR–MyD88 signalling, inflammatory cytokine production, osteocyte dysfunction, suppressed bone formation and enhanced alveolar bone resorption.

TLR pathways are vital to the processes of bone remodelling. For instance, enhanced OPG production and decreased osteoclastogenesis are associated with *P. gingivalis* opsonized to modify the crosstalk of FcγR–TLR [18], whereas prolonged TLR2/4 stimulation decreases RANKL and increases OPG to suppress bone resorption without inhibiting bone formation [40]. It was reported that *P. gingivalis* LPS can trigger inflammation in human brain microvascular endothelial cells by increasing the production of IL-6 and CCL2. The response occurred mainly through TLR4 signalling, involving the NF-κB, p38 MAPK and JNK pathways. These findings suggest a possible mechanism linking periodontal infection with inflammation in the brain and an increased risk of neurological conditions such as cerebrovascular disease and Alzheimer's disease [35].

Collectively, these studies highlight key proteins and genes involved in periodontal innate and adaptive immunity, inflammatory bone loss, osteocyte dysfunction and systemic comorbidities. The compiled list of genes and proteins was further analysed using STRING to generate a protein–protein interaction network, as depicted in **Figure 2**. The protein network demonstrates extensive connectivity among the compiled proteins and genes, indicating that they participate in closely related biological processes rather than acting independently. A dense central cluster is formed by inflammatory and innate immune mediators, including TLR2, TLR4, TNF, IL6, IL1B, MYD88, RELA and STAT3, highlighting the importance of Toll-like receptor and cytokine signalling. Several peripheral subclusters are also evident, including epigenetic regulators such as TET1–3 and DNMT1/3A/3B, as well as bone-remodelling proteins such as TNFSF11, TNFRSF11A, ACP5, ALPL and RUNX2. The multiple coloured edges represent different types of known and predicted associations, supporting substantial functional overlap between inflammatory, immune, metabolic and osteogenic pathways. Overall, the network suggests that periodontitis-related responses involve coordinated interactions among immune signalling, tissue remodelling and systemic regulatory proteins. Additional functional enrichment analyses were performed to determine their biological relevance. The enrichment results were organised into four categories: cellular component, biological process, Reactome pathway and molecular function, based on Gene Ontology and Reactome annotations [66].

Figure 3a highlights the subcellular locations where the enriched genes and their products are predominantly active. The highest signal and significance are observed in membrane-related structures, such as the external side of the plasma membrane, the membrane side and the cell surface. Other notable locations include the extracellular space, extracellular region, endoplasmic reticulum lumen and cytoplasmic vesicles [67]. This localisation is directly relevant to the function of TLR2 and TLR4, which are two of the major TLRs typically located on the cell

surface/outer membrane of innate immune cells, such as macrophages and monocytes. Their primary role is to act as pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs) originating from invading microbes outside the cell, such as LPS for TLR4 and lipopeptides/peptidoglycans for TLR2, which are components of the bacterial cell wall or outer membrane. The enriched GO terms therefore imply that the gene set likely includes TLR2 and TLR4 themselves and/or other critical components of their signalosome that are required for ligand binding and initiation of the inflammatory signalling cascade right at the plasma membrane [68]. This localisation is essential for the rapid detection of extracellular threats and the mounting of an immediate immune response.

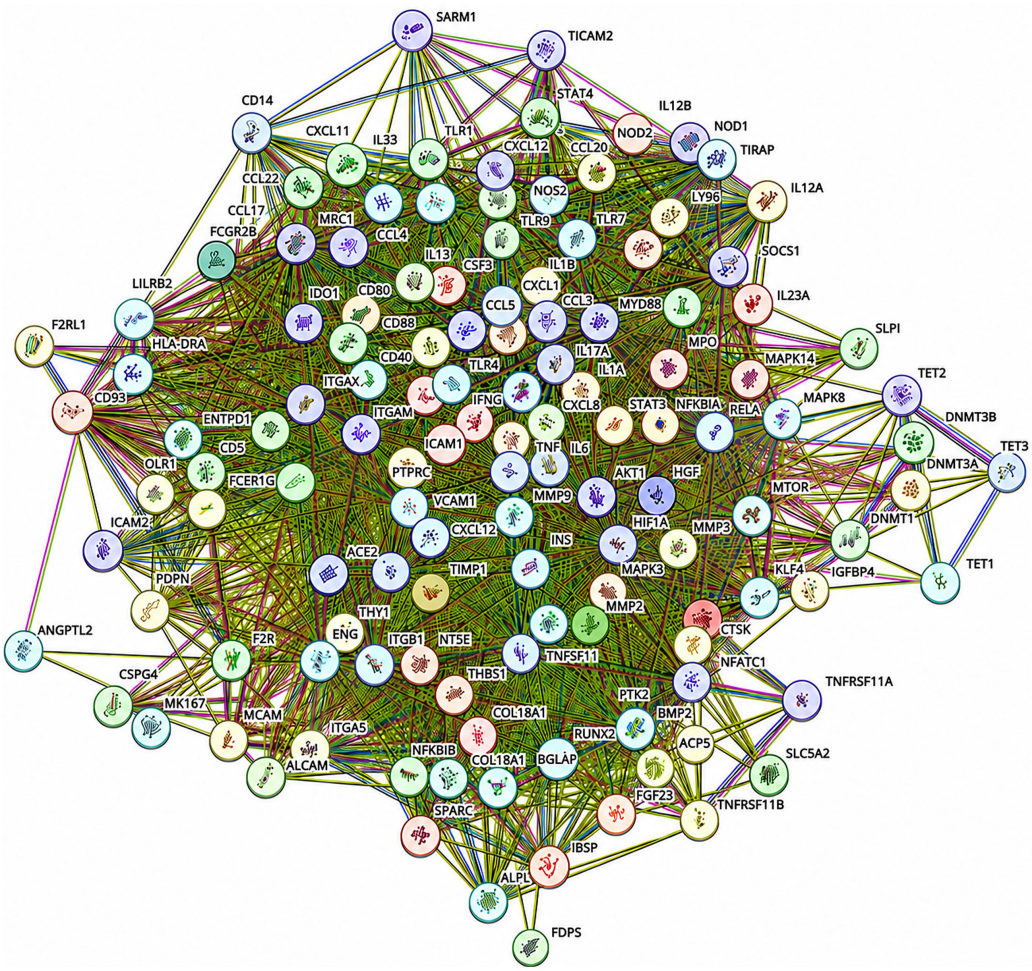


Figure 2. A protein-protein interaction (PPI) network generated based on the reported protein or gene.
Note: The relationship between proteins is indicated by colour. Deep Magenta, experimentally determined; sky blue, from curated database; green, gene neighbourhood; red, gene fusion; dark blue, gene co-occurrence; yellow, text-mining; black, co-expression; silver, protein homology.

Figure 3b illustrates the Gene Ontology (biological process) enrichment, it highlights how the analysed genes are strongly involved in immune and inflammatory responses. The most strongly enriched processes involved cellular responses to bacterial molecules and lipopolysaccharide, together with inflammatory responses. The proteins were also associated with the regulation of inflammatory mediators, particularly IL-6, IL-8 and tumour necrosis factor-related cytokines. The genes are most active in pathways triggered by LPS, a hallmark of Gram-negative bacteria. Key immune signalling routes such as the TLR pathway and MyD88-dependent signalling have an essential role, indicating activation of innate immunity [69].

Figure 3c demonstrates the ways in which the actions shown in **Figure 3b** are implemented through specific signalling pathways. It illustrates specific molecular pathways defined in the Reactome database, showing dominant enrichment in interleukin signalling cascades. It also emphasises active TLR pathways along with downstream

MyD88/MAL-mediated signalling and TRAF6-induced NF-κB/MAPK activation [69]. These are the pathways that lead to the release of downstream transcription factors and MAP kinases that in turn coordinate the expression of major pro-inflammatory cytokines [70,71].

The functional landscape of these coded genes is explained in **Figure 3d**. The main enriched molecular functions were cytokine activity, receptor ligand activity, cytokine receptor binding and chemokine activity. Additional enrichment in pattern-recognition receptor, integrin and chemokine-receptor binding suggests extensive involvement in immune-cell signalling and inflammatory cell recruitment.

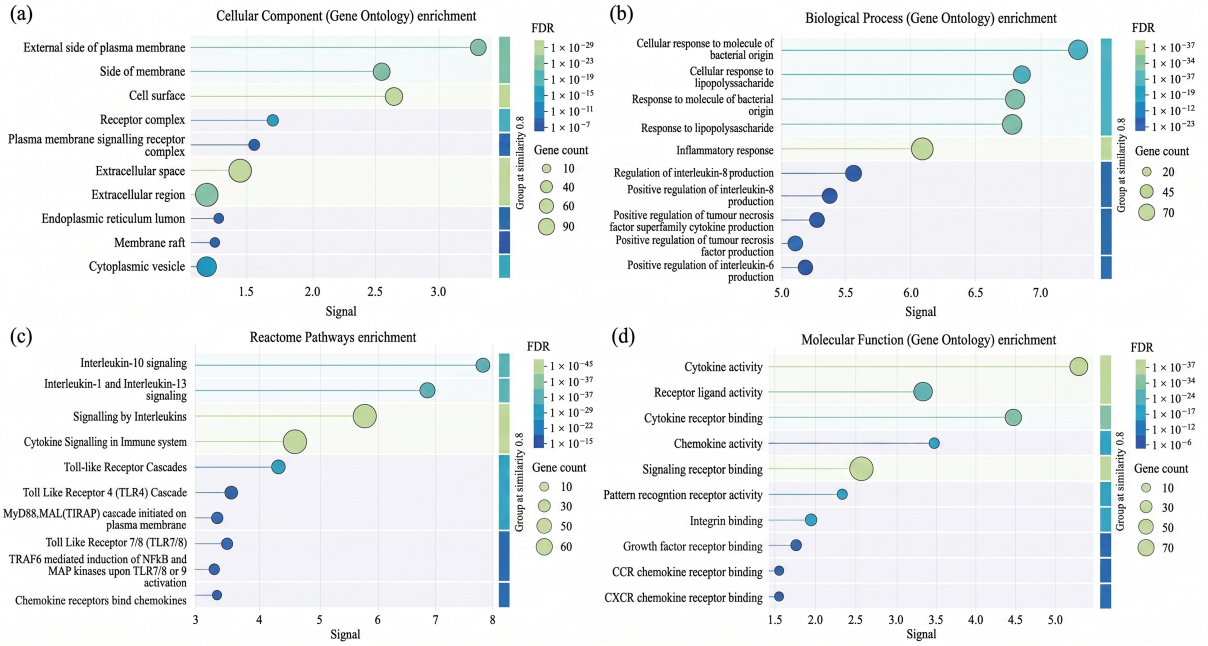


Figure 3. Functional analysis results, based on differentially expressed genes, are shown according to four major categories of enrichment: (**a**) cellular component (location of gene products), (**b**) biological process (associated physiological activities), (**c**) Reactome pathway (involved signalling and metabolic pathways) and (**d**) molecular function (specific biochemical activities).

The proposed proteins are mostly related to cell surface signalling and receptor binding, the main functional outcome of which occurs through the activation of the innate immune system. Specifically, the information implicates the Toll-like receptor signalling pathway, especially the TLR4–MyD88 cascade, as the regulatory nexus. The downstream response is the modulation of essential inflammatory cytokines (IL-6, IL-12), which determines the subsequent immune response.

3. miRNAs Associated with TLR2/4 Signalling Pathway

The review of miRNAs associated with TLR2 and TLR4 was conducted separately from the analysis of proteins and genes involved in the TLR2/TLR4 signalling pathways. Although TLR2 and TLR4 are closely related pattern-recognition receptors that share several downstream inflammatory signalling pathways, the references selected for this analysis were clearly associated with either TLR2 or TLR4. Owing to the limited number of relevant studies, miRNA data published between 2009 and 2024 were compiled from the literature and summarised in **Table 2**. For functional analysis, miRNAs reported to be associated with TLR2 and TLR4 were grouped separately and analysed using TAM 2.0 (http://www.lirmed.com/tam2/). All identified miRNAs were entered into the platform, followed by functional enrichment analysis. Cancer-related terms were masked to minimise disease-specific bias, and "Function" was selected as the annotation category. Statistical significance was determined using an FDR-adjusted p-value threshold of <0.05. The enrichment results were subsequently presented using the visualisation options available on the platform.

Table 2. Functional Roles of miRNAs associated with TLR2 and TLR4.

No.	TLR	miRNA	Function	Ref.
1	TLR 2	miR-19a/b	miR-19a/b act as negative regulators of TLR2-mediated inflammation. They directly target TLR2 mRNA, reducing TLR2 protein expression in rheumatoid arthritis fibroblast-like synoviocytes.	Philippe et al. [72]
2	TLR 2	miR-21	Loss of miR-21 increases gingival inflammation and alveolar bone loss, it is suggesting that miR-21 may have a protective role against periodontal tissue destruction.	Zhou et al. [73]
3	TLR 2	miR-105	It directly suppresses TLR2 protein translation and reduces TLR2-induced IL-6 and TNF-α production in gingival keratinocytes.	Benakanakere et al. [74]
4	TLR 2	miR-30b-3p, miR-125b-1-3p	miR-30b-3p and miR-125b-1-3p are elevated in periodontitis and positively associated with periodontal disease severity, inflammatory cytokine levels and clinical indicators such as probing pocket depth, clinical attachment loss and bleeding on probing.	Zhu and Zhong [75]
5	TLR 2	miR-143-3p	miR-143-3p promotes pro-inflammatory M1 macrophage polarisation and aggravates periodontal inflammation. It is enriched in extracellular vesicles derived from inflammatory periodontal ligament stem cells and directly targets PI3Kγ, thereby suppressing PI3K/AKT signalling and activating NF-κB signalling.	Wang et al. [76]
6	TLR 2	miR-143/145	*P. gingivalis* activates the TLR2–MyD88/TRIF–NF-κB pathway in vascular smooth muscle cells. miR-143/145 are functional mediators of communication between apoptotic vascular smooth muscle cells and macrophages, and are associated with periodontal infection and defective immune clearance in atherosclerotic plaques.	Xie et al. [77]
7	TLR 2	miR-146a	miR-146a acts as a negative-feedback regulator of TLR-mediated inflammation in human periodontal ligament cells.	Jiang et al. [78]
8	TLR 2	miR-155	miR-155 is enriched in extracellular vesicles released from *Porphyromonas gingivalis*-infected cells and is upregulated mainly through TLR2 signalling rather than TLR4 signalling.	Yoshida et al. [79]
9	TLR 2	miR-223	Suppresses the TLR2–MyD88–JNK pathway, reduces inflammatory cytokine production and promotes recovery from thrombophlebitis.	Li et al. [80]
10	TLR 4	miR-21	miR-21 acts as a negative regulator of TLR4-mediated inflammation. It suppresses TLR4 signalling, reduces pro-inflammatory cytokine production and limits periodontal inflammation and alveolar bone loss.	Zhou et al. [73]
11	TLR 4	miR-125a, miR-499a	Both miR-125a and miR-499a function as regulatory miRNAs whose genetic variations may modify inflammatory responses and predisposition to chronic periodontitis. Both are host genetic susceptibility factors for chronic periodontitis.	Venugopal et al. [81]
12	TLR 4	miR-146a	miR-146a acts as a negative regulator of TLR4-mediated inflammation. Preservation of miR-146a may help suppress TNF-α, IL-1β and IL-8 production.	Molteni et al. [82]
13	TLR 4	miR-146a/b	miR-146a acts as a key regulator of immune responses, inflammation and fibrosis by modulating inflammatory signalling pathways. It may serve as a potential biomarker and therapeutic target for chronic inflammatory and fibrotic diseases.	Liao et al. [83]
14	TLR 4	miR-155	The study indicates that miRNAs function as extracellular-vesicle-mediated regulators of intercellular communication during *P. gingivalis* infection. miR-155 is generally associated with pro-inflammatory signalling.	Yoshida et al. [79], Molteni et al. [82]
15	TLR 4	miR-200b, miR-200c	miR-200b and miR-200c act as negative regulators of TLR4-mediated inflammatory signalling. They reduce MyD88 expression, thereby suppressing activation of the MyD88-dependent NF-κB pathway. This decreases the production of pro-inflammatory mediators, including IL-6, CXCL9 and TNF-α, following LPS stimulation.	Wendlandt et al. [84]
16	TLR 4	miR-223	1) miR-223 acts as an anti-inflammatory regulator in the hippocampus. Aerobic exercise increases miR-223 expression, which is associated with suppression of the TLR4/MyD88/NF-κB signalling pathway, reduced IL-1β, increased IL-10 and improvements in depressive behaviour and hippocampal function in CUMS-induced mice. 2) miR-223 acts as a negative regulator of osteogenic differentiation in periodontal ligament-derived cells. It is upregulated in inflamed gingival tissues and is positively associated with periodontitis severity. miR-223 directly targets FGFR2 and TGFβR2, thereby reducing the expression of osteogenic markers such as OCN, OPN and Runx2 and suppressing mineralisation.	Zhang et al. [85], Qu et al. [86]

The miR-19 plays an essential role in regulating TLR2 expression in fibroblast-like synoviocytes, ultimately leading to a reduction in inflammation [72, 87]. With similar observations, the expression of miR-21 has been reported to influence lung inflammation in response to TLR2 agonists, with modifications impacting cytokine re-

sponses [73,88]. The miR-105 binds to the 3' UTR of TLR2 and influences the process of protein translation, thereby demonstrating an inverse correlation between miR-105 levels and TLR2 protein/cytokine responses [74]. Various reports have suggested that TLR2 activation could alter miR-125b levels and in turn influence downstream cytokine and differentiation pathways [89–91]. Both miR-30b-3p and miR-125b-1-3p are upregulated in periodontitis and are associated with greater disease severity and inflammation. Their expression levels are higher in gingival crevicular fluid from patients with periodontitis, particularly in severe cases and correlate positively with clinical periodontal parameters and inflammatory cytokines, including IL-1β, IL-6 and TNF-α. Both miRNAs may also serve as potential diagnostic biomarkers for periodontitis [75].

Furthermore, miR-143 has gained attention for its role in regulating smooth muscle cell fate, where it may function as a tumour suppressor. It is also linked to key biological processes such as tissue homeostasis, heart development, obesity and cancer [76]. The miR-143/145 cluster demonstrates broad anti-inflammatory and tumour-suppressive properties. Collectively, these findings suggest that miR-143 consistently downregulates TLR2 across multiple studies [77]. miR-146a may serve as a negative regulator of inflammatory responses and cytokine production in keratinocytes by targeting key downstream signalling components, IRAK1 and TRAF6 [78,92–94]. miR-147 is noted for its involvement in inflammatory pathways and its capacity to modulate cytokine expression [95].

Conversely, miR-155 induces an inflammatory response by targeting myosin light chain kinase and positively regulates inflammation by targeting negative regulators of TLR pathways, such as SHIP1 and SOCS1. Its upregulation indicates a significant component of the inflammatory response initiated by TLR ligands [96,97]. miR-195 plays a role in inhibiting pro-inflammatory profiles in macrophages during immune responses, directly targeting and negatively regulating TLR2 expression, leading to reduced production of downstream pro-inflammatory cytokines [98]. miR-223 is involved in regulating immune cell differentiation and has been shown that overexpression can inhibit TLR signalling pathways, thereby decreasing downstream inflammatory mediators. It plays a role in the feedback control of the TLR2/TLR4 axis [80]. let-7b, along with other members, has been identified as being regulated in the LPS/TLR2 immune axis and proposed as an early diagnostic or response marker, therefore showing functional effects reported in immune-related models [99].

miR-21 is implicated in regulating gene expression in cancer by targeting tumour suppressor genes, which influences essential biological processes such as cell proliferation, apoptosis and invasion. It specifically targets PDCD4, leading to a reduction in TLR4-mediated inflammatory responses and MKK4 [73,100]. Similarly, miR-92a, which is down-regulated upon LPS (TLR4) stimulation, has been shown that its overexpression can suppress the production of inflammatory cytokines through the targeting of MKK4 [101].

Generally, miR-125a could be upregulated in a TLR4-dependent manner during *Mycobacterium tuberculosis* (M.tb) infection, where it directly targets TRAF6 [81,102]. This targeting suppresses NF-kB activation, effectively reducing pro-inflammatory cytokines and therefore enhancing M.tb survival. In contrast, miR-125b increases in response to TLR4 ligation, repressing targets such as BIK and MTP18, which alter mitochondrial dynamics and promote a pro-inflammatory and apoptotic phenotype [103].

miR-155 acts by being induced by LPS (a TLR4 ligand), thereby suppressing negative regulators such as SOCS1 and SHIP1 to enhance TLR4 signalling [82,104]. Meanwhile, miR-146a/b serves as a negative regulator within the inflammation and innate immune system context [78,83,105]. Observation of miR-194 indicates that miR-194a-5p binds to the 3' UTR of TLR4, its overexpression results in reduced TLR4 levels, while CRISPR deletion of miR-194 corresponds with increased TLR4 and downstream inflammatory gene expression [106,107].

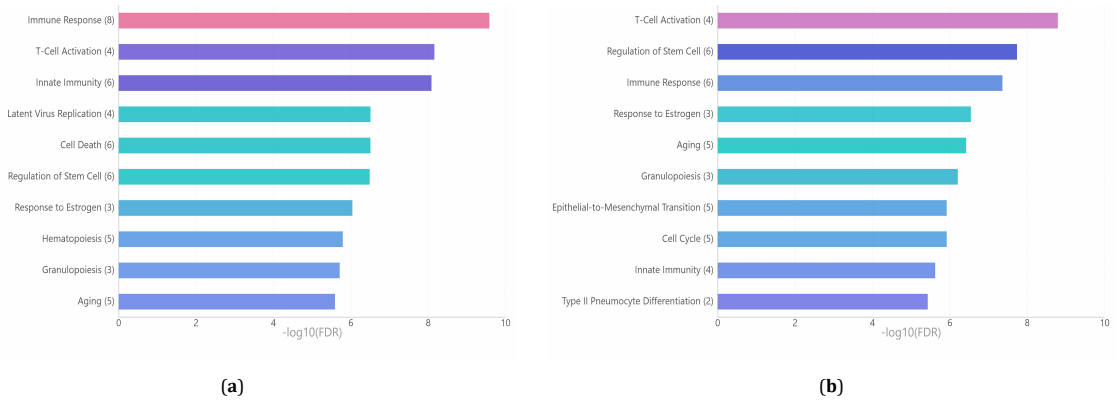
In addition to these, miR-200c modulates protein expression by affecting overall fundamental physiological properties, while promoting epithelial-mesenchymal transition (EMT) and cell migration [84,108]. Myeloid cells are particularly affected by miR-223, which is important for regulating immune cell differentiation and inflammation and therefore plays a significant role [85,86]. Both miR-1236 and miR-642a have been shown to inhibit TLR4 production after binding to specific 3' UTR region. The effectiveness of the binding is influenced by genetic polymorphisms such as the rs11536889, which may be found in both of these miRNAs.

A better understanding of miRNA regulation in the TLR2 and TLR4 pathways provides fundamental platform for developing targeted therapeutic strategies for inflammatory and infectious diseases. An important finding is the negative feedback mechanism. miR-146a and the miR-143/145 cluster function as negative feedback regulators in both pathways, indicating their potential as therapeutic candidates for addressing generalised systemic inflammation linked to conditions such as sepsis, chronic autoimmune disorders and chronic metabolic inflammation [77].

miRNAs play a crucial role in regulating immune responses by keeping inflammation under control and maintaining tissue balance. This could be achieved by fine-tuning multiple signalling pathways, which can significantly influence the production of pro-inflammatory cytokines and regulate pathways involved in chronic inflammation, such as rheumatoid arthritis and inflammatory bowel disease [109,110]. Recent studies suggest that miRNAs may contribute to the immunomodulatory effects of mesenchymal stromal cell-based therapies and can be transported by extracellular vesicles to regulate inflammatory signalling. These findings support their potential as therapeutic targets or delivery cargo for autoimmune and inflammatory diseases, although further studies are required to establish their clinical safety and efficacy [111,112].

Targeted administration of miRNA mimics or anti-miRs (oligonucleotides that inhibit pro-inflammatory miRNAs) to particular immune cells could be a potential therapeutic strategy [113]. For example, in sepsis, where excessive TLR4/LPS signalling drives pathology, delivering a miR-146a mimic encapsulated in a targeted nanoparticle could globally enhance the body's natural braking mechanism by suppressing IRAK1 and TRAF6, effectively resolving hyper-inflammation while minimising the risk of global immunosuppression [114]. In contrast, in conditions requiring a sustained, appropriate immune response, such as chronic infection or cancer immunotherapy, strategies could include using anti-miRs to block negative regulators such as miR-125a in target cells, thereby maintaining NF-kB activation and enhancing antimicrobial or anti-tumour immunity [81,102].

As depicted in **Figure 4**, both TLR2- and TLR4-associated miRNAs showed enrichment in immune-related and cellular regulatory functions. Shared functional categories included immune response, innate immunity, T-cell activation, regulation of stem cells, response to oestrogen, granulopoiesis and ageing, indicating that both miRNA groups may participate in the regulation of inflammation, immune-cell development and tissue homeostasis. However, the relative enrichment differed: the TLR2-associated miRNAs showed stronger enrichment for immune response and innate immunity, whereas TLR4-associated miRNAs showed particularly strong enrichment for T-cell activation and stem-cell regulation.



(**a**) (**b**)

Figure 4. Comparison of (**a**) TLR 2 activation and (**b**) TLR 4 activations from the aspect of functional study. The obtained miRNAs were analysed using TAM 2.0.

Distinct functional patterns were also observed. TLR2-associated miRNAs were uniquely enriched in latent virus replication, cell death and haematopoiesis, suggesting broader involvement in antiviral regulation, immune-cell production and cell survival. In contrast, TLR4-associated miRNAs were uniquely associated with epithelial-to-mesenchymal transition, cell-cycle regulation and type II pneumocyte differentiation, indicating greater involvement in cellular proliferation, tissue remodelling and epithelial differentiation. These findings represent functional enrichment patterns and should be interpreted as hypothesis-generating rather than evidence of direct receptor-specific mechanisms. Modulating this route may impact deeper cellular maintenance systems, providing advantages beyond rapid immune suppression [16,115].

4. Therapeutic Approach to Suppress TLR Activation

Monoclonal antibodies and aptamers are established and emerging approaches for targeting inflammatory pathways. Antibodies offer high target specificity but may have limited tissue penetration, immunogenicity and vari-

able patient responses [116]. In contrast, aptamers are smaller oligonucleotides designed to bind specific targets with high affinity, with advantages including low immunogenicity, ease of synthesis and tunable pharmacokinetics, which may facilitate more efficient targeting of inflamed tissues [117,118].

The innate immune system includes TLRs as important components. These receptors serve as PRRs that detect PAMPs and initiate immune responses. Among them, TLR2 and TLR4 are particularly important: TLR2 responds broadly to components of Gram-positive bacteria, while TLR4 is primarily responsible for sensing LPS from Gram-negative bacteria.

TLR2 often forms heterodimers with either TLR1 or TLR6, depending on the ligand. This dimerisation broadens its recognition capacity to include lipoteichoic acid, peptidoglycan and bacterial lipoproteins [119]. Upon ligand binding, TLR2 recruits adaptor proteins (such as MyD88 and TIRAP/MAL), triggering downstream signalling pathways that activate NF-κB and MAPKs, thereby driving pro-inflammatory cytokine production [120–122]. TLR4 primarily senses LPS via its co-receptor MD-2 (and CD14) and activates two major downstream pathways. The MyD88-dependent pathway leads to rapid NF-κB activation and the production of inflammatory cytokines. The TRIF-dependent (MyD88-independent) pathway leads to type I interferon responses, via TRIF and TRAM adaptors [17,123]. Beyond bacterial PAMPs, both TLR2 and TLR4 can also be activated by damage-associated molecular patterns (DAMPs), such as HMGB1, which are released by host tissues under stress or following injury. However, while TLR activation is critical for host defence, excessive or chronic activation of TLR2 and TLR4 contributes to pathological inflammation, autoimmunity and tissue damage [124,125]. Thus, therapeutic neutralisation of TLR2 and TLR4 has been pursued as a strategy to mitigate inflammation in various disease contexts.

Several therapeutic strategies have been explored to inhibit TLR2 and TLR4 activity. Monoclonal antibodies such as OPN-305, a humanised anti-TLR2 IgG4 antibody, demonstrated reduced inflammatory injury in ischaemia–reperfusion models and showed favourable safety and pharmacokinetics in a Phase I trial [126,127]. For TLR4, NI-0101, a humanised anti-TLR4 antibody, successfully blocked LPS-induced cytokine production in healthy volunteers. This randomised controlled trial evaluated NI-0101, a monoclonal antibody that blocks TLR4, in ACPA-positive rheumatoid arthritis patients who responded inadequately to methotrexate. Although NI-0101 successfully inhibited TLR4 activity and had a safety profile similar to placebo, it did not significantly improve disease activity or clinical response rates [128]. TAK-242 selectively binds to the intracellular domain of TLR4 and disrupts its interaction with the adaptor proteins TIRAP and TRAM. This suppresses downstream NF-κB, interferon-related signalling and inflammatory mediator production [129]. Preclinical studies have shown neuroprotective effects of TAK-242 in traumatic brain injury (TBI), reducing inflammation, neuronal loss and autophagy via inhibition of TLR4–MyD88/TRIF/NF-κB signalling [130]. In models of ulcerative colitis, TAK-242 modulated macrophage polarisation (less M1, more M2) and T helper cell balance (reduced Th1/Th17), via a mechanism that involves inhibition of the JAK2/STAT3 pathway [131].

Lipid A analogues, such as Eritoran, have been evaluated in sepsis, although large trials have shown limited clinical efficacy. In addition, natural compounds such as curcumin and resveratrol exhibit broad anti-inflammatory effects, partly through the suppression of TLR2/4-mediated NF-κB and MAPK signalling [132,133].

More recently, aptamers have emerged as highly promising modalities due to their strong affinity, low immunogenicity and excellent tissue penetration [24]. Aptamers can neutralise TLRs by direct binding to receptor ectodomains, disrupting dimerisation, blocking ligand recognition, or sequestering PAMPs such as LPS. Notably, RNA- and DNA-based aptamers targeting the TLR4/MD-2 complex have shown potent antagonistic effects *in vitro* and *in vivo* [134,135].

Neutralisation of TLR2 and TLR4 could help to treat a wide range of diseases. Recent studies have shown the evolving landscape of TLR2/4-targeting aptamers. The list of reported TLR 2 and TLR4 aptamers is shown in **Table 3**. The TLR4-binding DNA aptamer ApTOLL has progressed the furthest clinically. A Phase I trial in healthy volunteers demonstrated a safe record and a plasma half-life of ~9 h [134]. A technique called SELEX was used and successfully found a functional TLR2 aptamer, designated AP177, exhibiting strong affinity (Kd = 73 pM). It significantly inhibits TLR2, reducing NF-κB activation and suppressing cytokine release by over 80% *in vitro* [136]. Although this early study did not evaluate periodontitis directly, it established AP177 as a highly specific functional TLR2 aptamer and introduced IP-SELEX combined with functional screening. Its findings provide a foundation for developing next-generation TLR2 aptamers through core-sequence optimisation, receptor-conformation-specific selection, chemical stabilisation and validation in periodontal disease models.

Table 3. Reported aptamer sequence with binding affinity towards TLR 2 and TLR 4.

No.	Target of TLR	Aptamer Sequence	Status	Binding Affinity (nM)	Ref.
1	TLR2-AP1	TCCCTACGGCGCTAACGACGGGGGAGTTGTGCTCCCGAAAGGAGGTGCCACCGTGCTACAAC	*in vitro*	6.42	Chang et al. [136]
2	TLR2-AP2	TCCCTACGGCGCTAACTCCCGATAGGAGGCCCGTGGCCGTGTTATCGCCACCGTGCTACAAC	*in vitro*	1.99	Chang et al. [136]
3	TLR2-AP3	TCCCTACGGCGCTAACGGATCAAACATGCGCTCCAAGGAGTAGGGGCCACCGTGCTACAAC	*in vitro*	4.12	Chang et al. [136]
4	TLR2-AP4	TCCCTACGGCGCTAACCAGTGCTAGCCACTGCGGGGTTCCCTTGTTGCCACCGTGCTACAAC	*in vitro*	0.028	Chang et al. [136]
5	TLR2-AP5	TCCCTACGGCGCTAACGTATAAGTCGCCTGCATCACGGCCAGATTTGCCACCGTGCTACAAC	*in vitro*	0.097	Chang et al. [136]
6	TLR2-AP177	TCCCTACGGCGCTAACGTACTAGCGAGGGTATGGTGTGGGAATGTCGCCACCGTGCTACAAC	*in vitro*	0.073	Chang et al. [136]
7	TLR2	TCCCTACGGCGCTAACTTCTGCAAGAGGCCGTCAACGGGCGAGTTAGCCACCGTGCTACAAC	*in vitro*	19.25	Chang et al. [136]
8	TLR4-ST-6	AGCAGCACAGAGGTCAGATGAGGGCATCAAAGGGGGGAGGGCGGGTGGATTGGATGCCGACCTATGCGTGCTACCGTGAA	*in vitro*	35.62	Yang et al. [135]
9	TLR4-ST-6-1	AGGGCATCAAAGGGGGGAGGGCGGGTGGATTGGATGCCGA	*in vitro*	79.44	Yang et al. [135]
10	TLR4-ST-6-2	GGGGAGGGCGGGTGGATTGGATGCCGA	*in vitro*	80.22	Yang et al. [135]
11	TLR4- ApT#1R	GTTGCTCGTATTTAGGGCCACCGGCACGGGACAAGGCGCGGGACGGCGTAGATCAGGTCGACACCAGTCTTCATCC GC	*in vitro* and *in vivo*	0.2–200	Fernández et al. [137]
12	TLR4- ApT#1RT	CCACAGCTGGACTAGATGCGGCAGGGCGCGGAACAGGGCACGGCC	*in vitro* and *in vivo*	0.2–200	Fernández et al. [137]
13	TLR4- ApT#4F	GCGGATGAAGACTGGTGTGCCAATAAACCATATCGCCGCGTTAGCATGTACTCGGTTGGCCCTAAATACGAGCAAC	*in vitro* and *in vivo*	0.2–200	Fernández et al. [137]
14	TLR4- ApT#4FT	GAGCATAAATCCCGGTTGGCTCATGTACGATTGCGCCGCTATACCAAATAACCGTGTGG	*in vitro* and *in vivo*	0.2–200	Fernández et al. [137]

Therefore, TLR2 and TLR4 serve not only as frontline sentinels of innate immunity but also as major amplifiers of pathological inflammation. Therapeutic neutralisation by using antibodies, small-molecule inhibitors or high-affinity aptamers is an effective approach to re-establish immunological equilibrium. Aptamer technology continues to advance and may overcome several limitations associated with conventional biologics and small molecules, thereby positioning TLR-targeting aptamers as next-generation immunomodulators with significant therapeutic potential in inflammatory, infectious and neurovascular diseases.

5. Challenges and Future Prospects

Periodontitis therapy requires a delicate balance between dampening pathological inflammation and preserving innate immunity. Although TLRs are primary drivers of the disease, they are also essential for host defence. Consequently, broad TLR inhibition poses a risk: it may reduce inflammatory damage but at the cost of impaired wound healing and an increased vulnerability to secondary infections.

In patients with compromised immunity, the molecular pathways associated with TLR2/TLR4 are unlikely to have the same impact as in immunocompetent individuals. Studies indicate that the activation of TLR2 and TLR4 may initiate MyD88/TRIF-dependent signalling, NF-κB/MAPK activation and the generation of IL-6, IL-8, IL-1β and TNF-α; however, the downstream response may be modified when immune function is compromised or dysregulated. Conditions such as diabetes, chemotherapy, HIV infection, prolonged corticosteroid use, transplantation and ageing may compromise neutrophil function, macrophage clearance, antigen presentation and adaptive immune control. Consequently, periodontal pathogens such as *P. gingivalis* may survive despite TLR activation, resulting in persistent low-grade inflammation instead of efficient microbial eradication. This aligns with findings in the text indicating that *P. gingivalis* may elicit immunological tolerance, diminish dendritic cell activation and disrupt CD14-mediated recognition [21,42,44,55].

In immunocompromised individuals, TLR2/TLR4 signalling may persist, although its biological consequences may shift towards chronic inflammation, inadequate repair and increased periodontal damage. Ongoing microbial stimulation may perpetuate cytokine production, RANKL-mediated osteoclastogenesis and tissue degradation, while the host's ability to resolve inflammation and repair periodontal tissues is diminished. This has significant therapeutic implications: extensive suppression of TLR2/TLR4 may diminish inflammatory damage but might also undermine antimicrobial defence. Therefore, regulation of TLR pathways using aptamers, antibodies or miRNAs should be implemented through a precise strategy, informed by the immunological state, microbial load, cytokine profile and TLR expression, to rebalance host immunity rather than entirely suppressing it.

Indeed, therapeutically targeting TLRs is complex, owing to their functions and multi-connected signalling networks. TLR2 and TLR4 share adaptors and downstream targets. Modifying one pathway often leads to unwanted side effects or compensatory responses. This makes single-target therapies less effective, as the immune system can utilise other pathways to sustain the ongoing inflammation [14].

The potential of aptamers as high-affinity immunomodulators is frequently limited by their short half-life *in vivo*. To overcome this, researchers are developing new ways to protect them, such as PEGylation, structural modification and nanoparticle delivery to shield these molecules, and ensure they can survive longer and reach inflamed tissues. In addition to molecular stability, the field encounters a substantial translational gap. Because of differences in the immune landscape, the animal models frequently do not reflect human responses. Therefore, the transition to 3D gingival constructs and organ-on-chip models is imperative for better prediction.

Future strategies for periodontitis are evolving towards more advanced, multifaceted interventions. Synthetic biology has advanced considerably and aptamers can now be designed to target several inflammatory mediators simultaneously, rather than focusing on just one. Gene-level tools such as CRISPR and RNA interference provide better control over TLR expression than previous approaches. These new approaches mark a shift from general immunosuppression to precise, molecular-level modulation of the host response. miRNAs, such as miR-146a and miR-155, are also gaining attention because they help regulate inflammation linked to these immune receptors. By fine-tuning the duration and intensity of inflammation, they open the door to new RNA-based treatments that are more precise [78]. Today, periodontitis is not only a problem in the mouth, but it is also closely connected to overall health. Targeting TLRs at the source of periodontal infection may consequently reduce the risk of related systemic diseases. Integrating precision medicine, specifically patient-specific TLR profiling and microbiome analysis allows for personalised therapies that maximise efficacy while mitigating risk. In combination with delivery platforms such as hydrogels and liposomal carriers, these advancements represent a substantial progression. Together, these advances could make immune-targeted therapies for gum disease more effective and longer-lasting [35].

6. Conclusions

The enrichment analysis showed that the identified proteins are mainly involved in cell surface signalling, receptor binding and innate immune activation, as reflected by the molecular function, cellular component, biological process and Reactome pathway analyses. The TLR4–MyD88 cascade appeared to be one of the major regulatory pathways, with downstream associations with inflammatory cytokines such as IL-6 and IL-12. However, these findings should be interpreted as pathway-level associations and require experimental validation before causal or clinical conclusions can be made.

The miRNA analysis showed overlapping but distinct functional patterns between TLR2- and TLR4-associated networks. TLR2-related miRNAs were more closely associated with immune activation and inflammatory response pathways, whereas TLR4-related miRNAs showed broader associations with metabolic regulation, cellular stress, ageing and latent virus-related pathways. These observations suggest possible receptor-specific regulatory trends, but they should be considered hypothesis-generating rather than direct evidence for selective clinical targeting.

Aptamers may serve as promising molecular tools for modulating TLR2/TLR4-related inflammatory pathways because of their small size, high binding affinity, chemical stability, low immunogenicity and potential use in targeted delivery or aptasensor development. Nevertheless, the present analysis does not provide periodontal-specific comparative evidence showing that aptamers are superior to antibodies. Therefore, aptamers should be described as potential alternatives or complementary platforms, not established replacements for antibody-based therapy.

A key limitation of this review is that the conclusions are based on published literature and computational enrichment analyses, which identify biological associations but do not prove causality, therapeutic efficacy, or clinical superiority. Further *in vivo*, *in vivo* and clinical studies are needed to validate the roles of TLR2, TLR4, miRNA regulation and aptamer-based targeting in periodontal inflammation, bone remodelling and tissue regeneration. Overall, this study provides a mechanistic and bioinformatics-based framework to guide future experimental validation and the development of more precise immunomodulatory strategies for periodontitis.

Supplementary Materials

The supporting information can be downloaded at https://ojs.ukscip.com/uploads/2/files/TI-100534-Supplementary-Materials.zip.

Author Contributions

Conceptualisation, F.F.L.; methodology and literature search, M.A.B.A., Y.H.N. and N.L.Y.S.T.; data collection and analysis, M.A.B.A., Y.H.N. and N.L.Y.S.T.; visualization and figure preparation, F.F.L. and N.A.B.O.; manuscript preparation, M.A.B.A., Y.H.N. and N.L.Y.S.T.; writing—review and editing, F.F.L. and N.A.B.O.; supervision, F.F.L. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the Fundamental Research Grant Scheme, Ministry of Higher Education, Malaysia under FRGS/1/2019/SKK08/MAHSA/03/2.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

This study is based on previously published studies and publicly available data. No new datasets were generated. All source articles analysed during the study are cited in the reference list.

Acknowledgments

The authors gratefully acknowledge the valuable support and contributions of all individuals and institutions involved in this work.

Conflicts of Interest

The authors declare no conflict of interest financial or otherwise.

AI Use Statement

The research content, interpretation and conclusions were developed by the authors. The English language of the article was improved with ChatGPT. The authors reviewed and approved the final manuscript and take full responsibility for its content.

References

1. Bhuyan, R.; Bhuyan, S.K.; Mohanty, J.N.; et al. Periodontitis and Its Inflammatory Changes Linked to Various Systemic Diseases: A Review of Its Underlying Mechanisms. *Biomedicines* **2022**, *10*, 2659.
2. Păunică, I.; Giurgiu, M.; Dumitriu, A.S.; et al. The Bidirectional Relationship between Periodontal Disease and Diabetes Mellitus—A Review. *Diagnostics* **2023**, *13*, 681.
3. Lohiya, D.V.; Mehendale, A.M.; Lohiya, D.V.; et al. Effects of Periodontitis on Major Organ Systems. *Cureus* **2023**, *15*, e46299.
4. Tattar, R.; da Costa, B.D.C.; Neves, V.C.M. The Interrelationship between Periodontal Disease and Systemic Health. *Br. Dent. J.* **2025**, *239*, 103–108.
5. Martínez-García, M.; Hernández-Lemus, E. Periodontal Inflammation and Systemic Diseases: An Overview. *Front. Physiol.* **2021**, *12*, 709438.
6. van der Ploeg, G.R.; Brandt, B.W.; Keijser, B.J.F.; et al. Multi-Way Modelling of Oral Microbial Dynamics and Host-Microbiome Interactions during Induced Gingivitis. *NPJ Biofilms Microbiomes* **2024**, *10*, 89.
7. Peng, S.; Fu, H.; Li, R.; et al. A New Direction in Periodontitis Treatment: Biomaterial-Mediated Macrophage Immunotherapy. *J. Nanobiotechnol.* **2024**, *22*, 359.
8. Yan, B.; Yu, X.; Cai, X.; et al. A Review: The Significance of Toll-like Receptors 2 and 4, and NF-κB Signaling in Endothelial Cells during Atherosclerosis. *Front. Biosci. (Landmark Ed.)* **2024**, *29*, 161.
9. Dhakad, P.K.; Mishra, R.; Mishra, I. Toll-Like Receptor Expression during Inflammatory Processes in Human Diseases. *Rheumatol. Autoimmun.* **2025**, *5*, 1–14.
10. Fitzgerald, K.A.; Kagan, J.C. Toll-Like Receptors and the Control of Immunity. *Cell* **2020**, *180*, 1044–1066.
11. Duan, T.; Du, Y.; Xing, C.; et al. Toll-Like Receptor Signaling and Its Role in Cell-Mediated Immunity. *Front. Immunol.* **2022**, *13*, 812774.
12. Guerrero-Sabater, M.; Cosín-Villanueva, M.; Almiñana-Pastor, P.; et al. Expression of miRNAs in the Relation-

ship between Periodontitis and Cardiovascular Diseases: A Systematic Review. *Non-Coding RNA* **2025**, *11*, 37.
13. Zhang, J.; Chen, L.; Yu, J.; et al. Advances in the Roles and Mechanisms of Mesenchymal Stem Cell Derived MicroRNAs on Periodontal Tissue Regeneration. *Stem Cell Res. Ther.* **2024**, *15*, 393.
14. Bugueno, I.M.; Benkirane-Jessel, N.; Huck, O. Implication of Toll/IL-1 Receptor Domain Containing Adapters in *Porphyromonas gingivalis*-Induced Inflammation. *Innate Immun.* **2021**, *27*, 324–342.
15. Nativel, B.; Couret, D.; Giraud, P.; et al. *Porphyromonas gingivalis* Lipopolysaccharides Act Exclusively through TLR4 with a Resilience between Mouse and Human. *Sci. Rep.* **2017**, *7*, 15789.
16. Wang, K.; Huang, H.; Zhan, Q.; et al. Toll-Like Receptors in Health and Disease. *MedComm* **2024**, *5*, e549.
17. Tominari, T.; Matsumoto, C.; Tanaka, Y.; et al. Roles of Toll-Like Receptor Signaling in Inflammatory Bone Resorption. *Biology* **2024**, *13*, 692.
18. Pandruvada, S.N.; Ebersole, J.L.; Huja, S.S. Inhibition of Osteoclastogenesis by Opsonized *Porphyromonas gingivalis*. *FASEB BioAdv.* **2019**, *1*, 213–226.
19. Fernández, A.; Herrera, D.; Hoare, A.; et al. Lipopolysaccharides from *Porphyromonas endodontalis* and *Porphyromonas gingivalis* Promote Angiogenesis via Toll-Like-Receptors 2 and 4 Pathways In Vitro. *Int. Endod. J.* **2023**, *56*, 1270–1283.
20. Liu, S.; Liu, G.; Luan, Q.; et al. *Porphyromonas gingivalis* Lipopolysaccharide-Induced B Cell Differentiation by Toll-Like Receptors 2 and 4. *Protein Pept. Lett.* **2022**, *29*, 46–56.
21. Lu, W.; Gu, J.-Y.; Zhang, Y.-Y.; et al. Tolerance Induced by *Porphyromonas gingivalis* May Occur Independently of TLR2 and TLR4. *PLoS One* **2018**, *13*, e0200946.
22. Qiu, C.; Yuan, Z.; He, Z.; et al. Lipopolysaccharide Preparation Derived from *Porphyromonas gingivalis* Induces a Weaker Immuno-Inflammatory Response in BV-2 Microglial Cells than *Escherichia coli* by Differentially Activating TLR2/4-Mediated NF-κB/STAT3 Signaling Pathways. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 606986.
23. Kong, A.H.-Y.; Wu, A.J.; Ho, O.K.-Y.; et al. Exploring the Potential of Aptamers in Targeting Neuroinflammation and Neurodegenerative Disorders: Opportunities and Challenges. *Int. J. Mol. Sci.* **2023**, *24*, 11780.
24. Stephens, M. The Emerging Potential of Aptamers as Therapeutic Agents in Infection and Inflammation. *Pharmacol. Ther.* **2022**, *238*, 108173.
25. Ali Agha, A.S.; Alshaer, W.; Aburjai, T. Advancements and Challenges in Aptamer-Based Therapeutics and Diagnostics across Diverse Medical Domains: A Comprehensive Review. *Jordan J. Pharm. Sci.* **2024**, *17*, 344–361.
26. Lin, M.; Hu, Y.; Wang, Y.; et al. Different Engagement of TLR2 and TLR4 in *Porphyromonas gingivalis* vs. Ligature-Induced Periodontal Bone Loss. *Braz. Oral Res.* **2017**, *31*, e63.
27. Kim, H.Y.; Song, M.K.; Lim, Y.; et al. Effects of Extracellular Vesicles Derived from Oral Bacteria on Osteoclast Differentiation and Activation. *Sci. Rep.* **2022**, *12*, 14239.
28. Palm, E.; Demirel, I.; Bengtsson, T.; et al. The Role of Toll-Like and Protease-Activated Receptors and Associated Intracellular Signaling in *Porphyromonas gingivalis*-Infected Gingival Fibroblasts. *APMIS* **2017**, *125*, 157–169.
29. Hutcherson, J.A.; Bagaitkar, J.; Nagano, K.; et al. *Porphyromonas gingivalis* RagB Is a Proinflammatory Signal Transducer and Activator of Transcription 4 Agonist. *Mol. Oral Microbiol.* **2015**, *30*, 242–252.
30. Watanabe, N.; Yokoe, S.; Ogata, Y.; et al. Exposure to *Porphyromonas gingivalis* Induces Production of Proinflammatory Cytokine via TLR2 from Human Respiratory Epithelial Cells. *J. Clin. Med.* **2020**, *9*, 3433.
31. Tuladhar, A.; Guffroy, M.; Finnema, S.J.; et al. Investigation of Bone Toxicity in Drug Development: Review of Current and Emerging Technologies. *Toxicol. Sci.* **2025**, *208*, 207–224.
32. Hagan, M.L.; Tuladhar, A.; Yu, K.; et al. Osteocyte Sptbn1 Deficiency Alters Cell Survival and Mechanotransduction Following Formation of Plasma Membrane Disruptions (PMD) from Mechanical Loading. *Calcif. Tissue Int.* **2024**, *115*, 725–743.
33. Cheng, W.C.; van Asten, S.D.; Burns, L.A.; et al. Periodontitis-Associated Pathogens *P. gingivalis* and *A. actinomycetemcomitans* Activate Human CD14(+) Monocytes Leading to Enhanced Th17/IL-17 Responses. *Eur. J. Immunol.* **2016**, *46*, 2211–2221.
34. Mojtahedi, H.; Hossein-Khannazer, N.; Mahmoud Hashemi, S.; et al. Effects of Lipopolysaccharide from *Porphyromonas gingivalis* and *Escherichia coli* on Gene Expression Levels of Toll-Like Receptors and Inflammatory Cytokines in Human Dental Pulp Stem Cells. *Iran. J. Immunol.* **2022**, *19*, 299–310.
35. Sato, N.; Matsumoto, T.; Kawaguchi, S.; et al. *Porphyromonas gingivalis* Lipopolysaccharide Induces Interleukin-6 and C-C Motif Chemokine Ligand 2 Expression in Cultured hCMEC/D3 Human Brain Microvas-

cular Endothelial Cells. *Gerodontology* **2022**, *39*, 139–147.
36. Bekić, M.; Radanović, M.; Đokić, J.; et al. Mesenchymal Stromal Cells from Healthy and Inflamed Human Gingiva Respond Differently to *Porphyromonas gingivalis*. *Int. J. Mol. Sci.* **2022**, *23*, 3510.
37. Kajiwara, K.; Sawa, Y.; Fujita, T.; et al. Immunohistochemical Study for the Expression of Leukocyte Adhesion Molecules, and FGF23 and ACE2 in *P. gingivalis* LPS-Induced Diabetic Nephropathy. *BMC Nephrol.* **2021**, *22*, 3.
38. Ohgi, K.; Kajiya, H.; Goto-T, K.; et al. Toll-like receptor 2 activation primes and upregulates osteoclastogenesis via LOX-1. *Lipids Health Dis.* **2018**, *17*, 132.
39. Sun, J.-Y.; Li, D.-L.; Dong, Y.; et al. Baicalin inhibits toll-like receptor 2/4 expression and downstream signaling in rat experimental periodontitis. *Int. Immunopharmacol.* **2016**, *36*, 86–93.
40. Mendi, A.; Köse, S.; Uçkan, D.; et al. *Lactobacillus rhamnosus* Could Inhibit *Porphyromonas gingivalis* Derived CXCL8 Attenuation. *J. Appl. Oral Sci.* **2016**, *24*, 67–75.
41. Karlis, G.D.; Schöningh, E.; Jansen, I.D.C.; et al. Chronic exposure of gingival fibroblasts to TLR2 or TLR4 agonist inhibits osteoclastogenesis but does not affect osteogenesis. *Front. Immunol.* **2020**, *11*, 1693.
42. Su, H.; Yan, X.; Dong, Z.; et al. Differential Roles of *Porphyromonas gingivalis* Lipopolysaccharide and *Escherichia coli* Lipopolysaccharide in Maturation and Antigen-Presenting Functions of Dendritic Cells. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 2482–2492.
43. Palaska, I.; Gagari, E.; Theoharides, T.C. The effects of *P. gingivalis* and *E. coli* LPS on the expression of proinflammatory mediators in human mast cells and their relevance to periodontal disease. *J. Biol. Regul. Homeost. Agents* **2016**, *30*, 655–664.
44. Wilensky, A.; Tzach-Nahman, R.; Potempa, J.; et al. *Porphyromonas gingivalis* gingipains selectively reduce CD14 expression, leading to macrophage hyporesponsiveness to bacterial infection. *J. Innate Immun.* **2015**, *7*, 127–135.
45. Holden, J.A.; Attard, T.J.; Laughton, K.M.; et al. *Porphyromonas gingivalis* lipopolysaccharide weakly activates M1 and M2 polarized mouse macrophages but induces inflammatory cytokines. *Infect. Immun.* **2014**, *82*, 4190–4203.
46. Gokyu, M.; Kobayashi, H.; Nanbara, H.; et al. Thrombospondin-1 production is enhanced by *Porphyromonas gingivalis* lipopolysaccharide in THP-1 cells. *PLoS One* **2014**, *9*, e115107.
47. Cecil, J.D.; O'Brien-Simpson, N.M.; Lenzo, J.C.; et al. Differential responses of pattern recognition receptors to outer membrane vesicles of three periodontal pathogens. *PLoS One* **2016**, *11*, e0151967.
48. Ziauddin, S.M.; Montenegro Raudales, J.L.; Sato, K.; et al. Analysis of subgingival plaque ability to stimulate Toll-like receptor 2 and 4. *J. Periodontol.* **2016**, *87*, 1083–1091.
49. Blufstein, A.; Behm, C.; Nguyen, P.Q.; et al. Human periodontal ligament cells exhibit no endotoxin tolerance upon stimulation with *Porphyromonas gingivalis* lipopolysaccharide. *J. Periodontal Res.* **2018**, *53*, 589–597.
50. Albuquerque-Souza, E.; Balzarini, D.; Ando-Suguimoto, E.S.; et al. Probiotics alter the immune response of gingival epithelial cells challenged by *Porphyromonas gingivalis*. *J. Periodontal Res.* **2019**, *54*, 115–127.
51. Zhang, Y.; Li, X. Lipopolysaccharide-regulated production of bone sialoprotein and interleukin-8 in human periodontal ligament fibroblasts: The role of toll-like receptors 2 and 4 and the MAPK pathway. *J. Periodontal Res.* **2015**, *50*, 141–151.
52. Kajiwara, K.; Sawa, Y. Overexpression of SGLT2 in the kidney of a *P. gingivalis* LPS-induced diabetic nephropathy mouse model. *BMC Nephrol.* **2021**, *22*, 287.
53. Choi, Y.H.; Kim, B.S.; Kang, S.-S. Genomic DNA extracted from *Lactiplantibacillus plantarum* attenuates *Porphyromonas gingivalis* lipopolysaccharide (LPS)-induced inflammatory responses via suppression of Toll-like receptor (TLR)-mediated mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) signaling pathways. *Food Sci. Anim. Resour.* **2023**, *43*, 938–947.
54. Tada, H.; Suzuki, R.; Nemoto, E.; et al. Increases in IL-33 production by fimbriae and lipopeptide from *Porphyromonas gingivalis* in mouse bone marrow-derived dendritic cells via Toll-like receptor 2. *Biomed. Res.* **2017**, *38*, 189–195.
55. Waller, T.; Kesper, L.; Hirschfeld, J.; et al. *Porphyromonas gingivalis* outer membrane vesicles induce selective tumor necrosis factor tolerance in a Toll-like receptor 4- and mTOR-dependent manner. *Infect. Immun.* **2016**, *84*, 1194–1204.
56. Ohno, T.; Yamamoto, G.; Hayashi, J.I.; et al. Angiopoietin-like protein 2 regulates *Porphyromonas gingivalis* lipopolysaccharide-induced inflammatory response in human gingival epithelial cells. *PLoS One* **2017**, *12*, e0184825.
57. Ramenzoni, L.L.; Zuellig, R.A.; Hussain, A.; et al. Bacterial supernatants elevate glucose-dependent insulin

secretion in rat pancreatic INS-1 line and islet β-cells via PI3K/AKT signaling. *Mol. Cell. Biochem.* **2019**, *452*, 17–27.
58. Palm, E.; Demirel, I.; Bengtsson, T.; et al. The role of toll-like and protease-activated receptors in the expression of cytokines by gingival fibroblasts stimulated with the periodontal pathogen *Porphyromonas gingivalis*. *Cytokine* **2015**, *76*, 424–432.
59. Savitri, I.J.; Ouhara, K.; Fujita, T.; et al. Irsogladine maleate inhibits *Porphyromonas gingivalis*-mediated expression of toll-like receptor 2 and interleukin-8 in human gingival epithelial cells. *J. Periodontal Res.* **2015**, *50*, 486–493.
60. Gu, Y.; Raja, V.; Lee, H.-M.; et al. Therapeutic potential of a novel semi-synthetic-sulfated-polysaccharide to suppress inflammatory mediators in *P. gingivalis* LPS stimulated human monocytes/macrophages. *J. Inflamm. (Lond.)* **2021**, *18*, 26.
61. Xu, W.; Zhou, W.; Wang, H.; et al. Roles of *Porphyromonas gingivalis* and Its Virulence Factors in Periodontitis. *Adv. Protein Chem. Struct. Biol.* **2020**, *120*, 45–84.
62. Robling, A.G.; Bonewald, L.F. The Osteocyte: New Insights. *Annu. Rev. Physiol.* **2020**, *82*, 485–506.
63. Omi, M.; Mishina, Y. Roles of Osteoclasts in Alveolar Bone Remodeling. *Genesis* **2022**, *60*, e23490.
64. Yoshimoto, T.; Kittaka, M.; Doan, A.A.P.; et al. Osteocytes Directly Regulate Osteolysis via MYD88 Signaling in Bacterial Bone Infection. *Nat. Commun.* **2022**, *13*, 6648.
65. Yang, M.; Ma, Y.; Qu, X.; et al. Inhibition of Sclerostin Activity Promotes Bone Regeneration in Experimental Periodontal Disease: A Systematic Review and Meta-Analysis of Animal Models. *Exp. Ther. Med.* **2026**, *31*, 31.
66. Milacic, M.; Beavers, D.; Conley, P.; et al. The Reactome Pathway Knowledgebase 2024. *Nucleic Acids Res.* **2024**, *52*, D672–D678.
67. Watson, J.; Smith, M.; Francavilla, C.; et al. SubcellulaRVis: A Web-Based Tool to Simplify and Visualise Subcellular Compartment Enrichment. *Nucleic Acids Res.* **2022**, *50*, W718–W725.
68. Del Santos, N.; Vázquez-Ramírez, R.; Mendes, E.; et al. Impact of Mygalin on Inflammatory Response Induced by Toll-Like Receptor 2 Agonists and IFN-γ Activation. *Int. J. Mol. Sci.* **2024**, *25*, 10555.
69. Salauddin, M.; Bhattacharyya, D.; Samanta, I.; et al. Role of TLRs as Signaling Cascades to Combat Infectious Diseases: A Review. *Cell. Mol. Life Sci.* **2025**, *82*, 122.
70. Bhol, N.K.; Bhanjadeo, M.M.; Singh, A.K.; et al. The Interplay between Cytokines, Inflammation, and Antioxidants: Mechanistic Insights and Therapeutic Potentials of Various Antioxidants and Anti-Cytokine Compounds. *Biomed. Pharmacother.* **2024**, *178*, 117177.
71. Chiu, C.-Y.; Willis-Owen, S.A.G.; Wong, K.C.C.; et al. MAP3K8 Is a Potential Therapeutic Target in Airway Epithelial Inflammation. *J. Inflamm.* **2024**, *21*, 27.
72. Philippe, L.; Alsaleh, G.; Suffert, G.; et al. TLR2 expression is regulated by microRNA miR-19 in rheumatoid fibroblast-like synoviocytes. *J. Immunol.* **2012**, *188*, 454–461.
73. Zhou, W.; Su, L.; Duan, X.; et al. MicroRNA-21 down-regulates inflammation and inhibits periodontitis. *Mol. Immunol.* **2018**, *101*, 608–614.
74. Benakanakere, M.R.; Li, Q.; Eskan, M.A.; et al. Modulation of TLR2 protein expression by miR-105 in human oral keratinocytes. *J. Biol. Chem.* **2009**, *284*, 23107–23115.
75. Zhu, J.; Zhong, Z. The expression and clinical significance of miR-30b-3p and miR-125b-1-3p in patients with periodontitis. *BMC Oral Health* **2022**, *22*, 325.
76. Wang, Y.; Zhang, X.; Wang, J.; et al. Inflammatory periodontal ligament stem cells drive M1 macrophage polarization via exosomal miR-143-3p-mediated regulation of PI3K/AKT/NF-κB signaling. *Stem Cells* **2023**, *41*, 184–199.
77. Xie, H.; Qin, Z.; Ling, Z.; et al. Oral pathogen aggravates atherosclerosis by inducing smooth muscle cell apoptosis and repressing macrophage efferocytosis. *Int. J. Oral Sci.* **2023**, *15*, 26.
78. Jiang, S.-Y.; Xue, D.; Xie, Y.-F.; et al. The negative feedback regulation of microRNA-146a in human periodontal ligament cells after *Porphyromonas gingivalis* lipopolysaccharide stimulation. *Inflamm. Res.* **2015**, *64*, 441–451.
79. Yoshida, K.; Yoshida, K.; Mouri, Y.; et al. *Porphyromonas gingivalis* infection alters microRNA composition in extracellular vesicles. *J. Oral Biosci.* **2024**, *66*, 365–372.
80. Li, H.-L.; Liu, Y.-H.; Shang, X.-B.; et al. Effect of miR-223 on thrombophlebitis rats through regulating Toll-like receptor signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 2020–2027.
81. Venugopal, P.; Lavu, V.; Rao, S.R.; et al. Association of microRNA-125a and microRNA-499a polymorphisms in chronic periodontitis in a sample South Indian population: A hospital-based genetic association study.

Gene **2017**, *631*, 10–15.
82. Molteni, M.; Bosi, A.; Rossetti, C. The effect of cyanobacterial LPS antagonist (CyP) on cytokines and microRNA expression induced by *Porphyromonas gingivalis* LPS. *Toxins* **2018**, *10*, 290.
83. Liao, Z.; Zheng, R.; Shao, G. Mechanisms and application strategies of miRNA-146a regulating inflammation and fibrosis at molecular and cellular levels. *Int. J. Mol. Med.* **2022**, *51*, 7.
84. Wendlandt, E.B.; Graff, J.W.; Gioannini, T.L.; et al. The role of microRNAs miR-200b and miR-200c in TLR4 signaling and NF-κB activation. *Innate Immun.* **2012**, *18*, 846–855.
85. Zhang, Z.; Wang, M.; Zheng, Y.; et al. MicroRNA-223 negatively regulates the osteogenic differentiation of periodontal ligament derived cells by directly targeting growth factor receptors. *J. Transl. Med.* **2022**, *20*, 465.
86. Qu, H.; Liu, R.; Chen, J.; et al. Aerobic exercise inhibits CUMS-depressed mice hippocampal inflammatory response via activating hippocampal miR-223/TLR4/MyD88-NF-κB pathway. *Int. J. Environ. Res. Public Health* **2020**, *17*, 2676.
87. Li, J.; Lin, T.-Y.; Chen, L.; et al. miR-19 regulates the expression of interferon-induced genes and MHC class I genes in human cancer cells. *Int. J. Med. Sci.* **2020**, *17*, 953.
88. Cañas, J.A.; Rodrigo-Muñoz, J.M.; Sastre, B.; et al. MicroRNAs as potential regulators of immune response networks in asthma and chronic obstructive pulmonary disease. *Front. Immunol.* **2020**, *11*, 608666.
89. Aravindraja, C.; Vekariya, K.M.; Botello-Escalante, R.; et al. Specific microRNA signature kinetics in *Porphyromonas gingivalis*-induced periodontitis. *Int. J. Mol. Sci.* **2023**, *24*, 2327.
90. Peng, C.; Wang, H.; Zhang, W.-J.; et al. Inhibitory effect of miR-125b on hepatitis C virus core protein-induced TLR2/MyD88 signaling in THP-1 cells. *World J. Gastroenterol.* **2016**, *22*, 4354–4361.
91. Malleswarapu, M.; Kovuru, N.; Khan, N.; et al. Significance of TLR2 signaling during megakaryocyte development: Regulatory cross-talk of miR-125b, cytokine induction, and MAPK pathway during dengue infection. *Am. J. Transl. Res.* **2023**, *15*, 5972–5983.
92. Saba, R.; Sorensen, D.L.; Booth, S.A. MicroRNA-146a: A dominant, negative regulator of the innate immune response. *Front. Immunol.* **2014**, *5*, 578.
93. Zeng, R.; Xu, H.; Liu, Y.; et al. miR-146a inhibits biofilm-derived *Cutibacterium acnes*–induced inflammatory reactions in human keratinocytes. *J. Invest. Dermatol.* **2019**, *139*, 2488–2496.
94. Taganov, K.D.; Boldin, M.P.; Chang, K.-J.; et al. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12481–12486.
95. Jeepipalli, S.; Gurusamy, P.; Martins, A.; et al. Altered microRNA expression correlates with reduced TLR2/4-dependent periodontal inflammation and bone resorption induced by polymicrobial infection. *Microbiol. Spectr.* **2025**, *13*, e0016025.
96. Qayum, A.A.; Paranjape, A.; Abebayehu, D.; et al. IL-10-induced miR-155 targets SOCS1 to enhance IgE-mediated mast cell function. *J. Immunol.* **2016**, *196*, 4457–4467.
97. Weber, M.; Kim, S.; Patterson, N.; et al. MiRNA-155 targets myosin light chain kinase and modulates actin cytoskeleton organization in endothelial cells. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *306*, H1192–H1203.
98. Bras, J.P.; Silva, A.M.; Calin, G.A.; et al. miR-195 inhibits macrophages pro-inflammatory profile and impacts the crosstalk with smooth muscle cells. *PLoS One* **2017**, *12*, e0188530.
99. Akino Mercy, C.S.; Suriya Muthukumaran, N.; Velusamy, P.; et al. MicroRNAs regulated by the LPS/TLR2 immune axis as bona fide biomarkers for diagnosis of acute leptospirosis. *mSphere* **2020**, *5*, e00409-20.
100. Gaudet, A.D.; Fonken, L.K.; Watkins, L.R.; et al. MicroRNAs: Roles in regulating neuroinflammation. *Neuroscientist* **2018**, *24*, 221–245.
101. Lai, L.; Song, Y.; Liu, Y.; et al. MicroRNA-92a negatively regulates Toll-like receptor (TLR)-triggered inflammatory response in macrophages by targeting MKK4 kinase. *J. Biol. Chem.* **2013**, *288*, 7956–7967.
102. Niu, W.; Sun, B.; Li, M.; et al. TLR-4/microRNA-125a/NF-κB signaling modulates the immune response to *Mycobacterium tuberculosis* infection. *Cell Cycle* **2018**, *17*, 1931–1945.
103. Duroux-Richard, I.; Roubert, C.; Ammari, M.; et al. miR-125b controls monocyte adaptation to inflammation through mitochondrial metabolism and dynamics. *Blood* **2016**, *128*, 3125–3136.
104. Xin, Y.; Yuan, Q.; Liu, C.; et al. MiR-155/GSK-3β mediates anti-inflammatory effect of Chikusetsusaponin IVa by inhibiting NF-κB signaling pathway in LPS-induced RAW264.7 cell. *Sci. Rep.* **2020**, *10*, 18303.
105. Olsen, I.; Singhrao, S.K.; Osmundsen, H. Periodontitis, pathogenesis and progression: miRNA-mediated cellular responses to *Porphyromonas gingivalis*. *J. Oral Microbiol.* **2017**, *9*, 1333396.
106. Herrera-Uribe, J.; Zaldívar-López, S.; Aguilar, C.; et al. Study of microRNA expression in *Salmonella Ty-*

phimurium-infected porcine ileum reveals miR-194a-5p as an important regulator of the TLR4-mediated inflammatory response. *Vet. Res.* **2022**, *53*, 35.
107. Cai, K.; Ke, J.; Wang, Y.; et al. MIR-194 is related to the pathogenesis of asthma by regulating TLR4 expression. *Int. J. Clin. Exp. Pathol.* **2016**, *9*, 1327–1334.
108. Hsieh, P.-L.; Huang, C.-C.; Yu, C.-C. Emerging role of microRNA-200 family in dentistry. *Non-Coding RNA* **2021**, *7*, 35.
109. Smith, E.S.; Whitty, E.; Yoo, B.; et al. Clinical applications of short non-coding RNA-based therapies in the era of precision medicine. *Cancers* **2022**, *14*, 1588.
110. Xiao, X.; Mao, X.; Chen, D.; et al. miRNAs can affect intestinal epithelial barrier in inflammatory bowel disease. *Front. Immunol.* **2022**, *13*, 868229.
111. Giunti, D.; Marini, C.; Parodi, B.; et al. Role of miRNAs shuttled by mesenchymal stem cell-derived small extracellular vesicles in modulating neuroinflammation. *Sci. Rep.* **2021**, *11*, 1740.
112. Liu, H.; Chen, Y.; Yin, G.; et al. Therapeutic prospects of microRNAs carried by mesenchymal stem cell-derived extracellular vesicles in autoimmune diseases. *Life Sci.* **2021**, *277*, 119458.
113. Lee, S.W.L.; Paoletti, C.; Campisi, M.; et al. MicroRNA delivery through nanoparticles. *J. Control. Release* **2019**, *313*, 80–95.
114. Meng, W.-T.; Zhu, J.; Wang, Y.-C.; et al. Targeting delivery of miR-146a via IMTP modified milk exosomes exerted cardioprotective effects by inhibiting NF-κB signaling pathway after myocardial ischemia-reperfusion injury. *J. Nanobiotechnol.* **2024**, *22*, 382.
115. Gaál, Z. Role of microRNAs in immune regulation with translational and clinical applications. *Int. J. Mol. Sci.* **2024**, *25*, 1942.
116. Aboul-Ella, H.; Gohar, A.; Ali, A.A.; et al. Monoclonal antibodies: From magic bullet to precision weapon. *Mol. Biomed.* **2024**, *5*, 47.
117. Domsicova, M.; Korcekova, J.; Poturnayova, A.; et al. New insights into aptamers: An alternative to antibodies in the detection of molecular biomarkers. *Int. J. Mol. Sci.* **2024**, *25*, 6833.
118. Agnello, L.; Camorani, S.; Fedele, M.; et al. Aptamers and antibodies: Rivals or allies in cancer targeted therapy? *Explor. Target Antitumor Ther.* **2021**, *2*, 107–121.
119. Kawai, T.; Ikegawa, M.; Ori, D.; et al. Decoding Toll-like receptors: Recent insights and perspectives in innate immunity. *Immunity* **2024**, *57*, 649–673.
120. Rajpoot, S.; Wary, K.K.; Ibbott, R.; et al. TIRAP in the mechanism of inflammation. *Front. Immunol.* **2021**, *12*, 697588.
121. Colleselli, K.; Stierschneider, A.; Wiesner, C. An update on Toll-like receptor 2, its function and dimerization in pro- and anti-inflammatory processes. *Int. J. Mol. Sci.* **2023**, *24*, 12464.
122. Hu, W.; Spaink, H.P. The role of TLR2 in infectious diseases caused by mycobacteria: From cell biology to therapeutic target. *Biology* **2022**, *11*, 246.
123. Ciesielska, A.; Matyjek, M.; Kwiatkowska, K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. *Cell. Mol. Life Sci.* **2021**, *78*, 1233–1261.
124. Mansouri, A.; Akthar, I.; Miyamoto, A. TLR2 and TLR4 bridge physiological and pathological inflammation in the reproductive system. *Commun. Biol.* **2025**, *8*, 1008.
125. Ren, W.; Zhao, L.; Sun, Y.; et al. HMGB1 and Toll-like receptors: Potential therapeutic targets in autoimmune diseases. *Mol. Med.* **2023**, *29*, 117.
126. Arslan, F.; Houtgraaf, J.H.; Keogh, B.; et al. Treatment with OPN-305, a humanized anti-Toll-like receptor-2 antibody, reduces myocardial ischemia/reperfusion injury in pigs. *Circ. Cardiovasc. Interv.* **2012**, *5*, 279–287.
127. Reilly, M.; Miller, R.M.; Thomson, M.H.; et al. Randomized, double-blind, placebo-controlled, dose-escalating phase I, healthy subjects study of intravenous OPN-305, a humanized anti-TLR2 antibody. *Clin. Pharmacol. Ther.* **2013**, *94*, 593–600.
128. Monnet, E.; Choy, E.H.; McInnes, I.; et al. Efficacy and safety of NI-0101, an anti-toll-like receptor 4 monoclonal antibody, in patients with rheumatoid arthritis after inadequate response to methotrexate: A phase II study. *Ann. Rheum. Dis.* **2020**, *79*, 316–323.
129. Matsunaga, N.; Tsuchimori, N.; Matsumoto, T.; et al. TAK-242 (resatorvid), a small-molecule inhibitor of Toll-like receptor (TLR) 4 signaling, binds selectively to TLR4 and interferes with interactions between TLR4 and its adaptor molecules. *Mol. Pharmacol.* **2011**, *79*, 34–41.
130. Feng, Y.; Gao, J.; Cui, Y.; et al. Neuroprotective effects of resatorvid against traumatic brain injury in rat: Involvement of neuronal autophagy and TLR4 signaling pathway. *Cell. Mol. Neurobiol.* **2017**, *37*, 155–168.

131. Huang, X.; Lin, R.; Liu, H.; et al. Resatorvid (TAK-242) ameliorates ulcerative colitis by modulating macrophage polarization and T helper cell balance via TLR4/JAK2/STAT3 signaling pathway. *Inflammation* **2024**, *47*, 2108–2128.
132. Tu, X.K.; Yang, W.Z.; Chen, J.P.; et al. Curcumin inhibits TLR2/4-NF-κB signaling pathway and attenuates brain damage in permanent focal cerebral ischemia in rats. *Inflammation* **2014**, *37*, 1544–1551.
133. Jo, W.S.; Kim, S.D.; Jeong, S.K.; et al. Resveratrol analogue, HS-1793, inhibits inflammatory mediator release from macrophages by interfering with the TLR4-mediated NF-κB activation. *Food Sci. Biotechnol.* **2022**, *31*, 433–441.
134. Hernández-Jiménez, M.; Martín-Vílchez, S.; Ochoa, D.; et al. First-in-human phase I clinical trial of a TLR4-binding DNA aptamer, ApTOLL: Safety and pharmacokinetics in healthy volunteers. *Mol. Ther. Nucleic Acids* **2022**, *28*, 124–135.
135. Yang, G.; Zhang, S.; Wang, Y.; et al. Aptamer blocking S-TLR4 interaction selectively inhibits SARS-CoV-2-induced inflammation. *Signal Transduct. Target. Ther.* **2022**, *7*, 120.
136. Chang, Y.C.; Kao, W.C.; Wang, W.Y.; et al. Identification and characterization of oligonucleotides that inhibit Toll-like receptor 2-associated immune responses. *FASEB J.* **2009**, *23*, 3078–3088.
137. Fernández, G.; Moraga, A.; Cuartero, M.I.; et al. TLR4-binding DNA aptamers show a protective effect against acute stroke in animal models. *Mol. Ther.* **2018**, *26*, 2047–2059.