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Phlorotannin-Mediated Upregulation of LL-37 as an Antimicrobial Peptide Against *Porphyromonas gingivalis* in Periodontitis

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Abstract: *Periodontitis affects 74.1% of Indonesians, with Porphyromonas gingivalis as a key pathogen. Antibiotics remain the standard therapy but are limited by resistance and adverse effects, including gastrointestinal disturbances, allergic reactions, and taste alteration, highlighting the need for safer alternatives. Indonesia is rich in edible brown algae such as Ecklonia cava, Sargassum sp., Rugulopteryx okamurae, and Ascophyllum nodosum, which contain phlorotannins with antibacterial and anti-inflammatory properties. Emerging evidence indicates that phlorotannins may enhance LL-37, an endogenous antimicrobial peptide effective against P. gingivalis. This review explores the potential of phlorotannins to enhance the antimicrobial and immunomodulatory activity of LL-37 in periodontitis. A literature review was conducted focusing on (1) phlorotannin extraction and bioactivity, (2) its effects on LL-37, and (3) the role of LL-37 in periodontitis, selecting studies published within the last ten years. Brown algae–derived phlorotannins exhibit strong antimicrobial, antioxidant, and anti-inflammatory effects, particularly when extracted using microwave-assisted extraction at 180°C for 10 minutes with ethanol (1:20 w/v). Phlorotannins enhance LL-37 α-helical stability, increase antibacterial efficacy, reduce cytotoxicity, inhibit P. gingivalis biofilm formation, promote autophagy-mediated bacterial clearance, and support periodontal tissue regeneration. Phlorotannin-mediated enhancement of LL-37 represents a promising natural adjunctive strategy for periodontitis management, warranting further investigation.*

Keywords- *antimicrobial, LL-37, periodontitis, phlorotannin, Porphyromonas gingivalis*

I. Introduction

Periodontitis is an inflammatory disease triggered by infection in the periodontal tissues [1]. Periodontal pathogens detected in subgingival pockets and responsible for the pathogenesis and progression of periodontitis include *Porphyromonas gingivalis, Tannerella for sythensis, Treponema denticola, Prevotella intermedia, and Aggregatibacter actinomycetemcomitans* [2]. The formation of acquired pellicle on the tooth surface allows initial colonization by *Streptococcus*, *Veillonella*, and *Actinomyces*, which then develop into mature biofilms through specific interspecies coaggregation. *Fusobacterium nucleatum* acts as a bridging organism that connects early colonizers such as *P. gingivalis, T. forsythia, and T. Denticola* [3, 4]. The presence of these bacteria, especially *P. gingivalis* triggers an excessive immune response and periodontal tissue damage, and it has been shown to cause alveolar bone resorption through increased osteoclasts and decreased osteoblasts [2,4].

Clinically, initial periodontitis therapy can rely on scaling and root planing (SRP) as the gold standard and can be supplemented with systemic antibiotics as adjuvant therapy when SRP alone is not sufficiently effective [5, 6, 7]. Antibiotics have been a mainstay of bacterial infection control since the early 20th century [8, 9, 10]. The classes of antibiotics used, such as tetracyclines, aminoglycosides, macrolides, and quinolones, work through mechanisms such as protein synthesis inhibition, cell wall synthesis inhibition, membrane depolarization, or DNA synthesis inhibition [8, 11]. However, the use of systemic antibiotics carries the risk of side effects such as nausea, vomiting, diarrhea, abdominal pain, allergic reactions, taste disturbances, photosensitivity, angioedema, or cholestatic jaundice, as well as the risk of arrhythmia with the use of azithromycin [7, 12, 13,]. Inappropriate use also contributes to increased antimicrobial resistance, as demonstrated in studies by Chaimma et al. and Flávia Casale Abe et al., and reinforced by Ika et al.'s meta-analysis, which found that the prevalence of extended spectrum beta-lactamase in Indonesia reached 46.38%, indicating that nearly half of the bacterial samples studied were resistant to systemic antibiotics [14, 15, 16].

The limitations of systemic antibiotics in the long term have prompted the search for safer and more effective therapeutic alternatives. One of the body's natural defenses against infection is antimicrobial peptides (AMPs), small cationic peptides that play an important role in the innate immune system [17]. AMPs in the oral cavity are produced by the salivary glands, gingival crevicular fluid (GCF), and oral epithelium [3, 17], and are divided into six main groups, including cationic peptides and protease inhibitors. Two endogenous AMPs that play an important role in fighting periodontal pathogens are cathelicidin LL-37 and β-defensin-2 [3]. LL-37 is produced by various cells and functions to form pores in bacterial membranes, neutralize lipopolysaccharides (LPS), and enhance phagocytosis [17,18]. Additionally, LL-37 can induce autophagy, a process of degrading and recycling proteins and organelles to maintain intracellular homeostasis [19]. LL-37 expression increases in inflamed gingival tissue and correlates with the severity of periodontitis [17] making it an attractive alternative candidate for antibiotic-independent antimicrobial therapy.

In the search for bioactive compounds that can support the stability and effectiveness of LL-37, Indonesia offers substantial potential through its rich diversity of brown algae from the Phaeophyta group. However, its use is still limited to the production of alginate for the food and pharmaceutical industries [20, 21, 22]. In fact, brown algae contain phlorotannin (PL), unique polyphenolic compounds found in *Ecklonia cava*, *Sargassum sp.*, *Rugulopteryx okamurae*, and *Ascophyllum nodosum*, which have a simpler structure than terrestrial tannins and are composed of phloroglucinol polymerization [21].

In the field of dentistry, research on PL is still very limited, even though this compound is known to have antibacterial, antioxidant, anti-inflammatory, antiproliferative, antitumor, and anti-allergic activities [21, 22, 23]. The title PL-Mediated Upregulation of LL-37 as an Antimicrobial Peptide Against Porphyromonas gingivalis in Periodontitis was chosen based on the high prevalence of periodontitis in Indonesia, which is 74.1% in the population aged ≥15 years [24], as well as the need for therapeutic alternatives that do not rely on systemic antibiotics, given the limited effectiveness of antibiotic therapy, increasing antimicrobial resistance, and the urgency to develop therapeutic alternatives that do not rely on systemic antibiotics, given the limited effectiveness of antibiotics, increasing antimicrobial resistance, and the high burden of periodontitis, which necessitates a safer and more sustainable therapeutic approach.

II. METHOD

This narrative review focuses on the potential of LL-37 induced or enhanced by PL extracts from brown algae as an antimicrobial alternative in inhibiting periodontitis pathogens, thereby potentially replacing dependence on conventional antibiotics. However, due to the very limited literature discussing these three variables directly or simultaneously, the literature selection process was conducted through three separate search phases to ensure comprehensive and relevant scientific coverage.

All searches were conducted using the PubMed database, with a combination of specific keywords in each phase. Inclusion criteria were established using PICOS: studies with a periodontitis model (P), upregulation of LL-37 by PL (I), without PL (C), reports of results related to antibacterial, inflammatory, autophagy, structural changes, or biofilm (O), and clinical, in vivo, in vitro, or literature review studies (S). The literature considered was limited to publications from the last 10 years, open access, and relevant to the thematic focus of each phase. Articles could be in the form of clinical trials, in vivo, in vitro, literature reviews, and case reports. Studies using interventions other than PL – LL-37 –periodontitis were excluded.

2.1 Stage 1: Extraction of PL from Brown Algae

Keyword: *phlorotannin*, *brown algae*, *antimicrobial peptides (AMPs)*
Results: 2
The following table presents the inclusion and exclusion criteria for this stage of the literature selection process can be seen in TABLE 1.

Table 1. Inclusion and Exclusion Criteria of Stage 1: Extraction of PL from Brown Algae

Inclusion	**Exclusion**
Literatures from the past 10 years	Articles that are not accessible
Research on PL extracted from any species of brown algae	Research that does not extract PL from brown algae
Literatures describing the antimicrobial properties of PL	Literatures that do not evaluate the antimicrobial properties of PL

Included: 2

2.2 Stage 2: Effects of PL on LL-37

Keyword: *phlorotannin*, *LL-37*, *antimicrobial peptides (AMPs)*
Results: 1
The following table presents the inclusion and exclusion criteria for this stage of the literature selection process can be seen in TABLE 2.

Table 2. Inclusion and Exclusion Criteria of Stage 2: Effects of PL on LL-37

Inclusion	**Exclusion**
Literatures from the past 10 years	Articles that are not accessible

Studies evaluating the effect of PLon the expression, induction, or modulation of LL-37	Studies with interventions other than PL

Included: 1

2.3 Stage 3: Role of LL-37 against *P. gingivalis* in Periodontitis

Keyword: *LL-37*, *periodontitis*, *tissue regeneration*
Results: 36
The following table presents the inclusion and exclusion criteria for this stage of the literature selection process can be seen in TABLE 3.

Table 3. Inclusion and Exclusion Criteria of Stage 3: Role of LL-37 against *P. gingivalis* in Periodontitis

Inclusion	**Exclusion**
Literatures from the past 10 years	Articles that are not accessible
Literature discussing the role of LL-37 in periodontitis, including mechanisms against *P. gingivalis*, immune modulation, or inflammatory response	Literatures discussing antimicrobial peptides broadly without a specific emphasis on LL-37
	LL-37 interventions other than PL for modulation
	Studies investigating LL-37's effects in settings other than periodontitis
	Research focusing only on non-periodontal biomarkers or non-relevant conditions

Included: 4

In accordance with the narrative review format, no formal quality assessment tools were used. However, each article was selected based on methodological accuracy, strength of evidence and citations, direct relevance to the theme of PL - LL-37 - periodontitis, and its contribution to explaining the antimicrobial mechanism and biological effects of LL-37.

Through this three-phase approach, the review produced a comprehensive mapping of how PL from brown algae can play a role in modulating LL-37 and how LL-37 itself functions in controlling periodontitis pathogens, inflammation, and periodontal regenerative processes.

III. DISCUSSION

3.1 Extraction Techniques of Brown-Algae-Derived PL

PL is a bioactive compound from brown algae that can enhance LL-37 as an antibacterial agent for periodontitis. Therefore, PL extraction is essential [25]. There are several methods for extracting PL content, such as the conventional method using solvents and the modern extraction method, namely Microwave-Assisted Extraction, which utilizes rapid heating using high-pressure water [26].

The conventional extraction process usually involves drying and grinding the algae, followed by maceration or soaking in the solvent while stirring, then filtration and concentration of the extract using a rotary evaporator [26]. The materials that can be used in this method are ethanol, acetone, methanol, or a mixture of these materials [25, 26]. Polar organic solvents, especially ethanol and acetone, are capable of extracting polyphenolic compounds with high efficiency. The selection of an aqueous solvent (e.g., 70% ethanol) increases PL yield because the combination of water and ethanol polarity improves solubility. In addition, the use of low to moderate temperatures (≤40–50°C) helps maintain the stability of easily degraded compounds [26].

However, solvent methods have disadvantages such as their impact on the environment and the storage and disposal of solvents. Other alternative methods are still being researched to improve efficiency and sustainability while minimizing environmental impact [25].

Therefore, the use of a more modern extraction method, Microwave-Assisted Extraction (MAE), which works through rapid heating using high-pressure water with optimal conditions of 180 °C for 10 minutes, as it can dissolve more than 40% of the initial biomass and produce an extract in the form of alginate (3.2%) and phenolic content (2.3%) with high antioxidant activity thanks to polyphenols, while offering short extraction times, high efficiency, and minimal degradation of sensitive compounds. Another alternative is biopretreatment through Solid-State Fermentation (SSF) using Aspergillus awamori followed by enzymatic hydrolysis, which increases total reducing sugars, especially glucose, and breaks down cell walls, thereby increasing PL release efficiency [27]. In extract form, PL has environmentally friendly properties and is safe for consumption. Research shows that PL from brown algae, as a new food source, can be safely added to food supplements. The study adds information on maximum intake levels of 163 mg per day for adolescents aged 12-14 years, 230 mg per day for adolescents over 14 years, and 263 mg per day for adults [25].

3.2 Mechanistic Role of PL in Enhancing LL-37 Function

Only one piece of literature discusses the role of PL in LL-37. Based on the document by Li et al. [25], PL plays a crucial role in enhancing the effectiveness of LL-37 through comprehensive structural and functional modulation. Circular dichroism spectroscopy analysis revealed that the combination of PL and LL-37 induced significant changes in the secondary structure of the peptide, with an increase in the proportion of α-helix and β-fold accompanied by a decrease in the proportion of β-turn and random coil. This structural transformation has profound biological implications, given that peptides with an α-helix structure are amphipathic with one end as a hydrophilic region and the corresponding end as a hydrophobic region, which is the fundamental basis for the antimicrobial function of antimicrobial peptides. Previous studies have indicated that the α-helix conformation facilitates stronger binding between antimicrobial peptides and cell membranes, establishing a significant correlation between helicity and antibacterial activity. Furthermore, peptides that adopt a β-fold structure have disulfide bonds that contribute to the stabilization of the peptide structure, thereby maintaining its integrity during cell membrane penetration and enhancing its bactericidal functionality. Consequently, modifying the proportion of secondary structures in PL/LL-37 results in increased overall structural stability and ultimately improves its antibacterial properties [25].

PL substantially improves the safety and biocompatibility of LL-37 while maintaining and even enhancing its antimicrobial efficacy. Cytotoxicity evaluation using MC3T3-E1, BMSCs, and RAW264.7 cells demonstrated that high concentrations of LL-37 (150–300 μg/mL) exhibited significant cytotoxicity, particularly on day 5 of culture. However, the addition of 10 mg/mL PL dramatically mitigated the cytotoxicity of LL-37, particularly at high concentrations, suggesting that PL may interact with LL-37 and reduce its free concentration in the culture medium. This phenomenon is clinically relevant, given that previous studies have reported that although high concentrations of LL-37 have anti-inflammatory effects, the peptide can exacerbate periodontal tissue destruction due to its toxicity to host cells. Paradoxically, although LL-37 levels are elevated in the periodontal tissues of type 2 diabetes mellitus patients, these individuals remain susceptible to periodontal infection, likely due to the cytotoxic effects caused by high concentrations of LL-37 on host cells. Therefore, the PL/LL-37 combination offers a safer therapeutic solution by reducing the cytotoxicity of LL-37 while maintaining its antimicrobial efficacy [25]. PL synergistically enhances the antimicrobial activity of LL-37 against Porphyromonas gingivalis through multiple complementary mechanisms. Disc diffusion assay results showed that the PL/LL-37 combination (10 mg/mL PL, 50 µg/mL LL-37) exhibited potent antibacterial activity with an inhibition zone diameter of 11 mm, indicating that PL incorporation can enhance the antimicrobial efficacy of LL-37 against P. gingivalis. These results are particularly striking given that the concentration of LL-37 used (50 µg/mL) was below the minimum inhibitory concentration (MIC) previously reported for LL-37 alone against P. gingivalis (20 µM ≈ 90 µg/mL). Further quantitative evaluation via the diluted plate count method confirmed the antibacterial superiority of PL/LL-37 (10 mg/mL PL, 100 µg/mL LL-37) over LL-37 alone ($P < 0.01$), with efficacy comparable to chlorhexidine and minocycline without statistically significant differences. The antibacterial mechanism of PL/LL-37 involves the formation of ion channels in the microbial cell membrane and binding to bacterial membrane endotoxins, as observed through scanning electron microscopy, which revealed significant damage to the P. gingivalis cell membrane, including the formation of lacunae and plasma membrane rupture, resulting in leakage of intracellular contents. Even more impressively, PL/LL-37 demonstrated superior ability to inhibit bacterial adhesion, biofilm formation, and destruction of established P. gingivalis biofilm compared to LL-37 alone, with crystal violet staining confirming that both LL-37 ($P < 0.0001$) and PL/LL-37 ($P < 0.0001$) caused a considerable effect on the eradication of established bacterial biofilms, although PL/LL-37 showed superior efficacy in inhibiting P. gingivalis biofilm formation compared to LL-37 alone ($P < 0.01$) (Figure 1) [25].

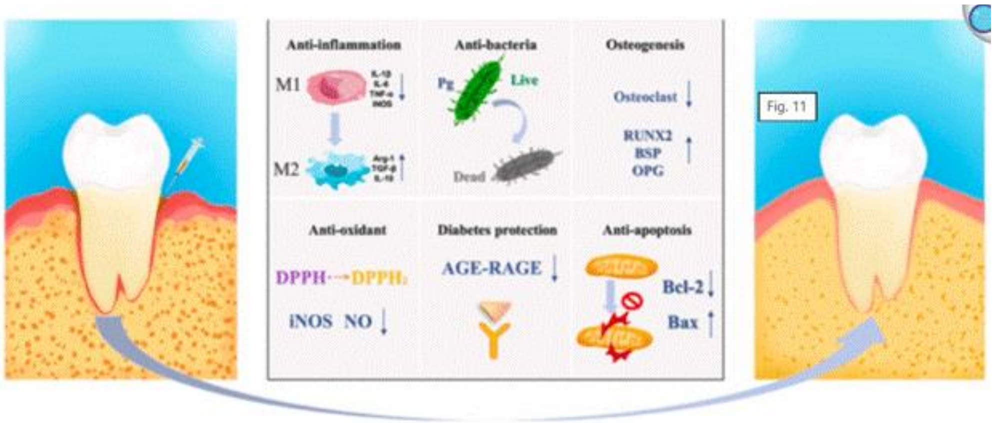

Fig 1. mechanisms of LL-37 in the pathogenesis and management of periodontitis (Li et al., 2025)

3.3 Functional Dynamics of LL-37 in Inflamed Periodontal Tissues and Its Interaction with Porphyromonas gingivalis

LL-37 plays a complex role in the inflamed periodontal environment, particularly because pathogens such as Porphyromonas gingivalis are able to internalize host cells and contribute to periodontitis and systemic diseases, making antagonism against this bacterium important [28]. Although P. gingivalis exhibits low sensitivity to LL-37 due to degradation by gingipains and its low affinity for the peptide, LL-37 still exhibits antimicrobial and immunomodulatory activity through another mechanism, namely autophagy. The increase in the LC3-II/LC3-I ratio and decrease in p62 in HaCaT cells indicate that LL-37 induces autophagy in a concentration- and time-dependent manner, and inhibition of autophagy with 3-MA eliminated the bacteriostatic effect of LL-37 on P. gingivalis, confirming that intracellular elimination mainly occurs through this pathway, rather than through a direct bactericidal effect [28].

In the inflamed periodontal environment, myeloperoxidase (MPO) activity converts thiocyanate to cyanate (OCN^-) and triggers carbamylation of LL-37, resulting in various structural modifications. LL-37C1 retains its antibacterial efficacy but loses its chemotactic function and becomes more cytotoxic due to increased hydrophobicity and α-helix structure. In contrast, LL-37C8 and LL-37C12,15 have much lower toxicity; LL-

37C12,15 is even the most effective variant in neutralizing LPS and suppressing TNF-α, despite a slight decrease in antimicrobial activity [30]. The charge change due to carbamylation also affects cell sensitivity: erythrocytes become more susceptible to hemolysis, while neutrophils are relatively resistant, so that the biological response of carbamylated LL-37 is greatly influenced by the tissue context.

Additionally, LL-37 modulates the response of gingival fibroblasts exposed to LPS. In an in vitro model, 10 ng/ml E. coli LPS produced an increase in CXCL8 equivalent to the response induced by 10 µg/ml P. gingivalis LPS, indicating an intrinsic difference in potency between the two endotoxins [29]. LL-37 at low concentrations (1–5 µg/ml) significantly reduced LPS-induced CXCL8 and IL-6 through inhibition of IκBα phosphorylation and degradation, thereby suppressing the TLR-NFκB pathway. However, at high concentrations, particularly 50 µg/ml, LL-37 actually increased CXCL8, CXCL1, CXCL2, and CXCL3, which enhanced neutrophil recruitment and NET release, demonstrating the dualism of LL-37, namely anti-inflammatory at low concentrations and pro-immune response at high concentrations. LL-37 also increases hepatocyte growth factor (HGF) production by fibroblasts in a dose-dependent manner—relevant because HGF levels are twice as high in periodontitis sites compared to healthy tissue—and induces SOCS3, a negative regulator of inflammation that also affects osteoclastogenesis [29]. The combination of these mechanisms indicates that LL-37 activity in periodontal tissue is highly influenced by its concentration, local inflammation levels, and chemical conditions such as cyanate exposure, which alters the structure and function of the peptide through carbamylation [28, 30].

In addition to these changes, periodontitis also causes increased expression of LL-37 and its receptor, formyl peptide receptor 2 (FPR2), in gingival tissue and gingival sulcus fluid. This increase reflects the activation of the innate immune response to the invasion of periodontitis-causing bacteria [28, 31]. However, despite its increased expression, the effectiveness of LL-37 is not optimal because this peptide is unstable and can be degraded by gingipain produced by P. gingivalis, which ultimately reduces the availability of LL-37 in its active form [28]. On the other hand, FPR2 expression remains high because its regulation is primarily influenced by local inflammation and increased LL-37 expression at the mRNA and protein levels, regardless of whether LL-37 is still active or has been degraded. This condition can trigger excessive FPR2 activation, which is known to enhance the proinflammatory response of gingival cells through increased cytokine secretion and contribute to periodontal tissue damage [28].

Therefore, the combination of PL and LL-37 is a promising approach because it protects the LL-37 structure from degradation by P. gingivalis gingipain, thereby increasing the peptide's resistance to proteolysis while strengthening its antibacterial activity and reducing its cytotoxicity to host cells [25].

IV. CONCLUSION

PL derived from brown algae, which can be obtained through ethanol solvent extraction or modern methods such as MAE and SSF, offer safe and stable biomolecules that can overcome the limitations of LL-37 in the inflammatory periodontal environment. Since LL-37 is easily degraded by gingipains and undergoes carbamylation, its combination with PL has been shown to improve structural stability, reduce cytotoxicity, and enhance antibacterial and antibiofilm effects against P. gingivalis, thereby opening up opportunities for a more effective therapeutic approach to periodontitis.

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