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Original Article

Targeting Receptor Activator of Nuclear Factor-κB Ligand-Mediated Bone Resorption: Promising Natural Cinnamic Acid Candidates for Periodontitis Prevention and Therapy

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Abstract

Background and Objective: Periodontitis is a major chronic inflammatory disease of the oral tissues, which is driven by a complex interplay between dysbiotic plaque biofilms and the host immune response. Receptor activator of nuclear factor-κB ligand (RANKL) plays a significant role in the RANK/RANKL/osteoprotegerin pathway, leading to bone resorption and periodontitis. Therefore, RANKL is a promising therapeutic target for the treatment and prevention of periodontitis. This study aimed to evaluate the potential of a series of cinnamic acids to inhibit the RANKL functional inhibitory residues (FIR).

Materials and Methods: Molecular docking analysis was conducted using AutoDock 4.0 to estimate the binding affinities of ten cinnamic acids to the RANKL FIR (PDB: 3URF). The specific binding modes and molecular interactions were subsequently analyzed and visualized using Discovery Studio Visualizer.

Results: Three cinnamic acids showed strong binding affinities, namely cynarin, chlorogenic acid (CGA), and rosmarinic acid, with binding free energy values (ΔGbinding) below -10 kcal/mol. The most potent inhibitor among these compounds was identified as cynarin, with an inhibition constant in the picomolar range (ki=9.53 pM). The most extensive hydrogen bonding was observed with cynarin, as indicated by interaction profiling, with five H-bonds formed.

Conclusions: The findings suggest cynarin, CGA, and rosmarinic acid as promising natural compounds for RANKL inhibition. Therefore, these compounds are positioned as potential candidates for novel therapeutic strategies aimed at preventing periodontitis progression.

Keywords: Bone resorption, Cinnamica acid, Drug, Inhibitor, Periodontitis, Receptor activator of nuclear factor-κB ligand (RANKL)

Introduction

Periodontitis represents a major chronic inflammatory disorder of oral tissues, driven by a complex interplay between dysbiotic plaque biofilms and the host's immune response. This interaction, modulated by genetic, systemic, and

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environmental risk factors, leads to the progressive and irreversible degradation of the periodontal ligament and alveolar bone [1-4]. As one of the leading causes of tooth loss in adults, the condition impairs both masticatory function and aesthetics, posing a significant oral health burden [5]. Furthermore, its implications extend beyond the oral cavity, with established associations between periodontal health and the risk of several systemic diseases [6, 7]. With severe forms of the disease affecting nearly one-fifth of the global adult population, periodontitis ranks among the world's most common non-communicable diseases, underscoring the critical importance of ongoing research in this field for both dental and general medicine [8, 9].

The regulation of bone resorption during orthodontic tooth movement (OTM) is centrally governed by the receptor activator of nuclear factor-κB ligand (RANKL)/RANK/osteoprotegerin (OPG) pathway. RANKL, a key osteoclastogenic cytokine from the tumor necrosis factor ligand family, is upregulated by various cells within the periodontal environment—including osteoblasts, osteocytes, and periodontal ligament fibroblasts—in response to mechanical stress [4, 10-17]. Its signaling receptor, RANK, is expressed on osteoclast precursors and mature osteoclasts; binding of RANKL to RANK initiates a signaling cascade that leads to osteoclast differentiation and activation [18]. This process is critically antagonized by OPG, a decoy receptor that binds RANKL and prevents its interaction with RANK, thereby suppressing osteoclastogenesis [19, 20]. The pivotal role of this axis in OTM is demonstrated by studies showing that local OPG gene transfer can effectively inhibit RANKL-mediated bone resorption and significantly reduce experimental tooth movement [21].

Naturally derived compounds offer promising avenues for therapeutic intervention. Cinnamic acid, a widespread plant metabolite found in sources such as cinnamon and honey, serves as a core structure for several bioactive phenolic derivatives [22-24]. These compounds, such as caffeic and ferulic acids, demonstrate multifunctional properties, with pronounced anti-inflammatory, antioxidant, and antimicrobial activities highlighted in the literature [25-29]. This range of bioactivity stems from the characteristic chemical structure of cinnamic acid, which enables effective interaction with cellular systems [30, 31].

Given that OPG inhibits RANKL through direct binding [32], it is hypothesized that the RANKL residues involved in OPG interaction constitute a functional inhibitory epitope. Accordingly, targeting this epitope with small molecules or peptides represents a rational approach to disrupting RANKL–RANK signaling. Building upon this premise, the present study aimed to evaluate the inhibitory potential of a diverse set of cinnamic acid derivatives against the functional inhibitory epitope of RANKL using AutoDock 4.0, with particular emphasis on their binding modes and binding affinities. The findings of this comparative analysis may facilitate the identification of novel plant-derived inhibitors, thereby providing a theoretical basis for the future development of herbal-based therapeutic strategies for the management of periodontitis.

Materials and Methods

Receptor Activator of Nuclear Factor-κB Ligand (RANKL) and Cinnamic Acids Structural Preparation

The crystal structure of human RANKL in complex with OPG (PDB ID: 3URF, 2.7 Å resolution) served as the structural basis for this study [32]. This complex was selected because it clearly defines the binding interface between RANKL and its natural inhibitor OPG, allowing us to map the target site precisely. This structure comprises RANKL (chain A, 162 residues) and OPG (chain B [chain Z], 171 residues). The functional inhibitory residues (FIR) of RANKL involved in OPG binding were mapped using the PDBsum server [33]. The isolated RANKL chain (A) was then prepared and energetically minimized using Swiss-PDBViewer [34]. During preparation, all water molecules were removed, and hydrogen atoms were added to the receptor.

A set of 10 cinnamic acid derivatives (e.g., caffeic acid, chlorogenic acid [CGA], ferulic acid) was selected for screening. Their molecular structures were built and energy-minimized to stable ground-state conformations using HyperChem [35].

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Docking simulations were subsequently performed to predict and compare the binding affinities of these compounds at the RANKL FIR site.

Molecular Docking

The computational docking procedure was performed using AutoDock 4.0 [36] to estimate the binding free energy ($\Delta G_{binding}$) of each cinnamic acid derivative to the FIR of RANKL. AutoDock 4.0 was selected for its established reliability in docking flexible ligands to rigid protein targets and its comprehensive scoring function. All calculations were performed on a workstation equipped with an Intel® Core™ i7-13650HX processor (2.60 GHz), 24 GB of RAM, and a 64-bit version of Windows. A semi-flexible docking approach was employed, in which the protein was held rigid, and the ligands were allowed to be flexible. Ligand flexibility included all rotatable bonds. The docking grid was defined to enclose the identified FIR. A grid box of dimensions 52 × 90 × 104 Å with a grid-point spacing of 0.375 Å was centered on the centroid of the key FIR residues (coordinates: x = 1.274, y = 3.668, z = 17.37 Å). This box size ensured all potential binding modes around the epitope were sampled. For each ligand, 50 independent docking runs were conducted using the Lamarckian Genetic Algorithm (LGA). The resultant poses were clustered with a root-mean-square deviation tolerance of 2.0 Å. The conformation with the most favorable (most negative) predicted $\Delta G_{binding}$ within the most populated cluster was selected for subsequent analysis and visualization using the Discovery Studio Visualizer (DSV) tool. Subsequently, the docked model pose with the most negative predicted $\Delta G_{binding}$ within the most populated cluster was selected for analysis and visualization using DSV. This protocol ensures the reproducibility of the docking results and selects the most statistically relevant binding pose.

Interaction Mode Analysis

To identify the most promising RANKL inhibitors from the docking screen, compounds were first ranked based on their predicted $\Delta G_{binding}$. Those exhibiting high-affinity binding, defined as a $\Delta G_{binding}$ value more negative than −10 kcal/mol, were shortlisted for further analysis. The threshold of −10 kcal/mol was used in this study as a benchmark for strong ligand-binding potential. The specific molecular interactions (e.g., hydrogen bonds, hydrophobic contacts) between these top candidates and the RANKL FIRs were then visualized and analyzed in detail using DSV. Hydrogen bonds and hydrophobic interactions were defined with a distance cutoff of 5.0 Å.

Results

Receptor Activator of Nuclear Factor-κB Ligand (RANKL) Functional Inhibitory Residues (FIR)

Analysis of the RANKL-OPG crystal structure using PDBsum identified six key amino acid residues within RANKL that constitute the primary interaction interface. Residues Lys181, Tyr241, and Lys257 were found to form hydrogen bonds with OPG. Additionally, His180, Lys257, Lys282, and Arg284 participated in salt bridges (Table 1). Collectively, these six residues were defined as the functional inhibitory epitope, playing a critical role in RANKL's biological activity. Figure 1 shows the protein-protein interaction network.

Table 1. Key RANKL Residues Forming the Functional Inhibitory Epitope Through Interactions With OPG, as Identified From PDBsum Analysis of the Crystal Structure (PDB ID: 3URF)

RANKL (Ligand, Chain A)	OPG (Receptor, Chain Z)	Bond Length (Å)
A) Hydrogen bond residues		
Lys181	Ile94	3.06
Tyr241	Glu95	2.49
Lys257	Glu95	3.1
B) Salt bridge residues		
His180	Glu93	3.78
Lys257	Glu95	3.1
Lys282	Glu58	3.87
Arg284	Glu58	2.72

Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin.

Gibbs Free Energy of Binding

Computational screening based on $\Delta G_{binding}$ identified several cinnamic acid derivatives as potential high-affinity inhibitors of the RANKL FIR. Notably, cynarin, CGA, and rosmarinic acid exhibited the strongest predicted binding, with $\Delta G_{binding}$ values of −15.03, −12.24, and −10.95

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kcal/mol, respectively. These correspond to remarkably low theoretical inhibition constants (Ki), ranging from picomolar (9.53 pM for cynarin) to low nanomolar concentrations (1.06 nM for CGA and 9.33 nM for rosmarinic acid). Table 2 presents the complete set of $\Delta G_{binding}$ and Ki values for all tested compounds, while a detailed energy breakdown for the top-ranked ligands is provided in Table 3.

Figure 2 shows a comparative visualization of the estimated Gibbs free energies for these leading compounds.

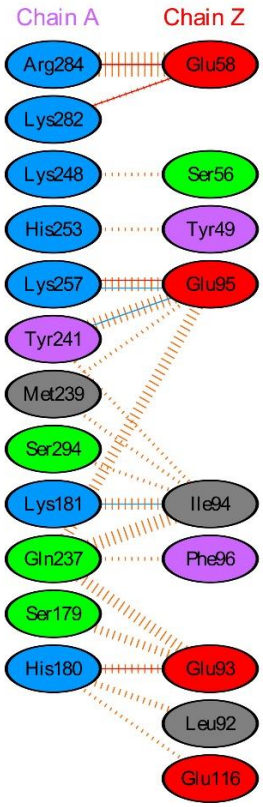

Figure 1. Interactions Between RANKL (Chain A) and OPG (Chain Z) Blue lines represent hydrophobic interactions, while thick red lines indicate salt bridge contacts.
Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin.

Table 2. Gibbs Free Binding Energy and Ki Values Between RANKL FIR and Tested Cinnamic Acids

Ligand ID	Ligand Name	$\Delta G_{binding}$	Ki
6124212	Cynarin (cynarine)	−15.03	9.53 pM
1794427	Chlorogenic acid	−12.24	1.06 nM
5281792	Rosmarinic acid	−10.95	9.33 nM
5281759	Caffeic acid 3-glucoside	−9.1	214.32 nM
5281787	Caffeic acid phenethyl ester	−6.47	18.19 uM
5372945	N-p-Coumaroyltyramine	−5.64	74.02 uM
689043	Caffeic acid	−5.27	137.24 uM
445858	Ferulic acid	−5.2	155.01 uM
637775	Sinapinic acid	−5.17	161.51 uM
444539	Cinnamic acid	−4.33	672.95 uM

Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; FIR, functional inhibitory residues; Ki, inhibition constant.

Table 3. Details of Energies and Ki Values Between the Top-Ranked Cinnamic Acids and RANKL FIR

Ligand Name	Intermolecular Energy (kcal/mol)	Total Internal Energy (kcal/mol)	Torsional Free Energy (kcal/mol)	Unbound System's Energy (kcal/mol)
Cynarin	-7.69	-15.67	6.26	-2.05
Chlorogenic acid	-7.06	-10.88	4.18	-1.53
Rosmarinic acid	-4.82	-11.62	4.47	-1.01

Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; FIR, functional inhibitory residues; Ki, inhibition constant.

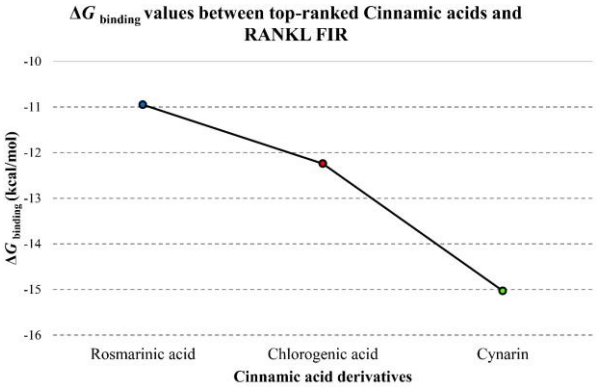

Figure 2. Comparison of calculated ΔG binding energies (kcal/mol) for Cynarin (Green), Chlorogenic Acid (Red), and Rosmarinic Acid (Blue) Bound to the RANKL FIR
Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; FIR, functional inhibitory residues.

Interaction Modes

Analysis of ligand–RANKL interactions indicated that cynarin exhibited a notable binding profile, forming multiple hydrogen bonds with Gly278 at distances of 2.95, 3.28, and 3.61 Å, as well as additional interactions with Phe280 (4.33 and 4.98 Å). In addition, cynarin established a hydrophobic interaction with Phe281 at a distance of 4.23 Å. CGA is primarily engaged in hydrogen bonding with Lys257, forming three hydrogen bonds at distances of 3.78, 4.48, and 4.61 Å, supported by a hydrophobic interaction with Met256 at 4.73 Å. Rosmarinic acid formed hydrogen bonds with Lys257 (3.86 Å), Gly278 (4.03 Å), and Gly279 (3.51 Å); however, no significant hydrophobic

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interactions were observed for this ligand. A detailed summary of all interaction distances is provided in Table 4. For this analysis, interactions beyond 5.0 Å were considered non-significant. Figure 3 shows the two- and three-dimensional representations of the top-ranked cinnamic acids within the RANKL FIR.

Table 4. Interaction Modes Between the Top-Ranked Cinnamic Acids and RANKL FIR

Ligand name	Hydrogen Bond (Distance Å)	Hydrophobic Interaction (Distance Å)
Cynarin	Phe280 (4.33, 4.98); Gly278 (2.95, 3.28, 3.61)	Phe281 (4.23)
Chlorogenic acid	Lys257 (3.78, 4.48, 4.61)	Met256 (4.73)
Rosmarinic acid	Lys257 (3.86); Gly278 (4.03); Gly279 (3.51)	N/A

Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; FIR, functional inhibitory residues; N/A, not available.

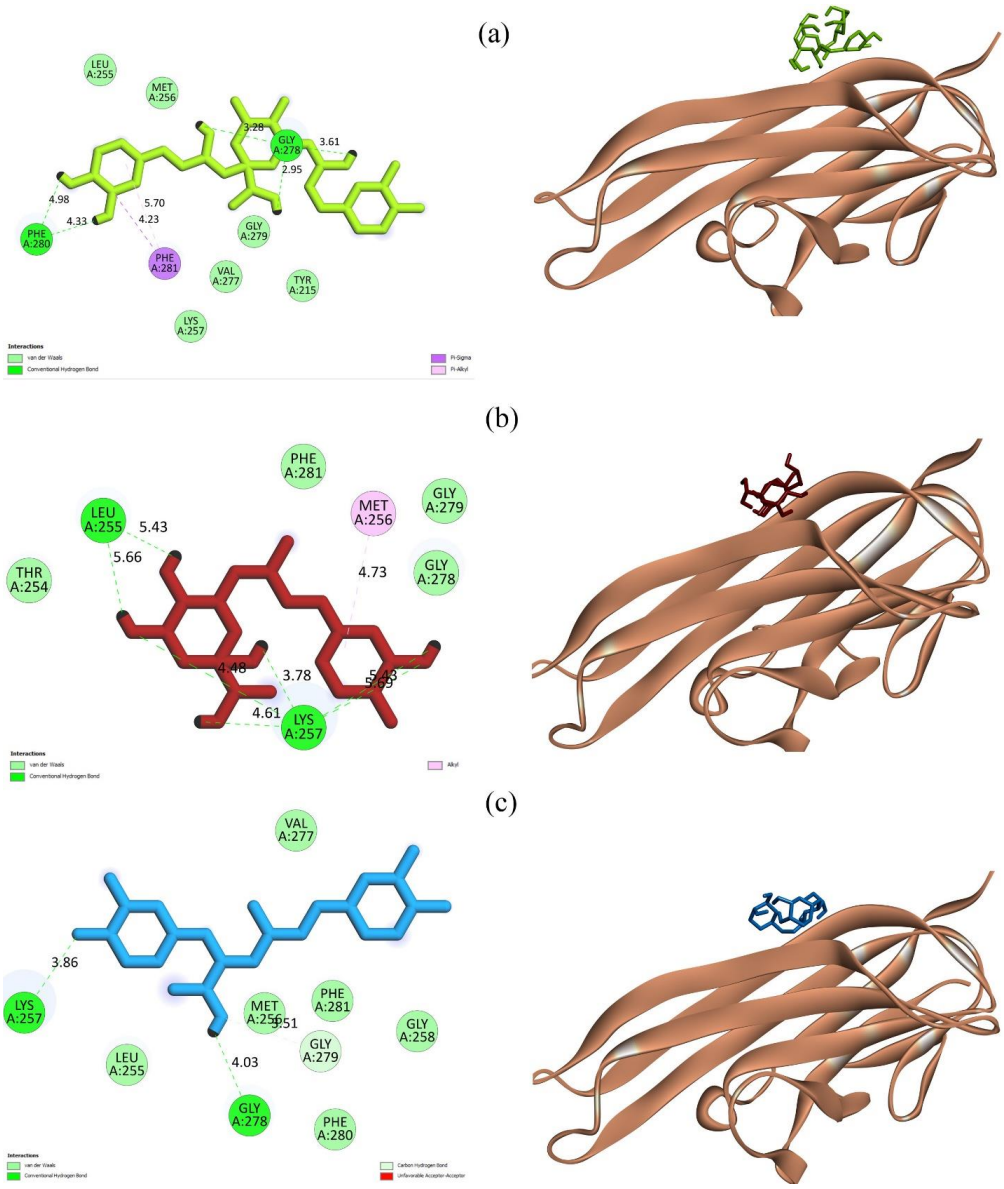

Figure 3. Two-Dimensional (Left) and Three-Dimensional (Right) Visualizations of the Binding Conformations and Interaction Patterns of the Most Potent Inhibitors, Including (a) Cynarin, (b) Chlorogenic Acid, and (c) Rosmarinic Acid, in Complex With the RANKL FIR

Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand; FIR, functional inhibitory residues.

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Discussion

A chronic inflammatory condition of multifactorial etiology, periodontitis is triggered by the accumulation of dysbiotic biofilm and marked by immune-inflammatory responses in the host. When preventive diagnostic measures and appropriate therapeutic interventions are not implemented, progressive destruction of periodontal tissues and eventual tooth loss are experienced, leading to negative effects on overall quality of life [37-43]. A positive correlation between RANKL+ senescent osteoblasts and bone resorption was reported in an earlier study by Wang et al. [44]. Consequently, RANKL has emerged as a novel therapeutic target for the management of periodontitis.

An in silico approach was employed in the present study to identify potential RANKL inhibitors derived from organic cinnamic acid compounds. Accordingly, a total of 10 well-known cinnamic acids were subjected to docking analysis against the RANKL FIR. Consequently, three metabolites, namely cynarin, CGA, and rosmarinic acid, demonstrated substantial binding affinity to the target protein, with $\Delta G_{binding}$ values below -10 kcal/mol. These three herbal compounds were therefore regarded as potential RANKL inhibitors in the current investigation.

Burdock (*Arctium lappa* L.) roots are recognized as a valuable source of the bioactive compounds, particularly CGA and cynarin, which can be utilized in nutraceutical food applications [45]. Rosmarinic acid is abundantly found in *Thunbergia laurifolia* Lindl., a plant known for its promising biological activities, including antioxidant and anti-inflammatory properties [46].

Chao et al. [47] investigated the therapeutic potential of cynarin for the treatment of inflammatory bone loss. Their study demonstrated that cynarin effectively suppressed osteoclast differentiation and function, both in cellular models and in a mouse model of inflammatory osteolysis. The compound exerted its effects by inhibiting the activation of the mitogen-activated protein kinase signaling pathway and simultaneously activating the protective nuclear factor erythroid 2–related factor 2 antioxidant pathway. In vivo, treatment with cynarin significantly improved trabecular bone structure, increasing bone volume and thickness. Furthermore, histological analyses confirmed that cynarin reduced the expression of osteoclast markers and inflammatory cytokines while promoting osteogenic markers. These findings reveal a dual mechanism of action for cynarin, positioning it as a promising candidate for the treatment of inflammatory bone-resorptive diseases.

Kwak et al. [48] performed a study to evaluate the effect of CGA on RANKL-induced osteoclast differentiation and signaling. In this investigation, RANKL-mediated osteoclast differentiation in bone marrow macrophages was found to be dose-dependently inhibited by CGA. The phosphorylation of p38, protein kinase B, extracellular signal-regulated kinase, and inhibitor of nuclear factor kappa-B (IκB) was suppressed, while IκB degradation was significantly prevented. Furthermore, messenger ribonucleic acid expression of key markers, including the nuclear factor of activated T-cells, cytoplasmic 1, tartrate-resistant acid phosphatase, and osteoclast-associated receptor, was downregulated by this treatment. In an in vivo murine model, bone loss induced by lipopolysaccharide was remarkably attenuated, as demonstrated by micro-computed tomography. These results suggest that CGA could be utilized as a potential therapeutic agent for inflammatory bone destruction.

Le et al. [49] performed a study to evaluate the effects of rosmarinic acid on bone metabolism and homeostasis. In this research, alkaline phosphatase activity was increased, and mineralization was induced in osteoblasts. The canonical Wnt signaling pathway was shown to be affected by rosmarinic acid through β-catenin stabilization. Furthermore, RANKL-induced osteoclastic differentiation and p38 mitogen-activated protein kinase activation were significantly inhibited. In a mouse model of bone loss, rosmarinic acid treatment improved bone mass. It was concluded that rosmarinic acid exerts dual regulatory effects on both osteoblastic and osteoclastic differentiation.

This computational study is subject to inherent limitations that should be acknowledged. The binding affinities and inhibition constants presented are theoretical predictions derived from static molecular docking, an approach that does not fully account for the dynamic nature of biological

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systems. Furthermore, although the results suggest strong inhibitory potential, this premise requires confirmation through experimental validation, such as *in vitro* enzymatic assays and cellular models, to verify functional RANKL inhibition.

Conclusion

This computational study employed molecular docking to evaluate a series of cinnamic acid derivatives for their potential to inhibit the functional inhibitory epitope of RANKL, a key mediator of bone resorption in periodontitis. The *in silico* screening identified three compounds, namely cynarin, CGA, and rosmarinic acid, as high-affinity candidates, with cynarin exhibiting the strongest predicted binding ($\Delta G_{binding}$= -15.03 kcal/mol, Ki=9.53 pM). The interaction profiles suggest that these compounds effectively engage the critical OPG-binding site on RANKL, thereby potentially mimicking the natural inhibition mechanism. Our findings, supported by existing literature on their anti-osteoclastic and anti-inflammatory properties, position these natural polyphenols as promising leads for novel therapeutic strategies against periodontitis. By potentially disrupting the RANKL/RANK/OPG axis, they offer a targeted approach to modulate host-mediated bone destruction. However, these *in silico* predictions require experimental validation. Future research should focus on *in vitro* assays to confirm RANKL inhibition and osteoclast suppression, followed by *in vivo* studies in preclinical models of periodontitis to assess their therapeutic efficacy and pharmacokinetics.

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Authors' Contributions

Conceptualization: **AT;** Data curation: **AT and PGH;** Formal analysis: **AT, PM, and MR;** Methodology: **AT, PM, MR, and FGP;** Writing - original draft: **AT;** Final edition: **SS.** The manuscript underwent editing for writing style using GenAI and was subsequently checked for grammar using Grammarly Premium software. All authors read and approved the final version of the manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval was not required, as this research used only computational analysis of existing data and involved no direct involvement of human or animal subjects.

Consent for Publication

Not applicable.

Conflict of Interest

The authors declared no conflicts of interest.

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