RESEARCH ARTICLE

Theaflavin as Potential Multi-Target Anti-Inflammatory Agent in Periodontitis: An *in silico* Approach

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Abstract

BACKGROUND: Periodontitis is a chronic inflammatory disease characterized by progressive periodontal tissue destruction and dysregulated inflammatory responses. Current therapies mainly target bacterial infection but are often less effective in controlling inflammation. Tea (*Camellia sinensis*) contains bioactive polyphenols with antimicrobial and anti-inflammatory properties, making it a promising alternative therapeutic candidate. However, molecular interactions of tea-derived compounds with inflammation-related proteins through molecular docking remain unclear. This study evaluate the binding affinity and interaction profiles of tea-derived compounds with inflammation-related to periodontitis protein targets using molecular docking.

METHODS: Ligand and protein structures were retrieved from public databases and prepared using standard optimization protocols. Toxicity and pharmacokinetic properties were predicted using ProTox-3.0 and SwissADME, respectively. Molecular docking was performed using CB-Dock 2.0 with AutoDock Vina, and ligand-protein interactions were analyzed using Discovery Studio.

RESULTS: All tested compounds, including catechin, epigallocatechin gallate (EGCG), theaflavin, and thearubigin showed low predicted toxicity. Theaflavin showed the strongest binding affinity across multiple targets, particularly against IRAK-4 (−9.8 kcal/mol), TLR4 (−9.2 kcal/mol), and IKK-β (−9.5 kcal/mol), supported by stable hydrogen bonds and hydrophobic interactions.

CONCLUSION: Among all compounds, theaflavin exhibit strong multi-target binding potential against key inflammatory proteins in periodontitis, followed by EGCG and thearubigin. These findings support their potential as alternative or adjunctive anti-inflammatory agents, although further *in vitro* and *in vivo* validation are required.

KEYWORDS: periodontitis, tea polyphenols, theaflavin, molecular docking, inflammation, NF-κB pathway

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Introduction

Periodontitis is a chronic inflammatory disease characterized by progressive destruction of periodotal tissues driven by pathogenic bacterial infection. Beyond its local effects, it is a significant public health concern due to its association with systemic conditions, including cardiovascular disease, diabetes mellitus dysregulation, adverse pregnancy outcomes, and respiratory infections.(1-3) The disease

is initiated by dysbiotic subgingival biofilms composed of key pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum.* (4) Inflammatory responses affect the gingiva, junctional epithelium, periodontal ligament, cementum, and alveolar bone, leading to attachment loss, periodontal pocket formation, and progressive bone resorption.(5-7)

Subgingival biofilm accumulation activates innate immune receptors, triggering pro-inflammatory mediator release and tissue destruction. This process is regulated by interconnected signaling pathways initiated by bacterial lipopolysaccharides and other virulence factors through pattern-recognition receptors.(8,9) Among these, key pathways involving toll-like receptor 4 (TLR4), myeloid differentiation factor 88 (MyD88), and nuclear factor kappa B (NF-κB) play central roles in cytokine production, and their persistent activation sustains inflammation and accelerates tissue damage.(10-14)

Current treatment strategies primarily rely on scaling and root planing combined with antimicrobial agents. Although effective in reducing bacterial load, these approaches are often insufficient to fully modulate host inflammatory responses and may lead to bacterial resistance or disease recurrence.(10) This limitation highlights the need for alternative therapies that target both microbial and inflammatory components. Natural products, particularly those derived from Camellia sinensis, have attracted attention due to their antimicrobial, antioxidant, and anti-inflammatory properties.(15-17)

Tea contains a variety of bioactive polyphenolic compounds, including catechin, epigallocatechin gallate (EGCG), theaflavin, and thearubigin, which contribute to its pharmacological effects.(12) Catechins, particularly EGCG, are among the most extensively studied tea polyphenols and have been reported to modulate inflammatory signaling pathways such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), while reducing the production of pro-inflammatory cytokines. (18-20) Likewise, theaflavins have been shown to inhibit cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and NF-κB signaling, whereas thearubigins contribute to antioxidant and anti-inflammatory activities through reactive oxygen species scavenging.(21) Furthermore, tea-derived polyphenols inhibit bacterial growth and biofilm formation while attenuating inflammatory responses through the downregulation of cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), highlighting their potential relevance in the management of periodontitis.(22) Given their distinct chemical structures and complementary biological activities, catechin, EGCG, theaflavin, and thearubigin were selected in the present study as representative bioactive polyphenols of Camellia sinensis, encompassing the major constituents of both green and black tea.(23) To comprehensively evaluate their potential anti-inflammatory interactions, molecular docking was performed with TLR4, MyD88, IRAK4, TRAF6, IKKβ, and NF-κB, which represent key sequential components of signaling pathway responsible for regulating inflammatory responses and periodontal tissue destruction.(8)

Although accumulating evidence supports the anti-inflammatory potential of tea-derived polyphenols, previous studies have mainly investigated individual compounds or focused on isolated inflammatory proteins. While these approaches provide valuable insights into ligand–protein interactions, ability to evaluate the coordinated modulation of multiple proteins involved in the complex inflammatory signaling network underlying periodontitis remains limited. Considering that periodontitis involves interconnected signaling pathways involving TLR4, MyD88, interleukin-1 receptor-associated kinase (IRAK-4), TRAF6, IκB kinase (IKK-β), and NFκB, a comprehensive evaluation of the interactions between tea-derived compounds and multiple inflammation-related protein targets is still lacking. This study was conducted to perform a comprehensive molecular docking analysis to evaluate the binding affinity and interaction profiles of tea-derived compounds against multiple inflammation-related protein targets. The findings provide molecular insight into their potential as multi-target anti-inflammatory agents and may support the future development of tea-derived compounds as adjunctive therapies for periodontitis.

Methods

Collection and Preparation of Ligand and Protein Structures

All active molecule data including thearubigin (Pubchem CID: 76182283), epigallocathechin gallate (EGCG) (Pubchem CID: 65064), catechin (Pubchem CID: 969516), alnustone (Pubchem CID: 5317598), alpha cedrene (Pubchem CID: 9064), and theaflavin (Pubchem CID: 135403798) were retrieved from the PubChem database along with their Canonical Simplified Molecular Input Line Entry System (SMILES) representations and downloaded in SDF format. Specific inhibitors for each protein target

were used as reference controls, including resatorvid (TLR4 inhibitor), ST2825 (MyD88 inhibitor), IRAK-4 inhibitor, TRAF6 inhibitor, IKK-β inhibitor, and Bay11-7082 (NF-κB inhibitor). Active molecules were selected based on their structural relevance, representing the principal polyphenolic classes of Camellia sinensis for subsequent computational analysis. Target protein data of TLR4 (PDB ID: 3FXI), MyD88 (PDB ID: 4EO7), IRAK-4 (PDB ID: 2NRU), TRAF-6 (PDB ID: 4K8U), IKK-β (PDB ID: 3RZF), NF-κB (PDB ID: 4Q3J) were obtained from the Protein Data Bank and downloaded in PDB format. Protein selection criteria included high structural quality, defined by a resolution range of 2.0–2.5 Å, absence of mutations, ≥90% of residues in favored regions, and no residues in disallowed regions.

ProTox-3.0 and SwissADME-Based Toxicity and Pharmacokinetic Evaluation

Toxicity profiles of the active compounds were predicted using ProTox-3.0 (Environmental Protection Agency, Washington, DC, USA, https://tox.charite.de/protox3/). The canonical SMILES of each compound were submitted to predict acute oral toxicity (LD_{50}), toxicity class, hepatotoxicity, immunotoxicity, mutagenicity, cytotoxicity, and carcinogenicity using machine learning-based toxicity models trained on experimentally validated toxicological datasets. These predictions provide an initial assessment of the potential safety profile of the compounds prior to experimental evaluation. Pharmacokinetic properties were subsequently assessed using SwissADME (Molecular Modelling Group, Lausanne, Switzerland, http://www.swissadme.ch). Canonical SMILES served as input to evaluate physicochemical properties, including molecular weight, molar refractivity, lipophilicity (Log P), aqueous solubility, number of heavy atoms, rotatable bonds, hydrogen bond acceptors, and hydrogen bond donors, together with drug-likeness based on Lipinski's Rule of Five. These parameters were analyzed to estimate the oral drug-likeness and pharmacokinetic suitability of each compound for potential therapeutic application.

Preparation and Energy Minimization of Ligands and Proteins

Each active molecule was prepared through energy minimization using PyRx–Virtual Screening Tool 1.2 (FastSpring, Amsterdam, Netherlands). Molecular structures were imported into the workspace and optimized using the Universal Force Field (UFF). Energy minimization was performed employing the conjugate gradient algorithm with a maximum of 200 iterations. Convergence was achieved when the energy gradient reached <0.01 kcal/mol·Å, ensuring a stable three-dimensional conformation. The optimized structures were subsequently exported in .pdb format for further analysis. Protein preparation was carried out using BIOVIA Discovery Studio 2016 (Dassault Systèmes, Vélizy-Villacoublay, France). Prior to docking, protein structures were inspected to remove crystallographic water molecules, co-crystallized ligands, and non-essential heteroatoms that could interfere with ligand binding. The cleaned protein structures were subsequently saved in Protein Data Bank (PDB) format and used for molecular docking analysis.

Molecular Docking and Binding Interaction Analysis

Molecular docking was carried out using CB-Dock 2.0 (https://cadd.labshare.cn/cb-dock2/php/index.php). Prepared ligands and target proteins were uploaded to predict binding interactions. The platform automatically detected up to five potential binding cavities and conducted docking simulations using AutoDock Vina as the docking engine. For each cavity, multiple binding poses were generated, and the optimal pose was selected based on the lowest binding affinity (Vina score, kcal/mol) and cavity suitability. Docking results were subsequently evaluated by considering the predicted binding affinity together with the consistency of ligand localization within the predicted binding cavity and the interaction profiles with key amino acid residues surrounding the binding pocket. This approach provides confidence that the selected docking poses represent energetically favorable and structurally plausible ligand–protein interactions. Ligand–protein interactions were subsequently visualized in both three-dimensional (3D) and two-dimensional (2D) formats using BIOVIA Discovery Studio 2016.

Results

Toxicity Prediction Profiles Indicate Low Toxicity and Favorable Safety Characteristics

The toxicity prediction results suggested that all tea-derived compounds exhibited favorable safety profiles based on the evaluated toxicity endpoints. According to the predicted oral LD_{50} values, catechin was classified as toxicity Class 6 (10,000 mg/kg), indicating the lowest predicted acute toxicity, followed by theaflavin (Class 5; 2,500 mg/kg), whereas EGCG and thearubigin were classified as toxicity Class 4 (1,000 mg/kg). None of the compounds were predicted to exhibit hepatotoxicity, immunotoxicity,

mutagenicity, or cytotoxicity, with consistently high inactivity probability scores across all endpoints. Among the evaluated compounds, catechin displayed the highest inactivity probabilities, particularly for immunotoxicity (0.96) and cytotoxicity (0.84), while EGCG also demonstrated consistently high inactivity probabilities. Overall, these predictions indicate comparable safety profiles among the investigated tea-derived compounds, with catechin showing the most favorable predicted toxicity profile (Table 1).

Physicochemical Evaluation of Tea-Derived Molecules

The physicochemical properties of the investigated tea-derived compounds demonstrated substantial variation in molecular size, structural complexity, and aqueous solubility. Thearubigin exhibited the highest molecular weight (902.72 g/mol), number of heavy atoms (65), rotatable bonds (12), and hydrogen bond donors and acceptors (HBD 13 and HBA 22), indicating a highly complex and flexible structure. In contrast, catechin showed the simplest profile, with the lowest molecular weight (290.27 g/mol), fewer heavy atoms (21), minimal rotatable bonds (1), and lower hydrogen bonding capacity (HBD 5 and HBA 6). All compounds showed relatively low lipophilicity values (Log P 0.83 to 1.17), suggesting moderate polarity and a balanced hydrophilic and lipophilic character. Catechin had the lowest lipophilicity, while Thearubigin showed the highest, although the differences were relatively small. A more distinct pattern was observed in water solubility, where catechin demonstrated the highest solubility (Log S −2.22), followed by EGCG (−3.56), theaflavin (−5.12), and thearubigin (−6.81), indicating that increasing molecular size and complexity are associated with reduced aqueous solubility (Table 2). Overall, compounds with larger molecular size and greater structural complexity tended to exhibit lower predicted aqueous solubility, whereas lipophilicity remained relatively consistent across the investigated compounds.

Molecular Docking Interaction

The molecular docking analysis demonstrated distinct differences in the predicted binding affinities of the investigated tea-derived compounds across the inflammation-related protein targets (Table 3). Among all ligands, theaflavin consistently exhibited the most favorable binding affinities, with Vina scores of −11.5 kcal/mol for TLR4, −8.6 kcal/mol for MyD88, −12.0 kcal/mol for IRAK4, −9.6 kcal/mol for TRAF6, −11.0 kcal/mol for IKKβ, and −8.6 kcal/mol for NF-κB. These values were consistently lower than or comparable to those of the corresponding reference inhibitors, indicating a strong predicted binding preference across multiple targets. The strongest predicted interaction was observed for the theaflavin–IRAK4 complex (−12.0 kcal/mol), followed by TLR4 and IKKβ, highlighting theaflavin as the ligand with the most favorable overall binding profile among the evaluated compounds.

Analysis of the docking poses revealed that theaflavin established multiple hydrogen bonds together with hydrophobic and π-mediated interactions within the binding pockets of the target proteins (Figure 1, Table 4). In the TLR4 complex, hydrogen bonds with ASP181, ARG234, ASP100, and ARG106 were complemented by van der Waals contacts and π-interactions involving ASP209 and GLY97. Similarly, the MyD88 complex was stabilized by hydrogen bonding with ASP162, LEU189, and ARG188, together with π-sulfur and π-cation interactions involving CYS203 and LYS190. The most extensive interaction network was observed in the IRAK4 complex, where theaflavin formed multiple hydrogen bonds with ASP272, SER269, ALA315, LYS213, VAL263, PRO266, and TYR264, in addition to hydrophobic interactions with VAL200, ALA211, and LEU318. Likewise, the IKKβ complex exhibited several hydrogen bonds with GLU149, ASP166, MET96, GLU97, and TYR98, reinforced by hydrophobic π-interactions involving LEU21, ALA42, VAL29, and ILE165. Although minor unfavorable contacts with MET192 and MET265

Table 1. Toxicity prediction profiles of selected ligands using Pro-Tox III.

Toxicty Test	Ligand			
	Thearubigin	EGCG	Catechin	Theaflavin
Toxicity Class (LD_{50})	Class 4 (1000 mg/kg)	Class 4 (1000 mg/kg)	Class 6 (10000 mg/kg)	Class 5 (2500 mg/kg)
Hepato-toxicity (probability)	Inactive (0.79)	Inactive (0.70)	Inactive (0.72)	Inactive (0.71)
Immuno-toxicity (probability)	Inactive (0.87)	Inactive (0.89)	Inactive (0.96)	Inactive (0.55)
Mutagenicity (probability)	Inactive (0.57)	Inactive (0.70)	Inactive (0.55)	Inactive (0.57)
Cytotoxicity (probability)	Inactive (0.61)	Inactive (0.82)	Inactive (0.84)	Inactive (0.69)

LD_{50}: lethal dose for 50% of the test population.

Table 2. Physiochemical properties of active molecules using SwissADME web-based platform.

Physiochemical	Ligand			
	Thearubigin	EGCG	Catechin	Theaflavin
Molecular weight (g/mol)	902.72	458.37	290.27	564.49
Number of heavy atoms	65	33	21	41
Number of rotatable bonds	12	4	1	2
Number of HBA	22	11	6	12
Number of HBD	13	8	5	9
Molar refractivity	216.99	112.06	74.33	143.98
Lipophilicity (Log P)	1.17	0.95	0.83	1.07
Water solubility (Log S / ESOL)	-6.81	-3.56	-2.22	-5.12

HBD: hydrogen bond donors; HBA: hydrogen bond acceptors; Log P: logarithm of the partition coefficient; Log S: logarithm of the aqueous solubility; ESOL: estimated solubility.

were identified in the IRAK4 complex, these interactions did not preclude the overall favorable docking score. In comparison, thearubigin, EGCG, and catechin generally produced less favorable binding affinities and fewer stabilizing interactions across the evaluated protein targets (Figure 1, Table 4).

Discussion

The present molecular docking analysis suggests that theaflavin possesses a more favorable multi-target binding profile than the other investigated tea-derived polyphenols across key proteins involved in periodontitis-associated inflammatory signaling. Rather than reflecting a single high-affinity interaction, the consistent binding of theaflavin to multiple components of the TLR4–MyD88–NF-κB signaling pathway indicates its potential to simultaneously engage several proteins within the same inflammatory network (Figure 1, Table 3). This binding pattern may be attributed to the structural characteristics of theaflavin. Consequently, theaflavin is more likely to form extensive hydrogen bonds together with hydrophobic and π-mediated interactions, which collectively contribute to ligand recognition, binding specificity, and stabilization of the ligand–protein complex (Table 1, Table 2). Hydrogen bonds contribute to binding specificity by facilitating directional interactions between ligands and amino acid residues within the binding pocket, whereas hydrophobic interactions enhance binding stability by promoting favorable nonpolar contacts and reducing the energetic cost associated with solvent exposure. The combination of these complementary interactions may therefore support the stronger predicted binding affinity of theaflavin across multiple inflammatory protein targets. Supporting these findings, previous molecular docking studies have demonstrated that tea-derived polyphenols interact with key inflammatory proteins. For example, epigallocatechin gallate (EGCG) has been reported to bind proteins involved in the NF-κB and MAPK signaling pathways, thereby suppressing inflammatory gene expression and cellular activation.(23) Similarly, integrative studies combining molecular docking with experimental validation have shown that tea-derived compounds can modulate the TLR4/NF-κB signaling axis, resulting in reduced cytokine production and attenuation of inflammatory responses.(24)

Table 3. Vina score interactions of active tea compounds with inflammation-related protein targets.

Active Molecules	Protein Target (Vina Score)					
	TLR4	MyD88	IRAK-4	TRAF6	IKK-β	NF-κB
Thearubigin	-10.4	-8.0	-10.9	**-9.7**	-10.0	-8.9
EGCG	-8.8	-7.1	-9.7	-9.3	-9.3	**-9.0**
Catechin	-7.7	-6.6	-8.6	-8.2	-8.2	-7.5
Theaflavin	**-11.5**	**-8.6**	**-12.0**	-9.6	**-11.0**	-8.6
Control molecule	-9.1	-8.1	-9.5	-8.0	-7.0	-5.6

The value written in bold indicate interactions with the highest Vina scores.

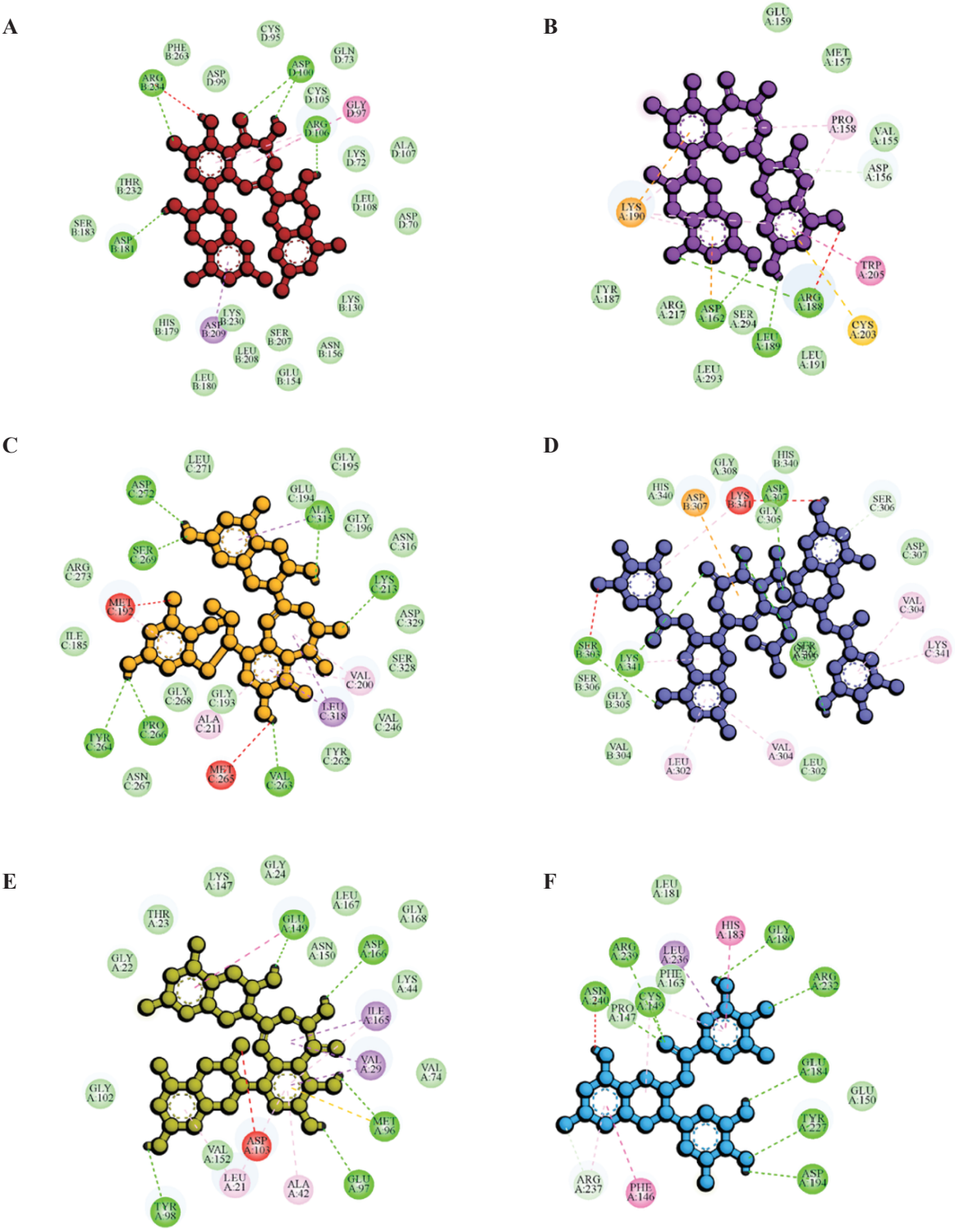

Figure 1. Representative molecular docking interactions between tea-derived polyphenols and inflammation-related protein targets associated with periodontitis. The displayed ligand–protein complexes represent the compounds with the most favorable docking results (lowest Vina scores) for each protein target, illustrating the predicted binding orientations within the corresponding binding pockets. (A) Theaflavin–TLR4; (B) Theaflavin–MyD88; (C) Theaflavin–IRAK4; (D) Thearubigin–TRAF6; (E) Theaflavin–IKKβ; and (F) Epigallocatechin gallate (EGCG)–NF-κB.

Table 4. Molecular docking interactions of tea-derived compounds and multiple inflammation protein.

Interaction	Hydrogen Bond Details	Van Der Waals Bonds	Other Bonds
Theaflavin - TLR4	ASP 181, ARG234, ASP100, ARG106	HIS179, LEU180, LYS230, LEU208, SER207,GLU154, ASN156, LYS130, ASP70, LEU108, ALA107, LYS72, CYS105, GLN73, CYS95, ASP99, PHE263, THR232, SER183	Pi-sigma: ASP209 Pi-Alkyl: GLY97
Theaflavin - MyD88	ASP162, LEU189, ARG188	TYR187, ARG217, LEU293, LEU191, ASP156, VAL155, MET157, GLU159	Pi-sulfur: CYS203 Pi-cation: LYS190
Theaflavin - IRAK-1	ASP272, SER269, ALA315, LYS213, VAL263, PRO266, TYR264	LEU271, GLU194, GLY195, GLY196, ASN316, ASP329, SER328, VAL246, TYR262, GLY193, GLY268, ASN267, ILE185, ARG273	Pi-sigma: LEU318 Pi-alkyl: VAL200, ALA211 Unfavorable bonds: MET192, MET265
Thearubigin -TRAF6	SER303, LYS341, ASP307	LEU302, VAL304, GLY305, SER306, HIS340, GLY308, GLY305, HIS340, SER306, ASP307	Pi-alkyl: LEU302, VAL304, LYS341
Theaflavin - IKK-β	GLU149, ASP166, MET96, GLU97, TYR98	GLY102, GLY22, THR23, LYS147, GLY24, LEU167, ASN150, GLY168, LYS44, VAL74, VAL152	Pi-alkyl: LEU21, ALA42 Pi-sigma: VAL29, ILE165
EGCG - NF-κB	GLU184, TYR227, ASP194, ASN240, ARG239, CYS149, GLY180, ARG232	ARG237, GLU150, PRO147, PHE163, LEU181	Alkyl: PHE146, HIS183 Pi-sigma: LEU236

The interaction of theaflavin with proteins within the TLR4–MyD88–NF-κB signaling axis suggests its ability to interfere with key steps in the inflammatory cascade. Modulation of this pathway is known to reduce the production of pro-inflammatory cytokines and limit tissue destruction. Consistent with this, previous studies have shown that tea polyphenols, including theaflavins and catechins, can inhibit NF-κB activation and suppress inflammatory mediator production.(25,26) Furthermore, theaflavin demonstrated strong binding interactions with IRAK-1, which are critical adaptor and kinase proteins within the TLR signaling cascade. The particularly high binding affinity toward IRAK-1 suggests that theaflavin may effectively inhibit kinase activity and downstream signal transduction. Since IRAK-1 plays a central role in propagating inflammatory signals leading to NF-κB activation, its inhibition can significantly attenuate inflammatory responses.(27) In addition, the interaction of theaflavin with IKK-β further supports its potential role in suppressing NF-κB activation. IKK-β is responsible for phosphorylating IκB, leading to the release and nuclear translocation of NF-κB. This is consistent with previous findings showing that inhibition of IKK-β can effectively block NF-κB mediated transcription of pro-inflammatory genes.(28-30) Considering that periodontitis is regulated by interconnected inflammatory signaling pathways rather than a single molecular target, evaluating ligand interactions across multiple proteins may provide a more comprehensive computational assessment than conventional single-target docking studies. From this perspective, compounds showing consistently favorable predicted interactions throughout the signaling cascade may represent suitable candidates for further experimental investigation.(8)

In addition to the anti-inflammatory properties, tea-derived phytochemicals have been widely investigated in periodontal applications using different formulations. Green tea extracts have been used as mouthwash, toothpaste, or local delivery agents can reduce plaque accumulation, gingival inflammation, and bleeding on probing. These effects are largely attributed to their antimicrobial activity against periodontal pathogens and their ability to modulate host inflammatory responses.(31,32)

Furthermore, the combined use of tea-derived polyphenols may provide enhanced therapeutic benefits. Multiple compounds such as catechins, EGCG, theaflavins, and thearubigins may act synergistically by targeting different components of inflammatory and microbial pathways. This multi-compound approach is particularly relevant in periodontitis, a disease characterized by complex and interconnected signaling networks. Previous studies have reported that combinations of tea polyphenols exhibit synergistic anti-inflammatory and antimicrobial effects, including enhanced inhibition of NF-κB signaling, reduced pro-inflammatory cytokine production, and improved suppression of periodontal pathogens.(33,34) Despite these promising findings, several limitations should be considered. This study is based on in silico molecular docking, which provides predictive insights into bioactive

compounds–protein interactions but does not fully represent biological complexity. Therefore, further validation through *in vitro* and *in vivo* studies is necessary to confirm the anti-inflammatory effects and therapeutic potential of these compounds. Additionally, factors such as bioavailability, stability, and optimal delivery systems should be explored in future research.

Conclusion

This study demonstrated that tea-derived bioactive compounds, particularly theaflavin, were predicted to exhibit favorable binding affinities toward multiple inflammation-related protein targets involved in periodontitis, including key components of the TLR4–MyD88–NF-κB signaling pathway. Among the investigated compounds, theaflavin showed the most favorable overall binding profile, suggesting its potential as a promising candidate for further investigation as a multi-target modulator of inflammatory signaling. Collectively, these computational findings provide molecular insight into the interactions between tea-derived polyphenols and inflammation-related proteins and support the selection of theaflavin as a candidate for subsequent experimental validation. Further *in vitro* and *in vivo* studies are required to confirm its biological activity, therapeutic potential, and clinical applicability in periodontitis management.

Authors Contribution

FS conceptualized and planned the study, while RAP, MLR, and AA contributed additional insights. FS and VEP conducted data collection and analysis, prepared the manuscript draft, and created the figures. All authors participated in critically revising the manuscript.

Ethical Statement

Ethical approval and informed consent were not required for this work.

Conflict of Interest

All authors declare that they have no competing interests.

References

1. Ketherin K, Sandra F. Osteoclastogenesis in periodontitis: Signaling pathway, synthetic and natural inhibitors. Mol Cell Biomed Sci. 2018; 2(1): 11-8. doi:
2. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, *et al.* Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018; 89 (Suppl 1): S173–82.
3. Sanz M, Marco Del CA, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, *et al*. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol. 2020; 47(3): 268–88.
4. Holt SC, Ebersole JL. Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia: The red complex, a prototype polybacterial pathogenic consortium in periodontitis. Periodontol 2000. 2005; 38(1): 72–122.
5. Mubarokah SN, Susilawati IDA, Sumarno S, Muliartha, IKG, Sargowo D. Porphyromonas gingivalis induced fragmentation of type IV collagen through macrophage-activated MMP-9:(in vitro study of collagenolytic mechanism in pathogenesis of Atherosclerotic plaque rupture). Indones Biomed J. 2009; 1(3): 88–96.
6. Fleming P, Andrews J. Periodontitis: orthodontic implications and management. British Dent J. 2024; 237: 334–40.
7. Gasner NS, Schure RS. Periodontal Disease. In: StatPearls. Treasure Island: StatPearls Publishing; 2026.
8. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015; 15(1): 30–44.
9. Esar S, Caroline, Jusak N, Kuncoro F, Srikanth K, Suleyman E, *et al.* 2-(3-(chloromethyl) benzoyloxy) benzoic acid increases CD4+ regulatory T-cell population and foxP3 expression in lipopolysaccharide-induced mice. Indones Biomed J. 2023; 15(4): 339–46.
10. Shang L, Deng D, Buskermolen JK, Roffel S, Janus MM, Krom BP, *et al.* Commensal and pathogenic biofilms alter Toll-like receptor signaling in reconstructed human gingiva. Free Radic Biol Med. 2021; 172: 123–35.
11. Puspitaningrum I, Ikawati M, Fakhrudin N, Nurrochmad A. Immunomodulatory effect of dioscorea esculenta L. on NF-κB, TLR-4, TNF-α, and IL-10 expressions in LPS-stimulated RAW 264.7 mouse macrophages. Indones Biomed J. 2025; 17(3): 307–16.
12. Meiliana A, Dewi NM, Wijaya A. Red meats and processed meat as the carcinogenic foods and phytochemical-chemoprevention. Indones Biomed J. 2019; 11(3): 225–39.
13. Hardiany NS, Yohana Y, Wanandi SI. TNFR, TRAF2, NF-κB mRNA levels of glioblastoma multiforme cells treated by conditioned medium of umbilical cord-derived mesenchymal stem cells. Indones Biomed J. 2019; 11(2): 217–24.
14. Rahayu RF, Prayitno A, Purwanto B, Soewondo W, Nurwati I, Pamungkasari EP, *et al.* Combination of metformin and magnesium citrate reduces TNF-α, NF-κB p65, IL-6, CD4, and MMP-9 expressions in diabetic model rats. Indones Biomed J. 2024; 16(6): 546–52.
15. Li Z, Li J, Huang X. Clinical trial landscape for periodontitis treatment: trend analysis and future perspectives. J Transl Med. 2024; 22: 907. doi: 10.1186/s12967-024-05697-4.
16. Nurhayati B, Rahayu IG, Rinaldi SF, Zaini WS, Afifah E,

Arumwardana S, *et al.* The antioxidant and cytotoxic effects of Cosmos caudatus ethanolic extract on cervical cancer. Indones Biomed J. 2018; 10(3): 243–49.
17. Parawansah P, Nurtamin T, Mulyawati SA, Nuralifah N, Misnaeni WOA. Immunomodulatory effect of Momordica charantia L. fruit ethanol extract on phagocytic activity and capacity of mice peritoneal macrophages. Indones Biomed J. 2018; 10(2): 144–7.
18. Afzal M, Safer AM, Menon M. Green tea polyphenols and their potential role in oral health and periodontal disease. Nutrients. 2015; 15(18): 3987. doi: 10.1007/s10787-015-0236-1.
19. Susanti E, Susilowati E. The Effect of green tea on the expression of npc1l1, abcg5, and abcg8 in the intestine of high fat diets-induced rats. Indones Biomed J. 2021; 13(2): 147–4.
20. Gunsi VS, Dirgahyu AP, Meitha K, Christianto A, Tan MI. In silico–guided design and endonuclease-based functional validation of sgRNAs targeting ERBB2 transmembrane and kinase domains. Indones Biomed J. 2026; 18(2): 164–72.
21. Legeay S, Rodier M, Fillon L, Faure S, Clere N. Epigallocatechin gallate: a review of its beneficial properties to prevent metabolic syndrome. Nutrients. 2015; 7(7): 5443–68.
22. Khan N, Mukhtar H. Tea polyphenols in promotion of human health. Nutrients. 2019; 11(1): 39. doi: 10.3390/nu11010039.
23. Luo Q, Luo L, Zhao J, Wang Y, Luo H. Biological potential and mechanisms of Tea's bioactive compounds: An Updated review. J Adv Res. 2024; 65: 345–63.
24. Capasso L, De Masi L, Sirignano C, Maresca V, Basile A, Nebbioso A, *et al.* Epigallocatechin gallate (EGCG): pharmacological properties, biological activities and therapeutic potential. Molecules. 2025; 30(3): 654. doi: 10.3390/molecules30030654.
25. Wang L, Jiang Y, Tao Q, Shi J, Lu M, Yao X. Integrated network pharmacology and molecular docking to elucidate the efficacy and potential mechanisms of tea ingredients in sepsis treatment. Biochem Genet. 2024; 62(3): 2253–67.
26. Zhang X, Zeng X, Zheng M, et al. Integrated network pharmacology, molecular docking, and experimental validation reveal the antifungal and anti-inflammatory mechanisms of Camellia oleifera seed extracts against oral thrush. Sci Rep. 2026; 16: 12244. doi: 10.1038/s41598-026-41303-x.
27. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol. 2010; 10(5): 295–306.
28. Pan MH, Lai CS, Ho CT. Anti-inflammatory activity of natural dietary flavonoids. Food Funct. 2018; 9(2): 665–79.
29. Li X, Jiang S, Tapping RI. Toll-like receptor signaling in cell proliferation and survival. Cytokine. 2010; 49(1): 1–9. doi: 10.1016/j.cyto.2009.08.010.
30. Wibowo BP, Kalim H, Khotimah H, Sujuti H, Rukmigarsari E, Erwan NE. AvrA Salmonella increases TLR4/NF-κB/β-catenin/TGF-β expressions of colorectal cancer mice model. Indones Biomed J. 2023; 15(6): 391–9.
31. Hayden MS, Ghosh S. Shared principles in NF-κB signaling. Cell. 2008; 132(3): 344–62.
32. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017; 2: 17023. doi: 10.1038/sigtrans.2017.23.
33. Reygaert WC. Green tea catechins: their use in treating and preventing infectious diseases. Biomed Res Int. 2018; 2018: 9105261. doi: 10.3390/molecules30030654.
34. Hirasawa M, Takada K. Multiple effects of green tea catechin on the antifungal activity of antimycotics against Candida albicans. J Antimicrob Chemother. 2004; 53(2): 225–29.