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Exploring the Mechanism of Action of Naringenin in the Treatment of Periodontitis Based on Network Pharmacology Methods

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ABSTRACT

Objective: This study aims to elucidate the potential molecular mechanisms of naringenin in treating periodontitis using network pharmacology, molecular docking, and bioinformatics analysis. Methods: Potential targets of naringenin were predicted using databases such as SwissTargetPrediction and TCMSP. Periodontitis-related genes were retrieved from GeneCards, DisGeNET, and OMIM. Common targets were identified via Venn diagrams, and a protein-protein interaction (PPI) network was constructed using STRING. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed with R. Molecular docking was conducted using AutoDock Vina to evaluate binding affinities between naringenin and core targets. Results: A total of 107 potential targets for naringenin were identified, with 49 overlapping with periodontitis-related genes. Key targets included IL1B, CXCL8, CD44, MMP2, EGFR, and ITGAM. Enrichment analysis revealed involvement in pathways such as HIF-1 signaling, cytokine-cytokine receptor interaction, and ferroptosis regulation. Molecular docking showed strong binding affinities. Conclusion: Naringenin exerts anti-periodontitis effects through multi-target interactions, primarily modulating inflammation, oxidative stress, and ferroptosis. This provides a theoretical basis for its clinical application.

KEYWORDS

Naringenin; Periodontitis; Network Pharmacology; Molecular Docking

1. INTRODUCTION

Periodontitis is a chronic inflammatory disease affecting periodontal tissues, characterized by gingival inflammation, periodontal pocket formation, alveolar bone resorption, and tooth mobility [1]. It is a major cause of tooth loss in adults and is associated with systemic conditions such as diabetes, cardiovascular diseases, and rheumatoid arthritis [2]. Current treatments include mechanical debridement, antibiotics, and surgery; however, these often face limitations like antibiotic resistance and incomplete resolution of inflammation [3]. Natural compounds with anti-inflammatory and antioxidant properties offer promising adjunctive therapies.

Naringenin, a flavonoid abundant in citrus fruits, exhibits potent anti-inflammatory, antioxidant, and anti-apoptotic effects [4]. Previous studies have demonstrated its therapeutic potential in various diseases, including radiation-induced lung injury by inhibiting ferroptosis [5] and periodontitis by modulating inflammatory cytokines [6]. Ferroptosis, a form of iron-dependent cell death involving lipid peroxidation and reactive oxygen species (ROS) accumulation, plays a key role in periodontitis progression [7]. However, the multi-target mechanisms of naringenin in periodontitis remain unclear.

Network pharmacology integrates systems biology and bioinformatics to predict drug-target interactions, offering a holistic view of traditional medicine [8]. This approach has been successfully applied to compounds like curcumin in periodontitis [9] and Astragali radix in anti-periodontitis effects [10]. In this study, we employed network pharmacology, combined with molecular docking, to explore naringenin's mechanisms in periodontitis treatment, focusing on inflammation, oxidative stress, and ferroptosis pathways.

2. MATERIALS AND METHODS

2.1. Identification of Naringenin Targets

The chemical structure of naringenin (PubChem CID: 932) was obtained from PubChem. Potential targets were predicted using SwissTargetPrediction (http://www.swisstargetprediction.ch/) with a probability threshold >0.1 [11]. Additional targets were sourced from TCMSP (https://tcmsp-e.com/) and DrugBank. Duplicates were removed using UniProt (https://www.uniprot.org/) for gene normalization.

2.2. Collection of Periodontitis Related Genes

Periodontitis-associated genes were retrieved from GeneCards (https://www.genecards.org/, relevance score >10), DisGeNET (https://www.disgenet.org/, score >0.1), and OMIM (https://omim.org/). Keywords included "periodontitis," "chronic periodontitis," and "aggressive periodontitis." Overlapping genes were identified using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/).

2.3. Construction of PPI Network and Core Target Screening

Common targets between naringenin and periodontitis were imported into STRING (https://string-db.org/, confidence score >0.7) to build a PPI network. The network was visualized in Cytoscape 3.9.1. Core targets were ranked by degree centrality using the CytoHubba plugin (top 10 nodes).

2.4. GO and KEGG Enrichment Analysis

GO (biological process, cellular component, molecular function) and KEGG pathway analyses were performed using DAVID (https://david.ncifcrf.gov/, $P < 0.05$). Results were visualized with bubble charts in R (ggplot2 package).

2.5. Molecular Docking

Crystal structures of core targets were downloaded from PDB (https://www.rcsb.org/). Naringenin (ligand) was prepared in Chem3D, and docking was performed with AutoDock Vina 1.1.2. Binding energies < -5 kcal/mol indicated stable interactions. Results were visualized in PyMOL.

2.6. Data Analysis

All analyses were conducted in triplicate. Statistical significance was assessed using Student's t-test in R ($P < 0.05$).

3. RESULTS

3.1. Potential Targets of Naringenin

From SwissTargetPrediction and other databases, 107 unique targets were identified for naringenin. These included cytochrome P450 enzymes (e.g., CYP19A1, probability 0.91), carbonic anhydrases (e.g., CA7, probability 0.91), and nuclear receptors (e.g., ESR1, probability 0.58).

3.2. Periodontitis-Related Genes and Common Targets

A total of 2795 periodontitis-related genes were collected. Venn analysis revealed 49 overlapping targets with naringenin, including IL1B, TNF, AKT1, IL6, PTGS2, MMP9, and CASP3.

3.3. PPI Network Analysis

The PPI network comprised 55 nodes and 146 edges (average degree 5.3). Core targets (top 10 by degree): IL1B (degree 18), CXCL8 (degree 16), CD44 (degree 14), MMP2 (degree 12), EGFR (degree 11), ITGAM (degree 10), TNF (degree 9), AKT1 (degree 8), IL6 (degree 7), and PTGS2 (degree 6).

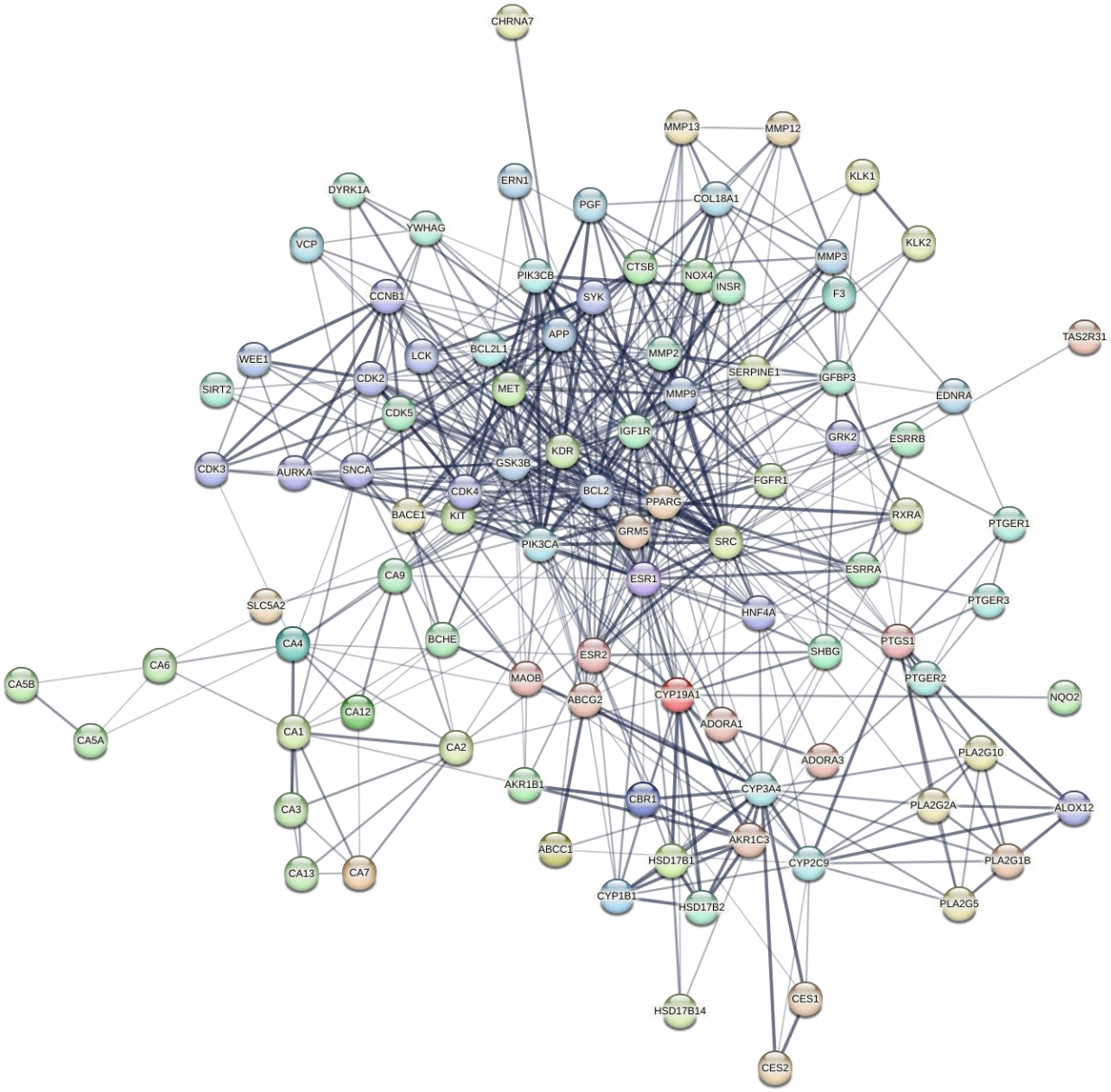

Figure 1. PPI network visualization

3.4. GO and KEGG Enrichment

GO analysis yielded 58 terms: biological processes (e.g., inflammatory response, P=1.2E-10), cellular components (e.g., extracellular space, P=4.5E-8), and molecular functions (e.g., cytokine activity, P=2.3E-7). KEGG pathways (125 total) included Nitrogen metabolism (P=2.08E-16), Arachidonic acid metabolism (P=4.39E-9), and Apoptosis (P=4.8E-4) (Figure 2, bubble plot).

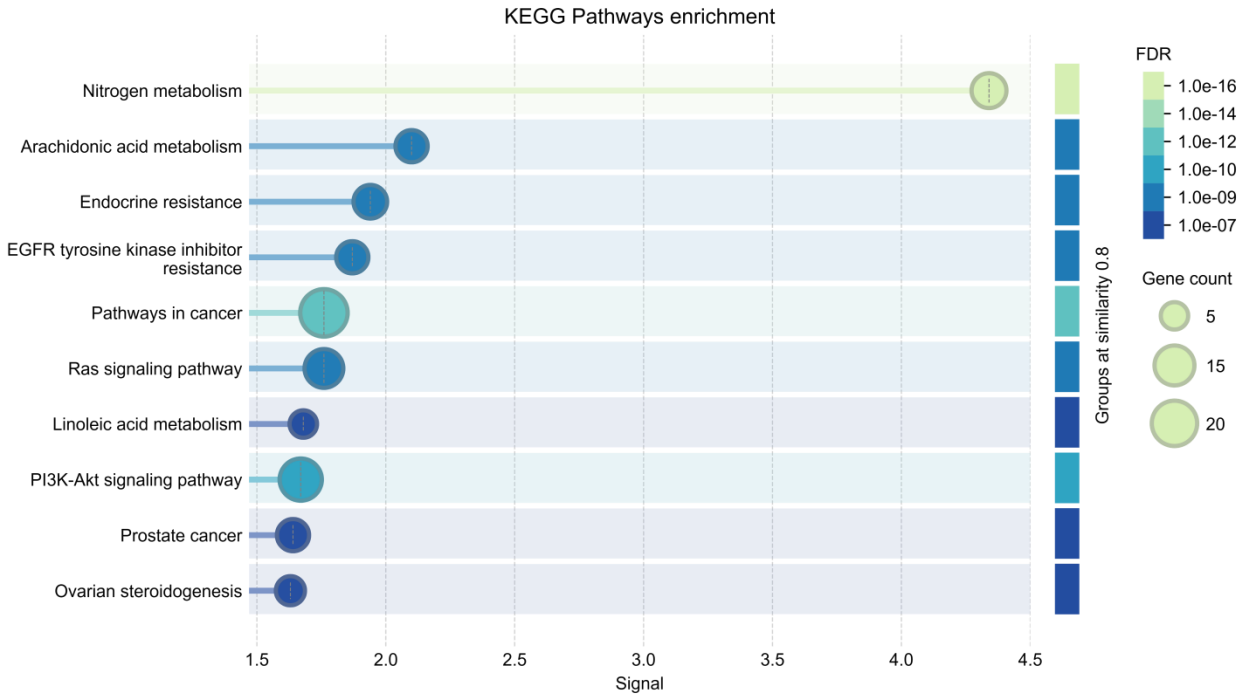

Figure 2. Top 10 KEGG pathways

3.5. Molecular Docking

Naringenin docked stably with core targets: IL1B (-7.8 kcal/mol), CXCL8 (-7.5 kcal/mol), CD44 (-7.2 kcal/mol), MMP2 (-7.0 kcal/mol), EGFR (-6.8 kcal/mol), and ITGAM (-6.5 kcal/mol). Key interactions included hydrogen bonds with residues like Arg-11 (IL1B) and Glu-29 (CXCL8)

4. DISCUSSION

This study reveals naringenin's multi-target mechanisms in periodontitis via network pharmacology. Overlapping targets like IL1B and CXCL8 align with inflammatory pathways central to periodontitis [12]. Ferroptosis inhibition, as seen in RILI models [5], suggests naringenin reduces oxidative stress and lipid peroxidation in periodontal tissues, consistent with curcumin studies [9].

KEGG enrichment highlights HIF-1 and cytokine pathways, implicating naringenin in hypoxia response and immune modulation. Molecular docking confirms strong affinities, supporting in vitro findings from similar studies on Astragali radix [10] and Cnidii Fructus [13].

Limitations include reliance on databases (potential false positives) and lack of in vivo validation. Future experiments should confirm these mechanisms in animal models.

5. CONCLUSION

Naringenin targets inflammation, oxidative stress, and ferroptosis in periodontitis through proteins like IL1B and CXCL8. This network pharmacology approach provides insights for developing naringenin-based therapies..

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REFERENCES

[1] Martínez García Mireya & Hernández Lemus Enrique. (2021). Periodontal Inflammation and Systemic Diseases: An Overview. Frontiers in Physiology, 12, 709438-709438. https://doi.org/10.3389/FPHYS.2021.709438

[2] Georgios S. Chatzopoulos, Ziou Jiang, Nicholas Marka & Larry F. Wolff. (2024). Periodontal Disease, Tooth Loss, and Systemic Conditions: An Exploratory Study. International Dental Journal, 74 (2), 207-215. https://doi.org/10.1016/J.IDENTJ.2023.08.002

[3] Saifullah Qazi & Sharma Abhishek. (2023). Current Trends on Innovative Technologies in Topical Wound Care for Advanced Healing and Management. Current drug research reviews, https://doi.org/10.2174/0125899775262048230925054922

[4] Yuanqiang Jia, Xinjing Zhou, Yanan Liu, Xiaoyong Liu, Feiyue Ren & Hongzhi Liu. (2025). Novel Insights Into Naringenin: A Multifaceted Exploration of Production, Synthesis, Health Effects, Nanodelivery Systems, and Molecular Simulation. Molecular nutrition & food research, 69 (18), e70066. https://doi.org/10.1002/MNFR.70066

[5] Junlin Jiang, Xianhui Deng, Chengkai Xu, Yaxian Wu & Jianfeng Huang. (2025). Naringenin inhibits ferroptosis to reduce radiation-induced lung injury: insights from network Pharmacology and molecular docking. Pharmaceutical biology, 63 (1), 11-10. https://doi.org/10.1080/13880209.2025.2465312

[6] Felipe A. Pinho-Ribeiro, Ana C. Zarpelon, Victor Fattori, Marília F. Manchope, Sandra S. Mizokami, Rubia Casagrande & Waldiceu A. Verri. (2016). Naringenin reduces inflammatory pain in mice. Neuropharmacology, 105, 508-519. https://doi.org/10.1016/j.neuropharm.2016.02.019

[7] Li Jie, Cao Feng, Yin He-Liang, Huang Zi-Jian, Lin Zhi-Tao, Mao Ning... & Wang Gang. (2020). Ferroptosis: past, present and future. Cell death & disease, 11 (2), 88. https://doi.org/10.1038/s41419-020-2298-2

[8] Lu Li & Supratik Kar. (2025). Leveraging network pharmacology for drug discovery: Integrative approaches and emerging insights. Medicine in Drug Discovery, 27, 100220-100220. https://doi.org/10.1016/J.MEDIDD.2025.100220

[9] GuzmánFlores Juan Manuel, ArevaloCaro Catalina Maria, MartínezEsquivias Fernando, IsiordiaEspinoza Mario Alberto & Francode la Torre Lorenzo. (2023). Molecular Mechanism of Curcumin on Periodontitis: a Pharmacological Network Study. Journal of oral biosciences, 65 (4), 379-385. https://doi.org/10.1016/J.JOB.2023.08.004

[10] Ningli Li, Bowen Wang, Mingzhen Yang, Miaomiao Feng, Xiaoran Xu, Cory J. Xian... & Yuankun Zhai. (2025). The Multi-Target Action Mechanism for the Anti-Periodontitis Effect of Astragali radix Based on Bioinformatics Analysis and In Vitro Verification. Nutrients, 17 (4), 627-627. https://doi.org/10.3390/NU17040627

[11] Molecular Modeling Group, SIB Swiss Institute of Bioinformatics, University of Lausanne, Quartier UNIL-Sorge, Bâtiment Amphipôle, CH-1015 Lausanne, Switzerland., Molecular Modeling Group, SIB Swiss Institute of Bioinformatics, University of Lausanne, Quartier UNIL-Sorge, Bâtiment Amphipôle, CH-1015 Lausanne, Switzerland., Department of Oncology, University Hospital of Lausanne, Ludwig Cancer Research - Lausanne Branch, CH-1011 Lausanne, Switzerland., Molecular Modeling Group, SIB Swiss Institute of Bioinformatics, University of Lausanne, Quartier UNIL-Sorge, Bâtiment Amphipôle, CH-1015 Lausanne, Switzerland. & Department of Fundamental Oncology, University of Lausanne, Ludwig Cancer Research - Lausanne Branch, Route de la Corniche 9A, CH-1066 Epalinges, Switzerland.. (2019). SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic acids research, 47 (W1), W357-W364. https://doi.org/10.1093/nar/gkz382

[12] Taheri Mohammad, Gholami Leila, Nicknafs Fwad, Hussen Bashdar Mahmud, ArsangJang Shahram, Sayad Arezou & GhafouriFard Soudeh. (2021). Transcript levels of cytokine coding genes in peripheral blood and tissues of patients with periodontitis. Human antibodies, 30 (1), 47-55. https://doi.org/10.3233/HAB-211507

[13] Miaomiao Feng, Xiaoran Xu, Ningli Li, Mingzhen Yang & Yuankun Zhai. (2025). [Mechanism of Cnidii Fructus in the treatment of periodontitis with osteoporosis based on network pharmacology, molecular docking, and molecular dynamics simulation]. West China journal of stomatology, 43 (2), 249-261. https://doi.org/10.7518/HXKQ.2025.2024275