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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

**Медицинские новости Грузии**

საქართველოს სამედიცინო სიახლენი

**GEORGIAN MEDICAL NEWS**

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**GMN: Georgian Medical News** is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

**GMN: Медицинские новости Грузии -** ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

**GMN: Georgian Medical News –** საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

**WEBSITE**

www.geomednews.com

## К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

**При нарушении указанных правил статьи не рассматриваются**.

## REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.**

## ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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# ELUCIDATING THE THERAPEUTIC MECHANISMS OF GUT MICROBIOTA METABOLITES IN PERIODONTITIS: A NETWORK PHARMACOLOGY APPROACH

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## Abstract.

**Background:** Periodontitis is a chronic inflammatory disease featured by progressive destruction of periodontal supporting tissues. Accumulating evidence indicates that gut microbiota-derived metabolites modulate periodontal inflammation via the gut-periodontal axis, yet the underlying mechanisms and therapeutic targets remain largely unknown.

**Methods:** This study adopted network pharmacology to explore the regulatory mechanisms of gut microbiota metabolites in periodontitis. Periodontitis-related genes and metabolite targets were obtained from public databases. Protein–protein interaction (PPI) network, GO and KEGG enrichment analyses, and a Microbiota-Substrate-Metabolite-Target (MSMT) network were constructed for systematic analysis.

**Results:** We identified 1954 periodontitis-related genes and 43 overlapping targets. Five core hub genes (IL6, AKT1, TP53, EGFR, TNF) were screened. These targets were mainly enriched in inflammatory responses and apoptosis regulation, and key pathways included PI3K-Akt, MAPK, IL-17, TNF and Toll-like receptor signaling.

**Conclusion:** Gut microbiota metabolites, particularly short-chain fatty acids, exert anti-periodontitis effects by regulating core hub genes and inflammatory-immune pathways. This study reveals the gut-periodontal axis mechanism and provides potential targets for periodontitis treatment.

**Key words.** Periodontitis, gut microbiota, metabolites, network pharmacology.

## Introduction.

Periodontitis is a chronic inflammatory disease affecting the supporting tissues of teeth, characterized by progressive destruction of the periodontal ligament and alveolar bone, ultimately leading to tooth loss if left untreated [1,2]. According to the Global Burden of Disease Study 2019, severe periodontitis affects approximately 1.1 billion people worldwide, making it one of the most prevalent chronic diseases and imposing substantial economic and social burdens on healthcare systems [3]. The pathogenesis of periodontitis involves complex interactions between pathogenic microorganisms, host immune responses, and environmental factors. While local microbial dysbiosis in the oral cavity has long been recognized as the primary etiological factor, emerging evidence suggests that systemic factors, particularly gut microbiota and their metabolites, may play crucial roles in modulating periodontal inflammation and disease progression [4,5].

The human gut microbiota, comprising trillions of microorganisms, functions as a metabolically active organ that produces numerous bioactive metabolites through fermentation of dietary components and endogenous substrates [6,7]. These metabolites, including short-chain fatty acids (SCFAs), tryptophan derivatives, bile acid metabolites, and phenolic compounds, exert profound effects on host physiology by modulating immune responses, inflammatory pathways, and metabolic homeostasis [8]. Recent studies have demonstrated bidirectional communication between oral and gut microbiota, termed the "oral-gut axis," whereby microbial translocation and metabolite circulation can influence inflammatory conditions at distant sites [9]. Accumulating evidence indicates that gut microbiota dysbiosis is associated with increased systemic inflammation and altered immune regulation, which may contribute to periodontal tissue destruction [10]. Furthermore, specific gut-derived metabolites such as butyrate, propionate, and indole derivatives have been shown to possess anti-inflammatory and immunomodulatory properties that could potentially ameliorate periodontitis [11].

Despite growing recognition of the gut-periodontal axis, the precise mechanisms by which gut microbiota metabolites influence periodontitis pathogenesis remain largely unexplored. Traditional pharmacological research typically focuses on single-target interventions, which may not adequately capture the complex, multi-factorial nature of periodontitis. Network pharmacology, an emerging interdisciplinary approach that integrates systems biology, bioinformatics, and pharmacology, enables comprehensive analysis of multi-component and multi-target interactions within disease networks [12,13]. By constructing integrated networks of "microbiota-substrate-metabolite-target-pathway" this methodology facilitates systematic identification of core therapeutic targets and signaling pathways, thereby providing mechanistic insights into how gut microbiota metabolites regulate disease processes. This approach has been successfully applied to elucidate the mechanisms of traditional Chinese medicines and natural products in treating various inflammatory diseases.

In this study, we employed network pharmacology methodologies to systematically investigate the therapeutic mechanisms of gut microbiota metabolites in periodontitis. By integrating data from multiple databases, we identified overlapping targets between gut microbiota metabolites and periodontitis, constructed protein-protein interaction (PPI) networks to screen core hub genes, and performed comprehensive Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. Furthermore, we established a multi-dimensional Microbiota-Substrate-Metabolite-Target (MSMT) network to elucidate the intricate relationships among gut microbiota species, their metabolic substrates, derived metabolites, and therapeutic targets.

## Materials and Methods.

### Identification of periodontitis-related disease targets:

We retrieved periodontitis-related targets from two independent databases. Using "periodontitis" as the keyword, periodontitis-associated genes were obtained from the Comparative Toxicogenomics Database (CTD, http://ctdbase.org, 2025-9-29) and GeneCards database (https://www.genecards.org, 2025-9-29). For the GeneCards database, only targets with a relevance score ≥10 was included in the analysis to ensure high confidence. Targets appearing in both databases were identified as core periodontitis-related genes using Venn diagram analysis and were selected for subsequent analysis.

### Identification of gut microbiota metabolites and their targets:

We acquired information on gut microbiota metabolites and human gut targets from the gutMGene database (http://bio-annotation.cn/gutmgene/, 2025-9-29). The metabolites were subsequently uploaded to the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) to obtain their corresponding SMILES (Simplified Molecular Input Line Entry System) format. The targets of gut microbiota metabolites were predicted using the Swiss Target Prediction database (http://www.swisstargetprediction.ch/), with the species parameter set as "Homo sapiens" and a probability score ≥ 0.1 used as the threshold to filter the predicted targets. Additionally, metabolism-related genes were extracted from the gutMGene database. Using Venn diagram analysis, we intersected the targets from Swiss Target Prediction and metabolism-related genes from gutMGene with the periodontitis-related targets to identify overlapping targets, which represent the core therapeutic targets through which gut microbiota metabolites regulate periodontitis.

### Protein-protein interaction (PPI) network analysis:

The overlapping targets between gut microbiota metabolites and periodontitis were uploaded to the STRING database (https://string-db.org, version 12.0) to construct a protein-protein interaction (PPI) network. The minimum required interaction score was set to 0.400 (medium confidence). The PPI network was subsequently visualized and analyzed using Cytoscape software (version 3.10.3, https://cytoscape.org/).

### Gene Ontology (GO) and KEGG pathway enrichment analysis:

To elucidate the biological functions and signaling pathways associated with the overlapping targets, we performed GO and KEGG pathway enrichment analyses using the clusterProfiler package in R software. GO analysis encompassed three categories: biological process (BP), cellular component (CC), and molecular function (MF). The enrichGO and enrichKEGG functions were employed to conduct the enrichment analyses with the organism parameter set as "Homo sapiens" (org.Hs.eg.db). Statistical significance was determined using $P < 0.05$ as the threshold, and the Benjamini-Hochberg method was applied to control the false discovery rate (FDR < 0.05) to identify the most significant GO terms and KEGG pathways.

### Construction of Microbiota-Substrate-Metabolite-Target (MSMT) network:

To comprehensively illustrate the regulatory mechanism by which gut microbiota metabolites affect periodontitis through core hub genes, we constructed an integrated MSMT network. The network was established by extracting information on gut microbiota species, their metabolic substrates, derived metabolites, and the core hub targets from the gutMGene database and literature review. The MSMT network was visualized using Cytoscape software, with different node colors representing different layers: gut microbiota (yellow), substrates (green), metabolites (blue), and target genes (red). This multi-dimensional network provides a systematic framework for understanding the complex interactions between gut microbiota-derived metabolites and periodontitis-related molecular targets.

### Statistical analysis:

All data processing and statistical analyses were performed using R software. GO and KEGG pathway enrichment analyses were conducted using the clusterProfiler package with the enrichGO and enrichKEGG functions. Statistical significance was determined using $P < 0.05$ as the threshold. The Benjamini-Hochberg method was applied to control the false discovery rate (FDR < 0.05) in multiple testing corrections for all enrichment analyses.

## Results.

### Identification of periodontitis-related disease targets:

To comprehensively identify genes associated with periodontitis pathogenesis, we retrieved disease-related targets from two independent databases. Using "periodontitis" as the keyword, we obtained 12,322 genes from the CTD and 2,795 genes from the GeneCards database. The Venn diagram analysis revealed 1,954 overlapping genes between these two databases (Figure 1), representing 14.8% of CTD genes and 69.9% of GeneCards genes. These 1,954 common targets were considered as the core periodontitis-associated genes and were selected for subsequent analysis.

### Identification of targets linking gut microbiota metabolites to periodontitis:

To identify the potential therapeutic targets through which gut microbiota metabolites exert their effects on periodontitis, we integrated data from multiple sources. First, we extracted metabolism-related genes from the gutMGene database (n=154) and targets associated with gut microbiota metabolites from the Swiss Target Prediction database (n=783). These targets were then intersected with the 1,954 periodontitis-related genes identified previously. As shown in the three-way Venn diagram (Figure 2A), we identified 43 overlapping targets, representing 0.3% of total periodontitis genes, which constitute the core targets mediating the regulatory effects of gut microbiota metabolites on periodontitis. To visualize the intricate relationship between gut microbiota, these therapeutic targets, and periodontitis, we constructed a Microbiota-Targets-Periodontitis network (Figure 2B). The network revealed diverse targets including inflammatory mediators (IL6, TNF), signaling molecules (MAPK1, MAPK3, MAPK8, MAPK14, AKT1), nuclear receptors (PPARG, VDR, AHR), and metabolic enzymes (CYP1A1, CYP1A2, CYP2D6, CYP3A4), suggesting that gut microbiota metabolites may modulate periodontitis through multiple biological pathways. These 43 targets were

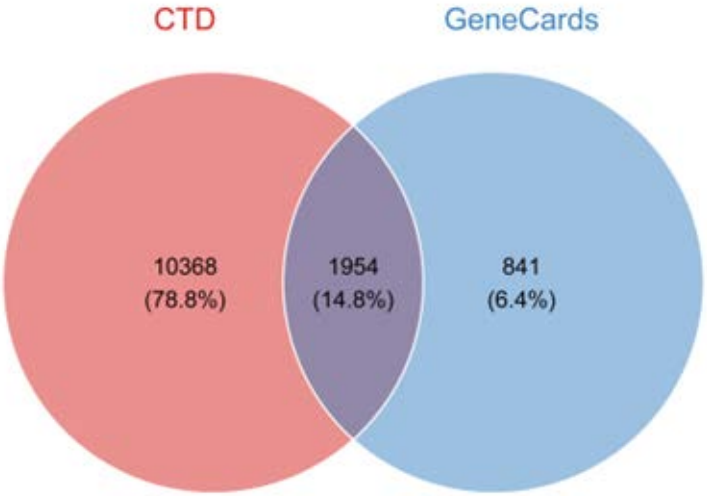


***Figure 1.*** *Identification of periodontitis-related genes from CTD and GeneCards databases. Venn diagram showing the overlap of periodontitis-associated genes between the CTD and GeneCards database.*

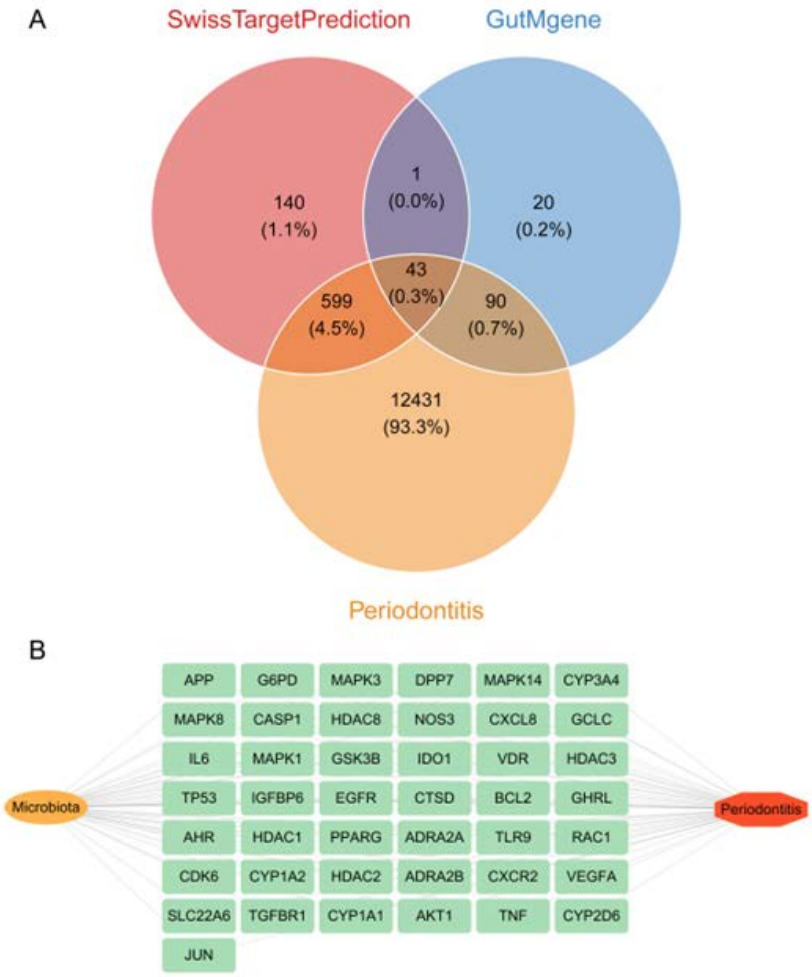


***Figure 2.*** *Identification of overlapping targets between gut microbiota metabolites and periodontitis. (A) Venn diagram illustrating the intersection of targets from Swiss Target Prediction database, gutMGene database, and periodontitis-related genes. (B) Network visualization depicting the relationship between gut microbiota, the 43 overlapping targets, and periodontitis.*

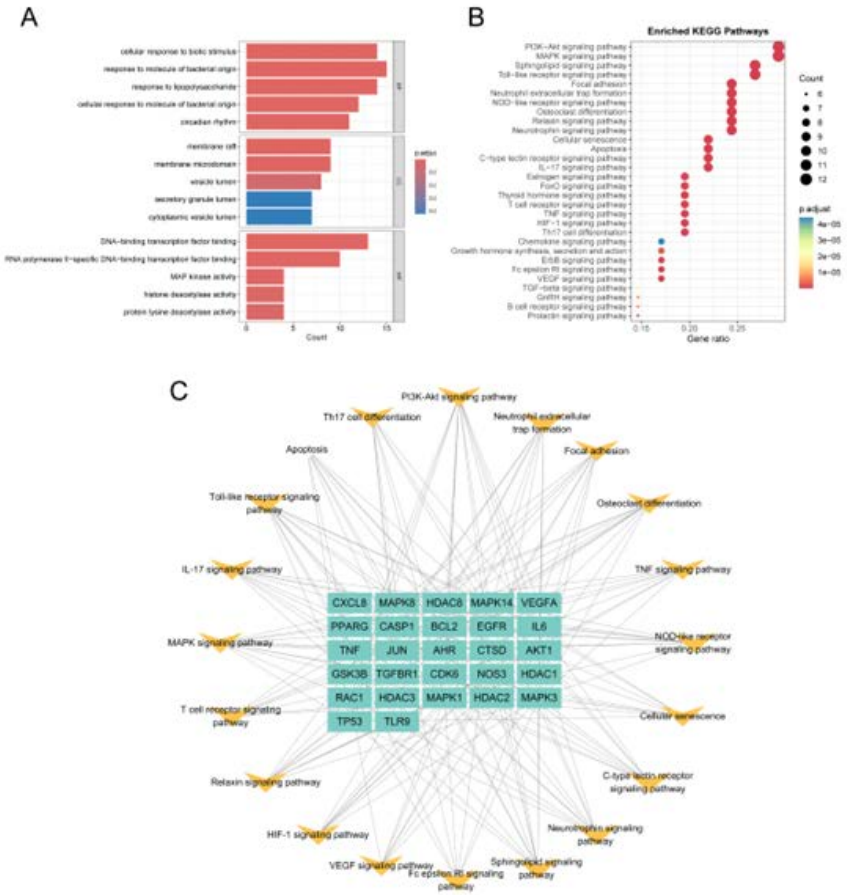


***Figure 3.*** *Functional enrichment analysis of the 43 overlapping targets. (A) GO enrichment analysis showing the top enriched biological processes (BP), cellular components (CC), and molecular functions (MF). (B) KEGG pathway enrichment analysis displaying the most significantly enriched signaling pathways. (C) Network visualization illustrating the relationships between the core targets and their associated KEGG pathways.*

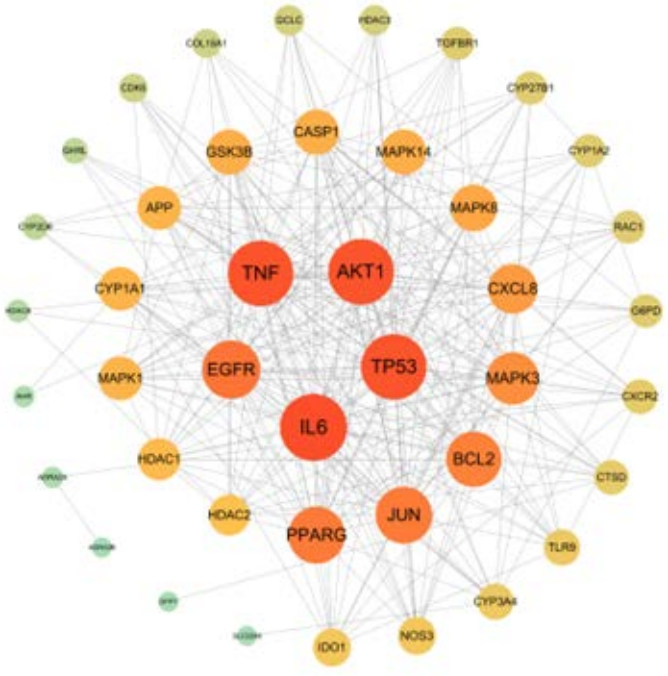


***Figure 4.*** *PPI network analysis of the 43 overlapping targets. The PPI network was constructed using the STRING database and visualized with Cytoscape software.*

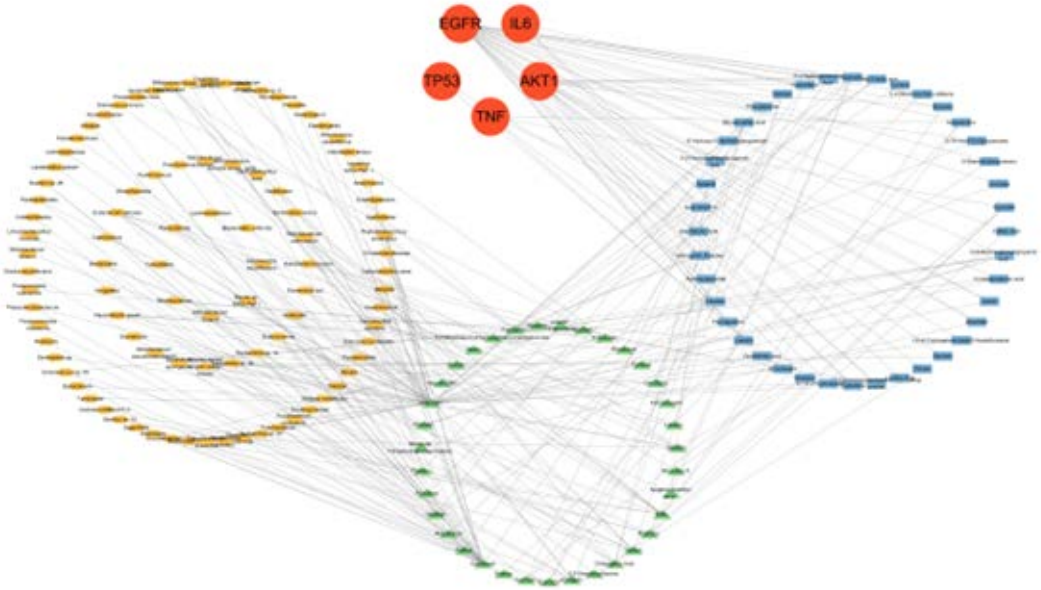


***Figure 5.*** *Comprehensive MSMT network linking gut microbiota to periodontitis through the five core hub genes. The network illustrates the complex relationships among gut microbiota species (yellow nodes), substrates (green nodes), metabolites (blue nodes), and periodontitis-related core hub target genes (red nodes).*

selected for subsequent protein-protein interaction and pathway enrichment analyses.

**GO and KEGG enrichment analysis of core targets:**

To elucidate the biological functions and signaling pathways through which gut microbiota metabolites regulate periodontitis, we performed comprehensive GO and KEGG enrichment analyses on the 43 overlapping targets. GO enrichment analysis (Figure 3A) revealed that these targets were predominantly involved in biological processes related to inflammatory responses, including cellular response to biotic stimulus, response to molecule of bacterial origin, response to lipopolysaccharide, and cellular response to molecule of bacterial origin. For cellular components, the targets were mainly localized in membrane raft, membrane microdomain, vesicle lumen, and secretory granule lumen. Molecular function analysis indicated significant enrichment in DNA-binding transcription factor binding, RNA polymerase II-specific DNA-binding transcription factor binding, MAP kinase activity, histone deacetylase activity, and protein-lysine deacetylase activity. KEGG pathway enrichment analysis (Figure 3B) identified several critical signaling pathways, with PI3K-Akt signaling pathway, MAPK signaling pathway, and Sphingolipid signaling pathway showing the highest significance. Other important pathways included Toll-like receptor signaling pathway, IL-17 signaling pathway, TNF signaling pathway, Th17 cell differentiation, NOD-like receptor signaling pathway, and neurotrophin signaling pathway. The target-pathway network (Figure 3C) demonstrated that key targets such as IL6, AKT1, MAPK1, MAPK3, MAPK8, MAPK14, TNF, and PPARG were hub nodes connecting multiple pathways, suggesting their central roles in mediating the therapeutic effects of gut microbiota metabolites on periodontitis. These results indicate that gut microbiota metabolites may ameliorate periodontitis primarily through modulating inflammatory responses, immune regulation, and cellular signaling transduction pathways.

**Construction and analysis of PPI network:**

To identify the core hub targets among the 43 overlapping genes, we constructed a PPI network using the STRING database with a minimum required interaction score of 0.4. The network was subsequently visualized using Cytoscape software (Figure 4). The PPI network comprised 43 nodes and 412 edges, with an average node degree of 19.2, indicating extensive interactions among these targets. Network topology analysis was performed using the "Analyze Network" function in Cytoscape, which calculated various topological parameters including degree centrality (DC), betweenness centrality, and closeness centrality for each node. Based on degree centrality ranking, we identified the top five core hub genes: IL6 (DC=33), AKT1 (DC=32), TP53 (DC=32), TNF (DC=32), and EGFR (DC=27), which exhibited the highest number of interactions within the network. Node size and color gradient in the visualization corresponded to degree centrality values, with larger and darker nodes representing higher connectivity. Additionally, other important nodes also demonstrated substantial connectivity within the network. These hub genes likely play pivotal roles in mediating the therapeutic effects of gut microbiota metabolites on periodontitis. The dense interconnections observed in the PPI network suggest that gut microbiota metabolites exert their anti-periodontitis effects through coordinated regulation of multiple targets rather than acting on isolated proteins, reflecting the multi-target and synergistic nature of metabolite-based therapy.

**Construction of the Microbiota-Substrate-Metabolite-Target (MSMT) network:**

To comprehensively elucidate the mechanism by which gut microbiota metabolites regulate periodontitis through the five core hub genes (IL6, AKT1, TP53, EGFR, and TNF), we

constructed an integrated MSMT network using Cytoscape software (Figure 5). This multi-layered network revealed the intricate connections between gut microbiota, their metabolic substrates, derived metabolites, and therapeutic targets. The network comprised four distinct node types: gut microbiota species (yellow), substrates (green), metabolites (blue), and target genes (red). Analysis of the MSMT network identified a diverse array of gut microbiota genera, including Bacteroides, Lactobacillus, Bifidobacterium, Clostridium, Eubacterium, Escherichia, Enterococcus, Faecalibacterium, and Prevotella, which are capable of producing bioactive metabolites relevant to periodontitis regulation. The substrates included various amino acids, carbohydrates, and lipid precursors, which are transformed by gut microbiota into a spectrum of metabolites. Key metabolites identified in the network included short-chain fatty acids, tryptophan derivatives, bile acid metabolites, and various other bioactive compounds. Notably, the network demonstrated that these metabolites could simultaneously interact with multiple target genes, while individual targets could be modulated by multiple metabolites, suggesting a synergistic and redundant regulatory mechanism. The MSMT network provides a comprehensive framework for understanding how gut microbiota-derived metabolites exert their therapeutic effects on periodontitis through coordinated regulation of inflammatory, apoptotic, and metabolic pathways mediated by the five core hub genes.

## Discussion.

Periodontitis represents a multifactorial inflammatory disease whose pathogenesis extends beyond local oral microbial dysbiosis to involve systemic factors, including gut microbiota and their derived metabolites. In this study, we employed network pharmacology approaches to systematically investigate the mechanisms by which gut microbiota metabolites regulate periodontitis. Through comprehensive bioinformatics analysis, we identified 43 overlapping targets between gut microbiota metabolites and periodontitis, with five core hub genes (IL6, AKT1, TP53, EGFR, and TNF) emerging as central regulators. Our findings revealed that gut microbiota metabolites primarily exert their therapeutic effects through modulation of inflammatory responses, immune regulation, and cellular signaling pathways, particularly the PI3K-Akt, MAPK, IL-17, and TNF signaling pathways. The MSMT network further demonstrated the complex interactions among diverse gut microbiota species, metabolic substrates, bioactive metabolites, and therapeutic targets, providing a comprehensive framework for understanding the gut-periodontal axis.

The identification of IL6, TNF, and AKT1 as core hub genes aligns with their well-established roles in periodontal pathogenesis. IL-6 and TNF-α are pivotal pro-inflammatory cytokines that orchestrate the inflammatory cascade in periodontitis, promoting osteoclastogenesis and alveolar bone resorption [14]. Elevated levels of these cytokines in gingival crevicular fluid and serum have been consistently associated with periodontal disease severity and treatment outcomes [15]. The AKT1 signaling pathway plays crucial roles in regulating cellular survival, proliferation, and metabolism, and its dysregulation has been implicated in periodontal tissue destruction [16]. Importantly, emerging evidence suggests that gut-derived short-chain fatty acids (SCFAs), particularly butyrate and propionate, can suppress IL-6 and TNF-α production through inhibition of NF-κB signaling and histone deacetylase (HDAC) activity, thereby attenuating systemic and local inflammation [17]. Our network analysis revealed that multiple gut microbiota metabolites, including butyrate, propionate, acetate, and indole derivatives, can simultaneously modulate these core targets, suggesting synergistic anti-inflammatory mechanisms. Furthermore, recent studies have demonstrated that oral administration of specific probiotic strains or SCFA supplementation can reduce periodontal inflammation and alleviate alveolar bone loss in animal models, supporting the therapeutic potential of gut microbiota-based interventions for periodontitis [18]. KEGG pathway enrichment analysis highlighted the PI3K-Akt, MAPK, IL-17, and TNF signaling pathways as key mechanisms mediating the effects of gut microbiota metabolites on periodontitis. The PI3K-Akt pathway serves as a central regulator of cellular metabolism, survival, and immune responses, and its activation has been shown to modulate periodontal ligament stem cell differentiation and osteogenic potential [19]. Gut-derived metabolites, particularly SCFAs, can activate the PI3K-Akt pathway through G-protein coupled receptors (GPCRs) such as GPR41 and GPR43, leading to enhanced anti-inflammatory responses and improved tissue repair [20]. The MAPK signaling cascade, comprising ERK, JNK, and p38 MAPK pathways, plays critical roles in transducing extracellular signals into cellular responses including inflammation, apoptosis, and differentiation. Dysregulated MAPK activation has been implicated in periodontal tissue destruction, and inhibition of specific MAPK isoforms has shown therapeutic benefits in experimental periodontitis models [21]. Additionally, the IL-17 signaling pathway has emerged as a crucial mediator of periodontal inflammation, with IL-17-producing T helper 17 (Th17) cells promoting neutrophil recruitment, inflammatory cytokine production, and osteoclastogenesis [22]. Intriguingly, recent studies have revealed that gut microbiota composition, particularly the abundance of segmented filamentous bacteria and specific Bacteroides species, profoundly influences Th17 cell differentiation and IL-17 production, suggesting that modulation of gut microbiota may indirectly affect periodontal Th17 responses [23]. Our MSMT network analysis revealed complex relationships among diverse gut microbiota genera including Bacteroides, Lactobacillus, Bifidobacterium, Faecalibacterium, and Prevotella, their metabolic substrates such as dietary fibers, amino acids, and bile acids, and derived bioactive metabolites. Among these metabolites, SCFAs (butyrate, propionate, acetate) emerged as particularly important mediators with multiple beneficial effects. Butyrate serves as the primary energy source for colonocytes and exerts potent anti-inflammatory effects through inhibition of NF-κB signaling and enhancement of regulatory T cell (Treg) differentiation [24]. Clinical studies have demonstrated that individuals with periodontitis exhibit reduced fecal SCFA levels and altered gut microbiota composition compared to periodontally healthy controls, suggesting potential causal relationships [25]. Beyond SCFAs, tryptophan-derived metabolites such as indole and

3-indolepropionic acid have shown anti-inflammatory and antioxidant properties by activating the aryl hydrocarbon receptor (AhR) pathway, which modulates immune cell differentiation and cytokine production [26]. The gut microbiota genus Lactobacillus, particularly L. paracasei and L. rhamnosus strains, can produce these beneficial metabolites and has been investigated as potential probiotic interventions for periodontal disease. Several clinical trials have reported that oral or systemic probiotic supplementation can improve periodontal clinical parameters, reduce pro-inflammatory cytokines, and modulate oral microbiota composition, although results remain heterogeneous due to variations in probiotic strains, doses, and treatment durations [27]. Despite providing novel insights into the gut-periodontal axis, this study has several limitations that warrant consideration. First, our analysis was based entirely on computational predictions and database mining without experimental validation. Future studies should incorporate in vitro cell culture experiments, animal models, and clinical investigations to validate the predicted targets, pathways, and metabolite-target interactions. Second, the gut microbiota data derived from the gutMGene database primarily represents fecal microbiota composition, which may not fully reflect the metabolically active microbial communities in different intestinal segments or their functional capacity in vivo. Metagenomic and metabolomic profiling of periodontitis patients compared to healthy controls would provide more direct evidence of gut microbiota-metabolite alterations associated with periodontal disease. Third, our network analysis identified numerous potential metabolites and targets but did not prioritize them based on therapeutic feasibility, bioavailability, or clinical relevance. Future research should focus on the most promising candidates for drug development or dietary interventions. Fourth, the unidirectional analysis from gut microbiota to periodontitis does not capture the bidirectional nature of the oral-gut axis, whereby periodontal pathogens may translocate to the gut and alter intestinal microbiota composition [28]. Finally, individual variations in gut microbiota composition, genetic background, dietary habits, and environmental factors may significantly influence the therapeutic responses to microbiota-based interventions, necessitating personalized approaches in future clinical applications. Nevertheless, this study provides a comprehensive framework for understanding how gut microbiota metabolites regulate periodontitis through multi-target and multi-pathway mechanisms, paving the way for development of novel microbiome-based therapeutic strategies for periodontal disease management.

## Conclusion.

This study employed network pharmacology to systematically elucidate the therapeutic mechanisms of gut microbiota metabolites in periodontitis. We identified 43 overlapping targets and five core hub genes (IL6, AKT1, TP53, TNF, and EGFR) mediating the regulatory effects. Enrichment analyses revealed that these metabolites primarily exert therapeutic effects through modulation of inflammatory and immune signaling pathways, including PI3K-Akt, MAPK, IL-17, and TNF pathways. The MSMT network illustrated complex interactions among gut microbiota species, metabolic substrates, bioactive metabolites, and therapeutic targets, highlighting the multi-target nature of metabolite-based therapy. Short-chain fatty acids, particularly butyrate, propionate, and acetate, emerged as pivotal anti-inflammatory metabolites. Our findings provide a comprehensive framework for understanding the gut-periodontal axis and offer insights for developing microbiome-based therapeutic strategies for periodontitis management. Future experimental validation and clinical studies are warranted to translate these predictions into practical applications.


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## Authors' contributions.

Data curation, Formal analysis and Funding acquisition: Haitao Lin and Liang Chen; Project administration and Supervision: Haitao Lin and Wenjie Wen; Writing-original draft: Haitao Lin; Writing-review and editing: Liang Chen. *Corresponding author: Liang Chen. All authors have read and agreed to the published version of the manuscript.

## Data Availability.

All data generated or analyzed during this study are included in this published article.

## Competing Interests.

The authors declare no competing interests related to this study.


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