

Therapeutic Potential of Luteolin in Periodontal Therapy - A Scoping Review Protocol

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This scoping review is aimed at evaluating the therapeutic potential of luteolin in periodontal therapy. Introduction: Periodontal disease is a destructive, inflammatory process of the tooth-supporting tissues resulting frequently in tooth loss. Current periodontal therapy includes surgical and non-surgical strategies. Plant-based adjuvant therapies have recently gained popularity due to their potent pharmacological qualities and negligible side effects. Luteolin is a flavonoid found in many herbs, vegetables, and fruits. It exhibits several biological activities useful in fighting periodontal diseases. Considering luteolin's promising biological properties, its anti-periodontal disease potential needs further investigation. In this article, we present the protocol of the planned scoping review which will map currently available research on luteolin's therapeutic potential in periodontal disease management. The scoping review is planned to be performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines (PRISMA-ScR). This review will include any study design in English that investigates the effects of luteolin in periodontal disease management. No date restrictions will be applied. A comprehensive literature review will be executed by screening relevant electronic databases such as PubMed, Scopus, and Web of Science as well as grey literature and hand screening of pertinent article reference lists and citations. A three-step synthesis process will be employed. Screening of the articles will be conducted by qualified reviewers who will extract information into a predesigned data collection instrument. We shall present the data in tabular format along with the narrative summary. Our proposed scoping review will outline the biological properties of luteolin that are beneficial in periodontal therapy and identify gaps in the scientific literature that require further research.

Keywords: Anti-inflammatory agents; Anti-oxidants; Luteolin; Periodontal diseases.

Periodontal disease is a chronic, multifactorial, inflammatory process of the tooth-supporting tissues resulting in its destruction and

sometimes loss of teeth.^{1,2} It arises as a result of host and microbial factors influencing inflammation. It can be described as an immuno-inflammatory

disease, determined by the interaction between bacterial colonization and host immunology.³ Chronic periodontitis is estimated to affect 30-35 per cent of the adult population worldwide.⁴

According to mounting evidence, many studies suggest that periodontal diseases pose a heightened risk for a variety of systemic disorders including cardiovascular diseases, stroke, preterm low birth weight, and diabetes. As a result, treating periodontal infection helps to prevent and manage these systemic diseases more effectively.¹ Current periodontal disease care involves both surgical and non-surgical approaches, as well as antibiotic administration. However, the rise in antibiotic resistance has restricted the use of therapeutic medications to treat oral illnesses.⁵

Adjuvant therapy has piqued the interest of academics and physicians due to its benefits over traditional treatment. Chlorhexidine is demonstrated to be the most effective adjuvant agent in preventing plaque buildup, gingivitis, and periodontitis. However, dental discolouration, dental calculus accumulation, burning sensation, and unpleasant taste have all been reported. Similarly, systemic antimicrobials have demonstrated considerable therapeutic benefits in terms of improving clinical periodontal parameters, but with an increased incidence of side effects. This has prompted the exploration of natural compounds that have higher biocompatibility, therapeutic value, safety, and lower cost.⁶ Among the various available possibilities for the management of periodontal diseases, oral care products consisting of plant-based compounds have garnered limelight owing to the positive pharmacological properties of their bioactive constituents.⁷

Luteolin is a type of flavonoid occurring in many fruits, vegetables, and herbs.⁸ The increased interest in this compound is due to its several beneficial biological activities, such as its antioxidant, anti-inflammatory, and antimicrobial effects which are helpful in fighting against periodontal diseases.^{5,9} Luteolin is non-toxic and represents a novel disease-preventing and therapeutic agent that can serve as a potential compound in the development of next-generation medicines.⁵

Existing literature on luteolin's effects in managing periodontal diseases reveals few studies of heterogenous methodologies^{1,9-13} showing

luteolin's anti-inflammatory, bone regeneration ability and antimicrobial activity against oral microbes.^{14,15} Considering these promising biological properties of luteolin, its anti-periodontal disease potential needs further investigation. This article presents the protocol for our scoping review, which will map the currently available research on luteolin's therapeutic potential in periodontal disease management.

MATERIALS AND METHODS

This study is planned as a scoping review and will be conducted as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.¹⁶ The primary review objective will be to explore the therapeutic potential of luteolin as an adjunct to standard therapy in the management of periodontal diseases. The secondary objective will be to report any adverse effects or toxicity of luteolin.

Search strategy

A thorough search of literature will be conducted in appropriate electronic databases: PubMed, Scopus, and Web of Science. To ensure the inclusion of all the relevant studies, grey literature such as Google Scholar will also be screened. This scoping review will be conducted from the inception of databases until May 2024 (approximately). In addition, the reference lists and citations of the retrieved papers will be hand-searched to find other eligible articles for inclusion. The corresponding authors of articles that do not have full-text access will be contacted and requested for full-text. The inclusion criteria will be original research articles of any study design written in the English language that investigates the effects of luteolin in the management of periodontal diseases. Review papers, news pieces, letters, editorials, and case studies will be excluded. Search keywords will include "Luteolin" and "Periodontal" or "Periodontitis" or "Gingival" or "Gingivitis". The search strategies can be accessed in **Table 1**. The search will be redone before publication to include any recently published papers.

Study Selection

Following the search, the results will be managed and duplicates will be eliminated using reference management software (Zotero, United

States). The review procedure will include two screening stages: (a) Title and abstract review and (b) Full-text review. In the first phase, a pair of qualified reviewers will separately screen titles and abstracts and mark them as 'include', 'exclude', or 'uncertain' in accordance with the selection criteria. Reasons for rejecting full-text publications that do not fit the inclusion criteria will be documented and reported in the scoping review. Resolution of any conflicts will be done through discussion, with the assistance of a third reviewer. In the second phase, full-text papers for publications designated as 'included' or 'uncertain' will be retrieved and assessed separately and in duplicate by the reviewers to ensure inclusion in accordance with the selection criteria. Any paper that remains classified as 'uncertain' following a thorough full-text evaluation will be considered by all team members until a decision for its inclusion or exclusion is reached. The results of the search will be reported in full in the final scoping review and presented in a PRISMA flow diagram.¹⁷

Data extraction

The research team developed draft data collection tools in tabular formats to extract the study characteristics. The study categories will be grouped as microbial studies, cell-line studies, animal studies and human trials. The draft data collection forms are presented in **Tables 2, 3, 4 and 5**. Pilot testing of these draft data collection forms was conducted to establish their functionality and to confirm high inter-reviewer reliability. Modifications in the draft data collection forms will be incorporated if necessary, during the data extraction process. The modifications will be detailed in the full scoping review. Data will be collected in duplicate, with a pair of independent reviewers extracting information from all included articles. To verify data accuracy, each reviewer's separate compiled data will be compared and any disparities will be deliberated further to ensure uniformity among the reviewers. Entire data will be collated into a single document and exported into a biostatistics computer program for further analysis.

The following information (where available) will be collected: Title, authors, publication year, country, publication type, objectives, study design, study population, sample

size, study methodology, luteolin origin, luteolin dosage, route of administration, duration of administration, periodontal pathogens, minimum inhibitory concentration (MIC), periodontal diagnosis, periodontal parameters, periodontal intervention, follow-up, Study outcomes, and conclusion. Data on reported complications if any will also be recorded. Authors of papers will be contacted to request missing or additional data, where required.

Data analysis and presentation

The data of the reviewed literature will be presented as tabular summaries and will be qualitatively analysed. The characteristics of the microbiological, cell-line, animal model and human trial studies will be outlined. From the evidence gathered the therapeutic potential of luteolin as an adjunct to standard therapy in the management of periodontal diseases will be discussed in detail and a note on the adverse effects or toxicity of luteolin reported in literature will be added.

RESULTS AND DISCUSSION

Luteolin exhibits a range of beneficial biological activities such as antioxidant, anti-inflammatory, anti-microbial, anti-allergy, anti-apoptotic, anti-tumour, anti-diabetic, cardioprotective, chemotherapeutic and neuroprotective properties.⁸ Plants high in luteolin content have been employed in many traditional medicinal modalities.¹⁸ Some studies have explored luteolin's therapeutic potential in a variety of diseases and generated promising results. Luteolin is known to possess anticancer properties in many cancer types.¹⁹⁻²² Few other studies have shown the potential of luteolin in the management of neurological diseases,^{23,24} cardiac diseases,^{25,26} diabetes²⁷ and dermatological diseases.^{28,29}

Existing literature on luteolin's effects in managing periodontal diseases reveals pre-clinical studies of heterogenous methodologies such as *in-vitro*^{1,10-12} and animal *in-vivo* models^{9,13} that have shown luteolin's ability to reduce inflammation, while also promoting bone tissue regeneration. Luteolin also exhibits great antimicrobial activity against oral microbes, including common periodontal pathogens.^{14,15} Hence the little available

Reviews revealed no existing or ongoing scoping or systematic reviews and meta-analysis on this topic. Hence, the conduct of a scoping review on this novel topic was planned.

Limitations

As our study is restricted to retrieving research papers published in the English language, our review methodology might not be able to identify all the relevant studies. Also, the heterogeneity and paucity of available literature prevent a systematic review or meta-analysis from being undertaken.

CONCLUSION

Our proposed scoping review will outline luteolin's biological properties that will be beneficial in its utilisation as an adjuvant in periodontal disease management and will also identify the gaps in the existing scientific literature and highlight further scope for research.

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Conflicts of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

All data relevant to the study are included in the article. Extended data is available by request.

Ethics Statement

This paper is a scoping review protocol, hence approval from a medical ethics committee is not essential.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Authors' Contributions

PBR, SB, and SVM conceptualized the research protocol. PBR and HKS developed the search strategy. PBR and VHR developed the data

extraction tools. PBR drafted the manuscript. PBR and UH edited the manuscript. PBR, SB, SVM, HKS, VHR, and UH approved the final version.

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