TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 10, Issue 2, Spring 2025

Review

Exploring Therapeutic Potential of Luteolin in Periodontal Therapy: A Scoping Review

Premalatha Bidadi Rajashekaraiah[1]*, Suman Basavaraju[2], Subbarao V. Madhunapantula[3], Sumana Kumar[4], Hemanth Kumar Somareddy[5], Veena Haranahalli Raghavan[6]

[1]Department of Oral Pathology and Microbiology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysuru- 570015, India
[2]Department of Periodontology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysuru- 570015, India
[3]Department of Biochemistry (A DST-FIST Supported Department), JSS Medical College, JSS Academy of Higher Education and Research, Mysuru- 570015, India
[4]Department of Microbiology , School of Life Sciences, JSS Academy of Higher Education and Research, Mysuru-570015, India
[5]Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru-570015, India
[6]Department of Periodontics, K.L.E.S Institute of Dental Sciences, Bengaluru, India

Received: 11 Jul 2024 **Revised:** 22 Oct 2024 **Accepted:** 26 Oct 2024

Abstract

Periodontal disease is a destructive inflammatory process of the tooth-supporting tissues, that frequently results in tooth loss. Traditional periodontal therapies that use conventional instrumentation, often struggle to eliminate the disease effectively in inaccessible tooth parts. In addition, currently employed adjuvant agents in periodontal therapy have many undesirable side effects. This has encouraged the exploration of natural compounds with higher biocompatibility, therapeutic index, safety and lower cost. Luteolin, a flavonoid found in many herbs, vegetables, and fruits, exhibits several beneficial properties for periodontal health, suggesting that it could be an effective therapeutic agent in countering periodontal diseases. However, further exploration of its therapeutic potential is necessary. Thus, this study aimed to review the current evidence on luteolin's therapeutic role in periodontal therapy. A comprehensive search in the scientific literature databases (PubMed, Scopus, and Web of Science) was conducted for studies investigating luteolin's role in periodontal therapy. The search yielded 106 papers and after discarding 86 papers that did not fit the inclusion criteria, 20 studies were considered for analysis. These included 11 studies on cell lines, 4 related to animal experiments, 3 on microbiological profiling and 2 on human participants. Data regarding the study characteristics were extracted and summarized. All the evidence gathered from the reviewed papers consistently demonstrated that luteolin has potent biological activities such as anti-inflammatory, antioxidant and antimicrobial properties that combat the etiopathogenic factors affecting the establishment and progression of periodontal diseases. In conclusion, luteolin holds considerable promise as an adjuvant therapeutic agent in periodontal disease management. With further research, it could become a key component in periodontal treatment strategies.

Keywords: Anti-inflammatory agents; Antioxidants; Luteolin; Periodontal diseases

http://doi.org/10.18502/tim.v10i2.19064

Citation: Rajashekaraiah PB, Basavaraju S, Madhunapantula SV, Kumar S, Somareddy HK , Raghavan VH . **Exploring Therapeutic Potential of Luteolin in Periodontal Therapy: A Scoping Review.** Trad Integr Med 2025;10(2):179-192. http://doi.org/10.18502/tim.v10i2.19064

*Corresponding Author: Premalatha Bidadi Rajashekaraiah
Department of Oral Pathology and Microbiology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysuru- 570015, India
Email: drpremalathabr_dch@jssuni.edu.in

Introduction

"Periodontal disease is a non-communicable[1], inflammatory illness characterized by a polymicrobial disruption of host homeostasis and a progressive breakdown of tooth-supporting tissues [2]. It arises as a result of microbial and host variables that influence inflammation and can be classified as an immuno-inflammatory disease caused by the interaction of microbial colonisation and host immunity"[3]. According to reports, approximately 90% of the world population has suffered from periodontal disease during their lifetime [4]. Periodontal disease is currently the world's twelfth most prevalent disorder, according to the Global Health Data Exchange database [5].

Globally, periodontitis is the primary cause of tooth loss among adults. These patients are at heightened danger of edentulism, multiple tooth loss and masticatory dysfunction which affects their nutrition, life quality and self-esteem; while also imposing significant socioeconomic consequences and healthcare costs [1]. Evidence from many studies implies that periodontal disease elevates the risk of several systemic disorders including stroke, diabetes, cardiovascular diseases and preterm low birth weight [6]. It is also linked with several major illnesses such as hypertension, Parkinson's and Alzheimer's disease [7]. As a result, treating periodontal disease helps to prevent and manage these systemic disorders more effectively [6]. Common clinical manifestations of periodontal diseases include toothache, gingival redness, swelling, bleeding, chewing difficulty, tooth mobility, and tooth loss [7].

Current periodontal disease management incorporates both nonsurgical and surgical strategies [8]. The main periodontal therapies are scaling and root planing and antibiotics administration. However, conventional instrumentation cannot effectively eliminate pathogens in inaccessible parts, such as furcation areas and deep periodontal pockets [7]. Also, antibiotics are linked to many adverse effects such as gastrointestinal disturbances, drug resistance, toxicity, sensitivity, and opportunistic infections [9,10]. Therefore, the search for safer and more effective periodontal disease prevention and treatment strategies has grown in relevance [7].

Adjuvant therapy has attracted the attention of practitioners and academics alike due to its advantage over conventional treatment modalities. Chlorhexidine is currently employed as the most effective adjuvant agent in periodontal therapy. However, many undesirable side-effects are reported with its usage such as dental discolouration, calculus, burning sensation and unpleasant taste. This has encouraged the exploration of natural compounds with higher biocompatibility, therapeutic index, safety and lower cost [10]. Phytotherapy is an emerging multidisciplinary science [9,11]. The study of phytotherapy in dentistry is especially important as there has been little research on oral disorders. There is a growing interest among the scientific community in discovering therapeutic plant species for dental applications [12]. Available studies show that several medicinal plants have positive biological activities, reduced side effects and toxicity. Thus, extracts of plants have the potential to be medications and provide novel options as adjuvants for periodontal therapy [9,11].

Luteolin (3′,4′,5,7-tetrahydroxy flavone) is a flavonoid substance that belongs to the class of flavones. It has garnered heightened attention owing to its therapeutic effects on several human diseases. Luteolin has surfaced as a major phytochemical with notable therapeutic relevance [13]. It is widely distributed among numerous plant species as an important dietary compound [14]. Many herbs, vegetables, fruits and medicinal plants contain luteolin [15]. In plants, luteolin is available as an aglycone molecule without a sugar moiety and as a glycoside molecule with a bound sugar moiety. Its molecular weight is 286.2 g/mol and its molecular formula is $C_{15}H_{10}O_6$ [16]. Luteolin exhibits a range of beneficial biological activities such as antioxidant, anti-inflammatory, antimicrobial, anti-allergy, anti-apoptotic, antitumor, antidiabetic, cardioprotective, chemotherapeutic and neuroprotective properties [17]. It is also regarded to be non-toxic. Plants high in luteolin content have been utilized in traditional Chinese, Iranian and Brazilian medicinal systems to treat inflammatory disorders [15]. Luteolin also finds widespread application in the food and biomedical industries [11]. Owing to its several beneficial biological properties, luteolin presents as a novel disease-preventing and therapeutic agent that can serve as a potential compound in the development of next-generation medicines in periodontal therapy [8].

Existing literature on luteolin's effects in managing periodontal diseases reveals few studies of heterogeneous research methodologies such as in vitro [6,18,20] and preclinical animal model studies [21,22]. These studies have shown luteolin's ability to reduce inflammation; while promoting bone tissue regeneration. Some studies have demonstrated luteolin's antimicrobial activity against oral microbes including the common periodontal pathogens [23,24]. Luteolin is known to possess periodontally beneficial properties such as anti-inflammatory, antioxidant and antimicrobial actions. These specific properties make it a potential compound in countering the etiopathogenesis of periodontal diseases [11]. Considering these promising biological properties of luteolin, its anti-periodontal disease potential needs further exploration and validation. An examination of Prospero, Medline, and the Cochrane databases of systematic reviews did not reveal any existing or ongoing scoping, systematic reviews or meta-analyses on this particular

topic. On a pilot exploration of the existing literature, we found very few papers with diverse research designs on this topic. In this article, we present our scoping review which will map the latest available data on luteolin's therapeutic potential in periodontal disease management.

Methods

The study was executed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. The following primary research question was framed: "What is the therapeutic potential of luteolin as an adjunct to conventional therapy in the management of periodontal diseases?" In addition, a secondary objective of studying the adverse effects or toxicity reported with luteolin was formulated.

Search strategy

A thorough search of the literature was undertaken in three relevant scientific databases: PubMed (access date: 30 April 2024), Scopus (access date: 30 April 2024) and Web of Science (access date: 10 May 2024). To ensure the inclusion of all the related studies, grey literature databases such as Google Scholar were also screened. This scoping review was conducted from the inception of databases until May 2024. Furthermore, the references of the retrieved publications were also examined to locate other related works for inclusion. The corresponding authors of articles without full-text access were contacted and requested to provide full-text. The inclusion criteria were, original research articles of *in vitro* and *in vivo* study design written in English that investigated the effects of luteolin in the management of periodontal diseases. *In silico* studies, review papers, news pieces, letters, editorials and case studies were excluded. Search keywords included were: "Luteolin" AND "Periodontal" OR "Periodontitis" OR "Gingival" OR "Gingivitis". The search strategies can be accessed in table 1. The search was reconducted before publication to include any recently published papers.

Study Selection

Following the search, the results were managed and duplicates were eliminated with the help of reference management software Zotero (zotero.org, Corporation of Digital Scholarship, Vienna, VA, USA). The review procedure included two screening phases: (a) Title and abstract review and (b) Full-text review. In the first phase, a pair of qualified reviewers separately screened titles and abstracts and marked them as 'include', 'exclude' or 'uncertain' as per the selection criteria. Any conflicts which arose were settled through discussion, which included the participation of a third reviewer. In the second phase, full-texts of publications identified as 'include' or 'uncertain' were retrieved and assessed separately and in duplicate by the reviewers to ensure inclusion as per the selection criteria. Any paper which remained classified as 'uncertain' following a thorough full-text evaluation was considered by all team members until a decision for its inclusion or elimination was reached. Explanations for rejecting the full-text publications were documented.

Data extraction

The research team developed draft data collection tools in tabular formats to extract the study characteristics. The included studies were categorized as microbial, cell-line, animal and human studies. These draft data collection forms were pilot-tested to establish their functionality and to ensure high inter-reviewer reliability. Data was collected in duplicate, with a pair of independent reviewers extracting information from all included articles. To verify data accuracy, each reviewer's compiled data was compared and any disparities were deliberated further to ensure uniformity among the reviewers. The entire data was collated into a single document.

The following information (where available) was collected: Title, authors, publication year, country, study objectives, design, population, sample size, methodology; luteolin origin, dosage, route of administration, duration of administration; periodontal pathogens, minimum inhibitory concentration (MIC); diagnosis, periodontal parameters, intervention, follow-up; study outcomes and conclusion. Data on reported complications if any was also recorded. Corresponding authors of studies were approached to obtain any missing or additional data.

Results

The search yielded 106 papers from all three databas-

Table 1. Search Strategy used in electronic databases

Sl no	Database	Search Strategy
1	PubMed	All Fields: (Periodontitis OR Periodontal OR Gingivitis OR Gingival) AND (Luteolin)
2	Scopus	Article Title-Abstract-Keyword: Periodontitis OR Periodontal OR Gingivitis OR Gingival AND Luteolin
3	Web of Science	Periodontitis OR Periodontal OR Gingivitis OR Gingival (All Fields) and Luteolin (All Fields)

es: 24 from PubMed, 52 from Scopus, and 30 from Web of Science. An additional search in the grey literature database and from reference lists of retrieved papers did not add to the existing list. On removal of duplicates, 59 papers were obtained. In the first phase, titles and abstracts of papers were screened. We excluded 38 papers that did not match our inclusion criteria and one paper was marked as uncertain. Total of 21 papers were included for the second phase of full-text screening. Subsequently, 20 papers were finalized for this scoping review after full-text screening and one paper was rejected. The reason for rejection is mentioned in table 2. The search results are presented in figure 1 as per the PRISMA 2020 flow diagram for systematic reviews [26].

This scoping review consists of evidence regarding luteolin's potential benefits in periodontal therapy obtained from papers published up to May 2024. This review considered both clinical and preclinical (*in vivo* and *in vitro*) articles. Only studies published in English were included if they addressed one of the objectives of our review. The retrieved papers were categorized as microbial, cell-line, animal and human studies and the data were compiled into the data collection tables.

Characteristics of microbiological studies

We found three studies assessing the antimicrobial properties of luteolin against periodontal pathogens. One study used luteolin extracted from perilla seeds [22] and the others used commercially procured luteolin [8,24]. Two papers studied the action of luteolin against the periodontal pathogen *Porphyromonas gingivalis* [8,22]. The other paper studied organisms from dental plaque [24] The study by Yamamoto & Ogawa showed that luteolin had the strongest anti-

Table 2. Reason for paper exclusion following full-text review

Sl no	Author, Year, Country	Objective of the study	Reason for exclusion	Incidental finding
1	Yoshizawa et al., 2007, Japan [25]	To identify class II human leukocyte antigen (HLA) -associated molecules mediating HLA class II-induced signals into the cells.	The primary study objective was not to assess luteolin's effects on gingival fibroblasts. Luteolin was used in the study as a focal adhesion kinase inhibitor.	Luteolin is a putative inhibitor of focal adhesion kinase. It hindered focal adhesion kinase phosphorylation and inhibited the production of HLA class II-induced cytokines in a dose-dependent manner.

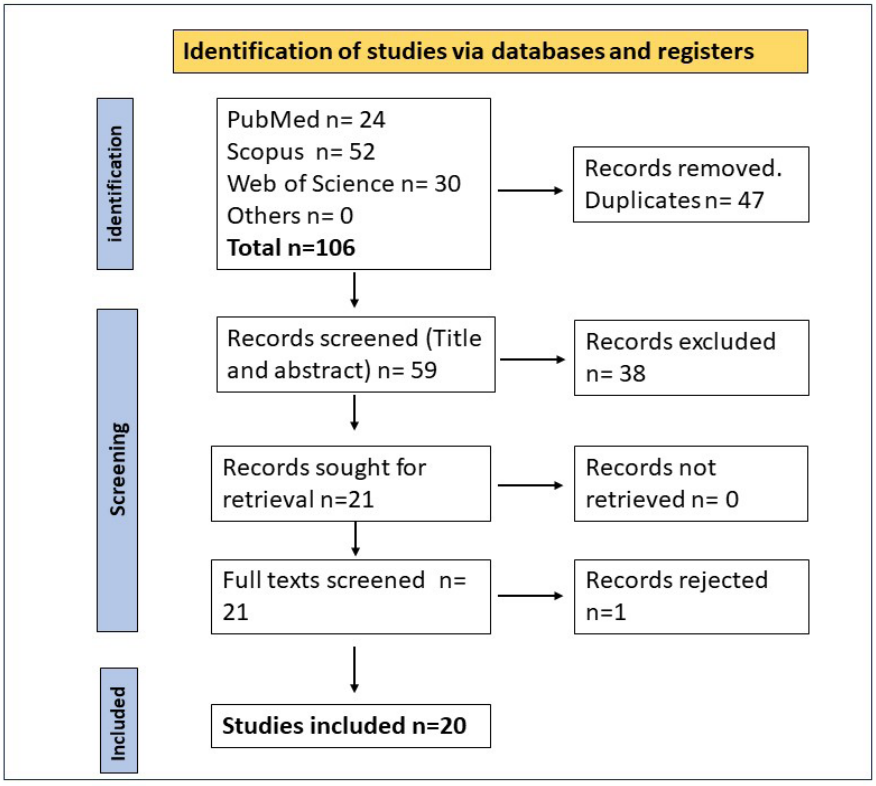

Figure 1. PRISMA 2020 flow diagram for systematic reviews

microbial effect among all the phenolic compounds extracted from perilla seeds against oral streptococci and various *P. gingivalis* strains [22]. The study by Gutierrez-Venegas G. et al. (2019) on dental plaque organisms showed that luteolin effectively inhibited bacterial and fungal growth [24]. The investigation by Kariu et al. on *P. gingivalis* showed that luteolin exerts a bacteriostatic effect rather than a bactericidal activity and significantly reduced *P. gingivalis* biofilm formation [8]. The microbial studies' characteristics are elaborated in table 3.

Characteristics of animal studies

Four animal studies-based papers met our inclusion criteria. All the studies used experimentally induced periodontitis in murine models as the study population. Three studies used microbial products [8,21,27] and the other study used the ligature method [22] to experimentally induce periodontitis in the animals. All the studies used commercially procured luteolin except the study by Kostic et al., where the ethanolic extract from the aerial parts of *Salvia sclarea* L. was used. High-Performance Liquid Chromatography analysis of the *Salvia sclarea* extract's chemical composition displayed the presence of rosmarinic acid, caffeic acid, luteolin, apigenin, luteolin-7-O-glucoside, and apigenin-7-O-glucoside [27]. It is worth noting that this investigation did not involve the study of luteolin exclusively, unlike the other three studies.

The investigation by Casili et al. studied luteolin's anti-inflammatory properties. They found that a 30 mg/kg oral dose of luteolin effectively reduced the tissue signs of inflammation, bone loss and inflammatory mediators in the Sprague-Dawley rats [21]. Yuce et al. studied luteolin's effect in preventing periodontitis. The authors of this study found that administration of luteolin at oral doses of 50 and 100 mg/kg effectively diminished periodontal inflammation and bone loss in the Wistar rats [22]. Kariu et al. displayed that luteolin notably inhibited the resorption of alveolar bone in periodontitis induced by *P. gingivalis* in C57BL mice [8]. Kostic et al. showed that *S. sclarea* extract significantly diminished inflammation and showed strong antioxidant effects in the Wistar rats [27]. Table 4 presents the characteristics of animal studies.

Table 3. Characteristics of microbial studies

Sl no	Author, Year, Country	Luteolin origin	Periodontal pathogens studied	Minimum Inhibitory Concentration (MIC) of luteolin	Conclusion
1	Yamamoto H & Ogawa T, 2002, Japan [22]	Perilla seed extract	*Porphyromonas gingivalis* strains: 381 RB24M-2 OMZ314 BH18/10 W50	381- 50 µg/mL RB24M-2- 25 µg/mL OMZ314- 12.5 µg/mL BH18/10-25 µg/mL W50-25 µg/mL	Luteolin, one of the perilla seeds components, exhibited the strongest antimicrobial effect among the phenolic compounds.
2	Gutierrez-Venegas G et al., 2019, Mexico [24]	Commercially available	Dental plaque microorganisms: *Aggregatibacter actinomycetemcomitans, Actinomyces naeslundii, Actinomyces viscosus, Enterococcus faecalis, Escherichia coli, Lactobacillus casei, Staphylococcus aureus, Streptococcus oralis and Streptococcus sanguinis* *Candida albicans*	*A. actinomycetem comitans* 1 mg/mL *A. naeslundii*- no effect *A. viscosus*- 5 mg/mL *E. coli*- 100 µM *Lactobacillus casei*-no effect *S. aureus*-1 mg/mL *S. oralis*- no effect *S. sanguinis*-no effect *C. albicans*- 5 mg/mL	Luteolin effectively inhibited bacterial and fungal growth.
3	Kariu et al., 2024, Japan [8]	Commercially available	*Porphyromonas gingivalis* ATCC 33277	80 µM	Luteolin has a bacteriostatic effect rather than a bactericidal activity on *P. gingivalis* and markedly reduced its biofilm formation.

Table 4. Characteristics of the animal studies

Sl No:	Author, Country, Year	Animal model	Luteolin origin	Luteolin dose, Route, Duration	Objective of the study	Periodontitis induction	Outcomes	Conclusion
1	Casili et al., 2020, Italy.[21]	Sprague-Dawley male rats weighing 200–230 g	Commercially available	Luteolin was administered daily at different doses (10, 30, and 100 mg/kg) orally. The animals were sacrificed after 14 days.	To investigate luteolin's anti-inflammatory properties in rats in a model of LPS-induced periodontitis.	A single intragingival injection of 1 µL LPS (10 µg/µL) derived from *Salmonella typhimurium* in sterile saline solution.	Luteolin (30 and 100 mg/kg) could reduce loss of alveolar bone, tissue damage and neutrophilic infiltration. Luteolin treatment also diminished the collagen fiber concentration, mast cell degranulation and NF-κB activation, as well as the presence of pro-inflammatory enzymes (COX-2 and iNOS) and cytokines (TNF-α and IL-6)	Luteolin has good anti-inflammatory capacities. Its use could provide valuable support in the pharmacological therapy of periodontitis. .
2	Yuce HB et al., 2019, Turkey.[22]	Wistar male rats weighing 230 to 250 g	Commercially available	Luteolin 50 mg/kg and 100 mg/kg orally. The rats were sacrificed after 11 days	To evaluate luteolin's effect in preventing experimental periodontitis by examining morphological and histological tissue alterations.	Ligature method. 4-0 silk sutures were inserted in a subgingival position around the lower first right molar tooth.	Both doses of luteolin reduced the loss of bone and periodontal inflammation. Both the doses markedly elevated expressions of TIMP-1 and BMP-2 and reduced levels of MMP-8. 100 mg/kg luteolin notably reduced iNOS levels, elevated OPG and reduced RANKL levels.	Luteolin significantly enhanced periodontal health in an experimental model of ligature-induced periodontitis.
3	Kariu et al., 2024, Japan.[8]	C57BL male mice of 4 weeks of age	Commercially available	100 µL of 400 µm luteolin in 5% carboxy methyl cellulose was administered into the buccal cavity employing a feeding needle on days 12, 14, 16, 18, 20, and 22-62. The mice were sacrificed on day 63.	To evaluate luteolin in vivo anti-bacterial activities using experimental *P. gingivalis*-induced periodontitis in the murine model.	*P. gingivalis*-induced periodontitis using oral gavage model of experimental mouse periodontitis.	Luteolin significantly inhibited alveolar bone resorption.	Luteolin is a potential therapeutic agent that targets *P. gingivalis* by inhibiting its growth, biofilm formation and resorption of alveolar bone in the oral cavity.
4	Kostić M et al., 2017, Serbia.[27]	Wistar male rats, 10 weeks old	Ethanolic extract from the *Salvia sclarea* 's aerial parts composed of rosmarinic acid, caffeic acid, luteolin, apigenin, luteolin-7-O-glucoside, apigenin-7-O-glucoside.	Water-diluted *S. sclarea* extract was administered twice daily by oral gavage (200 mg/kg body weight). The rats were sacrificed after 10 days.	To examine the immunological and histological effects of an ethanolic extract of *S. sclarea* on LPS-induced periodontitis in rats.	A Hamilton microsyringe was used to inject 10 µg/µL of *Escherichia coli* LPS diluted in a sterile saline solution into the interdental papilla between the first and second right maxillary molars twice daily for 10 days.	Treatment with *S. sclarea* extract significantly diminished inflammation by decreasing IL-1β, IL-6 and TNF-α levels, decreasing gingival lesions and preserving alveolar bone resorption. A noticeably fewer inflammatory cells and numerous fibroblasts were observed. In addition, the extract displayed strong antioxidant effects.	*S. sclarea* extract exhibited anti-inflammatory properties in LPS-induced periodontitis. Thus, it has a role as a therapeutic substance in periodontal diseases.

Abbreviations: LPS: lipopolysaccharide, IL: interlaukin, TNF: tumor necrosis factor, COX: cyclooxygenase, iNOS: inducible nitric oxide synthase, NF-κB: nuclear factor-κB, MMP: matrix metalloproteinase, TIPM: Tissue inhibitors of metalloproteinases.

Characteristics of cell line studies

We found 11 cell line-based studies that met our study's inclusion criteria. The cell lines investigated were human periodontal ligament cells (HPDLC), [18,20] human gingival fibroblasts (HGF), [19,28,29,30] human gingival epithelial cell line, [8] rat embryonic cardiomyocyte H9c2 cell line, [31,32] and rat macrophage-like RAW264.7 cells [6]. One study used multiple cell lines, i.e cancer cells (human promyelocytic leukaemia HL-60 cells, Human oral squamous cell carcinoma cell lines) and normal human oral cells (gingival fibroblast, pulp cells and periodontal ligament fibroblasts) [33]. All these studies used commercially sourced luteolin except one, which used luteolin glycosides obtained from the methanol extract of the *Sasa senanensis* (Franch. & Sav.) Rehder leaf [33].

The objectives of all these included studies were heterogeneous. However, they strived to elucidate various biological properties of luteolin. The investigation by Liu et al. showed that luteolin was effective in maintaining the pluripotency of HPDLC [18]. Another study by Quan et al. disclosed that luteolin promoted the proliferation and osteogenic differentiation of HPDLC [20]. Other studies showed the effects of luteolin as follows: Inhibiting inflammatory responses in HGF [19,30] and cardiomyoblast cells [31] which were induced by *P. gingivalis*-derived lipopolysaccharide (LPS); inhibiting inflammatory mediator expression in HGF treated with LPS derived from *Salmonella enteritidis*; [29] inhibiting the effect of lipoteichoic acid (LTA) derived from *Streptococcus sanguinis* in HGF [28] and rat embryonic cardiomyocytes H9c2 cell line; [32] strongly suppressing pro-inflammatory mediators NO and IL-6 production that was induced by *Prevotella intermedia*-derived LPS in rat macrophage-like RAW264.7 cells [6]. Another study showed that luteolin can reverse LPS-inhibited cellular proliferation in HGF [29]. The investigation by Matsuta et al. demonstrated the potent radical scavenging activity of luteolin [33].

Three of these studies also assessed the safety of luteolin. Kariu et al. found that luteolin does not exhibit cytotoxicity in human gingival epithelial cells [8]. Similarly, Matsuta et al. found no cytotoxic effect in normal human oral cells and human cancer cell lines [33]. Gutie'rrez-Venegas et al. (2006) discovered that luteolin did not damage DNA or impair cell viability even at greater concentrations [29]. Table 5 presents the characteristics of cell line studies.

Characteristics of human studies

We found two articles on human subjects that broadly studied dietary flavonoids' effects in maintaining periodontal health. Both of them did not specifically examine the effects of luteolin and had a prospective observational study design. The study by Alhassani et al. examined the link between habitual flavonoid consumption and periodontitis incidence in 34,940 male health professionals aged between 40 and 75 years and periodontally healthy at baseline for 24 years. They employed the Food Frequency Questionnaire (FFQ) to evaluate the dietary intake of the subjects. They found no notable link between total flavonoid intake and the self-reported periodontal disease incidence during the 24-year follow-up period [34].

Another investigation by Sparrow et al. examined the relationship between a sustainable improvement in outcomes of periodontal therapy at 3–4 years post-scaling & root planing (SRP) and increased intake of fruits, vegetables, vitamin C, and total flavonoids in 43 subjects aged 37 to 93 years and diagnosed with moderate to severe periodontal disease. They used clinical parameters, salivary inflammatory markers and FFQ to assess the outcomes. They found that higher flavonoid consumption was linked with diminished probing depth and salivary IL-1β levels at 3–4 years post-SRP in subjects who received regular periodontal maintenance therapy [35]. The human studies' characteristics are elaborated in table 6.

Discussion

To our knowledge, this paper is the first to compile and summarize the available information on luteolin's therapeutic potential in periodontal disease management. A systematic review or meta-analysis was deemed unsuitable because of the high heterogeneousness of the research methodologies and the limited number of available studies. Hence a scoping review approach was considered.

Therapeutic potential of luteolin in periodontal therapy

Luteolin has successfully been launched as a supplementary diet compound and integrated into cosmetic products. It is utilized in many traditional medicinal systems for the management of inflammatory diseases and hypertension [36]. Luteolin possesses various chemopreventive activities [14]. Numerous cell line and animal-model-based studies have explored luteolin's therapeutic potential in several diseases and yielded promising results. Luteolin is known to possess anticancer properties in many types of cancers such as colorectal carcinoma, [37,38] breast cancer, [39,40] ovarian cancer, [41] myeloid leukaemia, [42] glioblastoma, [43,44] nasopharyngeal cancer, [45] liver cancer [46] and oral cancer [47]. Few studies have shown luteolin's other beneficial effects such as neuroprotective function in Alzheimer's [48] and Parkinson's disease; [49] cardioprotective activity; [50,51] antidiabetic effect; [52] positive effects in dermatological diseases such as psoriasis, [53,54] contact and atopic dermatitis [55,56]. Luteolin, when utilized

Table 5. Characteristics of the cell-line studies

Sl no	Author, Year, Country	Cell studied	Luteolin origin	Luteolin dose, Duration	Objective of the study	Result	Conclusion
1	Liu et al., 2016, China.[18]	HPDLC	Commercially available	Cells were induced with luteolin at the concentration of 0, 1, 5, and 10 mmol/L and the incubation was maintained for 0, 3 and 5 days.	To investigate the influence of luteolin on HPDLC pluripotency via interaction with downstream signals such as the cell cycle, proliferation, apoptosis, Oct-4/Sox2/c-Myc expression, and multilineage differentiation with luteolin administration.	Luteolin reduced cell proliferation, enhanced apoptosis, and stopped HPDLC in the G2/M and S phases. It increased the expression of Oct-4, Sox2, and c-Myc in a time and dose-dependent manner while suppressing lineage-specific differentiation. PCR arrays profiled several signals in HPDLC following luteolin therapy, among which NFATc1 was the main upregulated gene. Notably, inhibiting the NFATc1 signal with INCA-6 markedly reduced mRNA and protein expression of Oct-4, Sox2, and c-Myc in HPDLC with luteolin treatment, showing that NFATc1 may operate as an upstream modulator of Oct-4/Sox2 signal.	Luteolin efficiently maintains the HPDLC pluripotency through activation of the Oct-4/Sox2 signal via NFATc1.
2	Gutie´rrez-Venegas G and Contreras-Sa´nchez A, 2013, Mexico.[19]	HGF	Commercially available	HGF cells were incubated with luteolin 10 μM for 30 minutes before treatment with LPS.	To study luteolin's role in the inhibition of MAPK and AKT (serine/ threonine kinase) activation and its role in *P. gingivalis*-derived LPS-induced COX-2 transcription.	Luteolin inhibited MAPK and AKT. It blocked MAPK and AKT activation to levels below basal levels. It also inhibited LPS-mediated COX-2 expression.	Luteolin blocks the *P. gingivalis* LPS actions in HGF. These observations indicate that luteolin can be utilized as a therapeutic substance in periodontal disease.
3	Gutie´rrez-Venegas et al., 2014, Mexico.[28]	HGF	Commercially available	The HGF cells were incubated with 10 μM luteolin for 30 minutes before LTA treatment.	To elucidate luteolin's effects on ERK1/2, p38 and AKT activation and COX-2 synthesis in HGF treated with *Streptococcus sanguinis*-derived LTA.	Treatment with luteolin inhibited ERK1/2, p38 and AKT phosphorylation and remarkably diminished LTA-mediated COX-2 expression to below basal levels in HGF.	Luteolin inhibits the effect of LTA in HGF.
4	Gutiérrez-Venegas et al., 2017, Mexico.[31]	Rat Cardiomyoblasts- H9c2 cell line	Commercially available	Cells were incubated with 10 μM luteolin for one hour followed by LPS treatment.	To examine the regulatory role of luteolin, in the signalling pathways stimulated by *P gingivalis*-derived LPS treatment in cardiomyoblasts.	Treatment with luteolin inhibited LPS-mediated ERK1/2 , p38 and JNK phosphorylation; IκB degradation; and inflammatory Cox-2 protein expression.	Luteolin blocks LPS-induced inflammatory responses in cardiomyoblast cells.
5	Gutiérrez-Venegas et al., 2006, Mexico.[29]	HGF	Commercially available	Cells were incubated with 10 μM luteolin for 30 min before treatment with *Salmonella enteritidis*-derived LPS.	To evaluate luteolin's ability to regulate NO production in LPS-stimulated HGF, and to study its effect in decreasing phosphorylation in MAPK family members, protein kinase B (Akt), (NF-κB) activation, inducible NOS expression and NO synthesis.	Luteolin disrupted LPS signalling pathways by blocking the activation of numerous mitogen-activated protein kinase family members and inflammatory mediator expression.	Luteolin hinders inflammatory mediator expression in LPS-treated HGF. Moreover, it does not damage DNA or influence cell viability even at higher concentrations. It reverses LPS-inhibited cellular proliferation.
6	Gutiérrez-Venegas et al. 2007, Mexico.[30]	HGF	Commercially available	Cells were incubated with 10 μM luteolin for 30 min before LPS treatment.	To examine luteolin's effect on LPS-activated transduction mechanism regulation in HGF and to investigate its role in activating MAPK induced by *P. gingivalis*-derived LPS.	Luteolin displayed significant inhibitory effects on MAPK activation, COX-2 expression, IL-1β and PGE2 synthesis.	Luteolin inhibits inflammatory mediator expression in LPS-treated HGF.

7	Gutiérrez-Venegas G and Giroshi Bando-Campos C. 2010, Mexico.[32]	Rat embryonic cardiomyocytes H9c2 cell line	Commercially available	Cells were incubated with luteolin 10 µM for 30 min before LTA treatment.	To investigate luteolin's effect on the activation of MAPK family members, protein kinase B (AKT), and IL-1β expression by H9c2 cells upon stimulation with LTAderived from *S. sanguis*.	Luteolin pretreatment decreased LTA-induced ERK1/2, JNK, p38, and AKT phosphorylation and IL-1β gene expression.	Luteolin interferes with LTA signal transduction.
8	Kariu et al., 2024, Japan.[8]	Human gingival epithelial cell line, Ca9-22	Commercially available	125-500 µm of luteolin was added to cells and placed for 4 hours.	To determine luteolin's cytotoxicity on human gingival epithelial cells.	Incubation of human gingival epithelial cells with luteolin did not result in significant death of cells.	Luteolin is safe and does not exhibit cytotoxicity.
9	Quan H et al., 2019, China.[20]	HPDLC	Commercially available	Luteolin at concentrations of 0.01, 0.1, 1, 10 and 100 µmol/L	To study the luteolin's effect on osteogenic differentiation of HPDLC.	All concentrations of luteolin increased cell viability, ALP activity and calcified nodule content in HPDLC. Luteolin boosted BMP2, OCN, OSX, RUNX2, β-catenin and cyclin D1 expression at concentrations of 0.01, 0.1 and 1 µmol/L. The strongest effects were observed with 1 µmol/L of luteolin. Furthermore, 1 µmol/L luteolin reduced the inhibitory action of a Wnt/β-catenin pathway inhibitor.	Luteolin could promote HPDLC proliferation and osteogenic differentiation, increase the osteogenic differentiation-related gene expression and activate the Wnt/β-catenin pathway. These characteristics of luteolin can contribute to its therapeutic use in periodontal disease.
10	Choi E et al., 2011, Korea.[6]	Rat macrophage-like RAW264.7 cells	Commercially available	Luteolin at concentrations of 5, 10, 25, and 50 µM	To examine whether luteolin could down-regulate the proinflammatory mediators (NO and IL-6) production in RAW264.7 cells stimulated with *Prevotella intermedi*a-derived LPS and to elucidate the probable mechanisms of action.	Luteolin strongly suppressed the production of NO and IL-6 in macrophages induced by LPS from *Prevotella intermedi*a. The underlying mechanism of action of luteolin includes NF-kB and STAT1 pathways inhibition in LPS-stimulated macrophages.	Luteolin could help to prevent the host-destructive processes triggered by these two proinflammatory mediators. It has the potential to be an effective host response modulator in treating inflammatory periodontal disease.
11	Matsuta et al 2011., Japan.[33]	Human promyelocytic leukaemia HL-60 cells Human oral squamous cell carcinoma cell lines (HSC-2, HSC-3, HSC-4) Normal human oral cells: HGF, HPC and HPDLF	Luteolin glycosides i.e Luteolin 6-C-β-D-glucoside, luteolin 7-O-β-D-glucoside and luteolin 6-C-α-L-arabinoside were obtained from the methanol extract of the leaf of *Sasa senanensis.*	For the cytotoxic activity assay, the cells were incubated with various concentrations of the test compounds in a fresh medium for 48 hours. For the determination of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and superoxide anion radical scavenging activity, 100 µL and 40 µL of test compounds were used, respectively.	To investigate various biological activities of luteolin glycosides.	Luteolin glycosides did not exhibit cytotoxicity towards any of the normal oral cells, the carcinoma cell lines or the HL-60 cells up to the concentration of 800 µg/mL. The scavenging activity of luteolin glycosides against DPPH and superoxide anion radicals was similar to quercetin and higher than tricin.	Luteolin glycosides did not exhibit cytotoxicity and had potent radical scavenging activity.

Abbreviations: HPDLC: Human Periodontal Ligament Cells, HGF: Human Gingival Fibroblasts, LPS: lipopolysaccharide, LTA: Lipoteichoic acid, MAPK: Mitogen-Activated Protein Kinase, COX: cyclooxygenase, ERK1/2: Extracellular Signal-Regulated Kinases, p38: Stress-Activated Kinase, AKT: Ak Strain Transforming gene, JNK: c-Jun N-terminal kinases, IκB: Inhibitor of kappa B, NO: Nitric Oxide, NF-κB: Nuclear Factor Kappa B, NOS: Nitric Oxide Synthase, IL-1β: Interleukin-1β, PGE2: Prostaglandin E2, ALP: Alkaline Phosphatase, BMP2: Bone Morphogenetic Protein 2, OCN: Osteocalcin, OSX: Osterix, RUNX2: Runt-related transcription factor 2, HPC: Human Pulp Cells.

Table 6. Characteristics of the human studies

Author, Country, Year	Study design	Study population	Luteolin origin	Luteolin dose, Route, Duration	Objectives	Periodontal Diagnosis	Research tools/ Periodontal Parameters/ Indices	Periodontal intervention	Follow-up	Outcomes	Conclusion
Alhassani et al., 2020, USA.[34]	Prospective observational study.	Total: 34,940 health professionals. Sex: Male Age: 40- to 75 years	Dietary	Not specified	To examine the association between habitual flavonoid consumption and incidence of periodontitis.	Periodontally healthy at baseline	FFQ to assess dietary intakes.	None	24 years	No significant association between total flavonoid consumption and the self-reported periodontal disease incidence during the 24-year follow-up period.	No link was found between habitual flavonoid consumption and periodontitis risk.
Sparrow et al., 2020, Canada.[35]	Prospective observational study.	Total: 43 subjects. Sex: 23 females, 20 males Age: 37–93 years	Dietary	Not specified	Primary objective: To study the relationship between a sustainable improvement in periodontal therapy outcomes at 3–4 years post-SRP and increased consumption of fruit, vegetables, vitamin C, and total flavonoids. Secondary objectives: To examine whether the PD reduction noted at 2–4 months post-SRP is sustained at 3–4 years post-SRP and if PD is correlated with salivary IL-1β, IL-6 and CRP	Moderate to severe periodontal disease	Clinical outcomes: PD, BOP and plaque score; salivary levels of inflammatory markers (IL-1β, IL-6 and CRP) FFQ to assess dietary intakes.	Periodontal maintenance therapy	3-4 years	Higher flavonoid consumption was associated with decreased PD and salivary IL-1β levels at 3–4 years post-SRP in subjects who received regular periodontal maintenance. These associations persisted when other confounders were considered.	Higher flavonoid consumption was linked with lower IL-1β. In addition, regular supportive periodontal therapy sustained the improved PD at 3–4 years post-SRP irrespective of smoking status.

Abbreviations: FFQ: Food Frequency Questionnaire, SRP: Scaling and Root Planing, PD: pocket depth, IL: Interleukin, CRP: C-Reactive Protein, BOP: Bleeding on Probing.

as a supplementary diet compound, has been proven to manage obesity [57,58]. Recent research papers have also observed that luteolin possesses antiviral activity and is beneficial against COVID-19 infection [59].

Few investigators have examined luteolin's effects on periodontal diseases, mainly through animal-based studies. Yuce et al. in their research studied luteolin's effects on morphological and histological tissue alterations in Wistar rats in an experimental ligature-induced model of periodontitis. They observed that luteolin administration diminished bone loss by elevating osteoblast cell counts, Osteoprotegerin (OPG) levels and decreasing Receptor activator of nuclear factor kappa-B ligand (RANKL) levels. In addition, it attenuated periodontal inflammation by markedly elevating the expression of Tissue Inhibitor of Metalloproteinases-1 (TIMP-1) and Bone Morphogenic Protein-2 (BMP-2) and decreasing Matrix Metalloproteinase-8 (MMP-8) and inducible nitric oxide synthase (iNOS) levels. They concluded that luteolin successfully improved periodontal health by decreasing inflammation, osteoclastic and collagenase activity and increasing the activity of osteoblasts [22]. Casili et al. in their study investigated luteolin's anti-inflammatory activities in Sprague-Dawley rats with periodontitis induced by *Salmonella typhimurium*-derived lipopolysaccharide. Their results showed that luteolin diminished loss of alveolar bone, tissue damage, neutrophilic infiltration, collagen fibres concentration, mast cell degranulation, and NF-κB activation. Moreover, there was a significant decrease in cytokines (tumor necrosis factor (TNF)-α, and interleukin (IL)-6) and pro-inflammatory enzymes (cyclooxygenase (COX-2), iNOS). Thus, they confirmed that luteolin could alleviate periodontitis symptoms [21]. Investigation by Kariu et al. exhibited that oral administration of luteolin diminished resorption of alveolar bone in *P. gingivalis* infection-initiated periodontitis in a murine model (C57BL mice) [8]. Another study by Kostic et al. on LPS-induced periodontitis in Wistar rats showed that treatment with *Salvea sclarea* extract, which was composed of luteolin and luteolin-7-O-glucoside along with other phenolic and flavonoid compounds, notedly reduced the process of inflammation by decreasing the levels of IL-1β, IL-6, and TNF-α. Histologically, lesions of the gingival tissue and resorption of alveolar bone were reduced. Inflammatory cell numbers were reduced and fibroblasts were increased. The extract also exhibited strong antioxidant effects [27]. Many cell line-based studies have shown luteolin exhibiting valuable antiperiodontal disease activities such as effectively maintaining the pluripotency [18] and promoting cell proliferation and osteogenic differentiation in human periodontal ligament; [20] blocking the action of bacterial lipopolysaccharide [19] and lipoteichoic acid; [28,29] inhibiting the inflammatory mediator expression in human gingival fibroblasts [30] and suppressing the proinflammatory mediators in macrophages [6].

The antioxidant properties of luteolin are well known. Two of our included papers studied the antioxidant properties of plant extracts consisting of luteolin as one of their composition. The research by Kostic et al. examined the antioxidant effects of *Salvia sclarea* extract using in vitro complementary tests: 2,2-diphenyl-1-picrylhydrazyl (DPPH) and β-carotene/linoleic acid models and found that the extract displayed robust antioxidant activity in both systems. They also postulated that the potent antioxidant properties could contribute to its anti-inflammatory capacity in periodontal disease [27]. Another study by Matsuta and co-workers on the radical scavenging activity of luteolin glycosides derived from the *Sasa senanensis* leaf extract against DPPH and superoxide anion radicals revealed that luteolin glycosides possessed very potent radical scavenging activity [33]. Luteolin's antimicrobial properties are well recognized [11] We found three papers studying luteolin's antimicrobial effects on oral bacteria linked to the establishment of periodontal diseases. All the studies observed that luteolin has significant antimicrobial action against periodontal pathogens [8,23,24].

Our literature search revealed two prospective observational studies on human subjects broadly examining the dietary flavonoids' effects on periodontal health. Both studies gave contradictory results [34,35]. However, we did not find any human clinical trials investigating exclusively luteolin's therapeutic effects in periodontal diseases. Thus, all evidence gathered from the reviewed papers reveals that luteolin has potent biological properties such as anti-inflammatory, antioxidant and antimicrobial properties that are beneficial in combating the etiopathogenic factors affecting the establishment and progression of periodontal diseases.

Despite all the positive biological qualities, the major hindrance reported in literature towards developing luteolin-based pharmaceuticals is its poor bioavailability [13]. The oral route might not be effective as luteolin is poorly absorbed from the intestine. Hence, there is a need to discover different delivery methods to enable its use as a medication [36]. Delivery methods such as micelles, liposomes, nanoemulsions, and amorphous solid dispersions can improve its bioavailability and therapeutic efficacy [11]. Furthermore, luteolin's limited aqueous solubility diminishes its possibility as a therapeutic candidate. A potential method to enhance aqueous solubility is to use nanoparticle technology [13].

Adverse effects or toxicity reported with luteolin

The application of plant-origin substances in therapy

appears particularly successful, as fewer side effects are reported with these compounds. Luteolin is one of the safe plant-based food components, that humans have consumed since the beginning of time [29]. Luteolin is considered to be nontoxic [15]. Studies have demonstrated that oral administration of luteolin has a median lethal dose (LD_{50}) of more than 5000 mg/kg in rats and more than 2500 mg/kg in mice [60,61]. This roughly translates to 219.8−793.7 mg/kg for human usage. Some studies have observed that even at a high concentration of 30 μM, luteolin did not demonstrate harmful effects on healthy cells or cause significant adverse reactions [36].

We considered the adverse effects or toxicity of luteolin as a secondary objective of our review and found three papers among our included studies that assessed the safety of luteolin. In the investigation by Matsuta et al. luteolin glycosides did not demonstrate cytotoxicity against any of the normal human oral cells (gingival fibroblasts, pulp cells and periodontal ligament fibroblasts); human oral squamous cell carcinoma cell lines (HSC-2, HSC-3, HSC-4) or the human promyelocytic leukaemia cells (HL-60) up to 800 μg/mL [33]. Similarly, Kariu et al. examined luteolin cytotoxicity towards human gingival epithelial cells (Ca9-22) and did not find prominent cell death after four hours of incubation with luteolin at 125-500 μM concentration [8]. Study by Gutierrez-Venegas et al. investigated the luteolin's effects on cellular proliferation, DNA integrity and cell viability in LPS-treated human gingival fibroblasts. Their observations revealed that luteolin treatment reversed the inhibition of HGF proliferation and treatment with 10 μM luteolin for different time periods did not affect DNA integrity. Cell viability test disclosed that luteolin doses of 1–300 μM did not notably impact cell survival [29].

However, the United States Food and Drug Administration has not granted luteolin a Generally Recognized as Safe status. Many studies have focused on rats and mice, with no reports of toxicological effects in other animal models or humans. Further research assessing luteolin's toxicological effects is needed before labelling luteolin as a completely safe compound [15].

Limitations

This paper's limitations include the scarcity of eligible studies that were identified. We also acknowledge that our review methodology might not have identified all relevant studies, for example, papers published in non-English languages. A significant challenge that emerged was that there were no human-based studies exploring luteolin's therapeutic effects in periodontal diseases. Another limiting factor of this paper lies within the heterogeneity of research methodologies between the included studies. Heterogeneity and paucity of available literature prevented a systematic review or meta-analysis from being undertaken.

Recommendations

This scoping review emphasizes the scarcity of research studies exploring the therapeutic potential of luteolin in periodontal conditions. Specifically, there is a need for evidence from randomized controlled human trials, as we did not find any investigation on human subjects after an extensive literature review. Furthermore, research assessing luteolin's safety in humans is needed. With more research in this field, there may be enough studies to undertake future systematic reviews and meta-analyses, which could provide more conclusive evidence.

Conclusion

Luteolin, a flavonoid known for its extensive health benefits, holds promise as a drug with a wide range of applications. The positive outcomes from in vitro and animal studies indicate that luteolin is not only a potent anti-inflammatory, antimicrobial and antioxidant agent but also is effective and safe, which could be beneficial in managing periodontal diseases. Furthermore, these properties offer a potential advantage over traditional chemical therapies, with the possibility of fewer adverse effects. Hence, all the evidence gathered from this scoping review suggests that luteolin may perform a remarkable role in preventing and treating periodontal diseases. While the preclinical findings are promising, translating these results into clinical practice is challenging. Additional long-term clinical trials involving human subjects to establish luteolin's efficacy, dosage and long-term safety in periodontal diseases are essential. In summary, luteolin has shown significant potential as a beneficial therapeutic agent in periodontal disease management. With further research it could become a key component in periodontal treatment strategies, offering a more natural approach with potentially reduced side effects.

Conflict of Intersts

None.

Acknowledgements

None.

References

[1] Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. J Clin Periodontol 2017;44:456-462.

[2] Machado V, Botelho J, Amaral A, Proença L, Alves R, et al. Prevalence and extent of chronic periodontitis and its risk factors in a Portuguese subpopulation: A retrospective cross-sectional study and analysis of clinical attachment loss. PeerJ

2018;6:e5258.
[3] Woelber JP, Reichenbächer K, Groß T, Vach K, Ratka-Krüger P, et al. Dietary and nutraceutical interventions as an adjunct to non-surgical periodontal therapy—A systematic review. Nutrients 2023;15:1538.
[4] Gasner NS, Schure RS. Periodontal Disease; StatPearls Publishing: Treasure Island, FL, USA, 2020. Available online: https://www.ncbi.nlm.nih.gov/books/NBK554590/
[5] Nocini R, Lippi G, Mattiuzzi C. Periodontal disease: The portrait of an epidemic. J Public Health Emerg 2020;4:10.
[6] Choi E, Jin J, Choi J, Choi I, Kim S. Effects of luteolin on the release of nitric oxide and Interleukin-6 by macrophages stimulated with lipopolysaccharide from Prevotella intermedia. J Periodontol 2011;82:1509-1517.
[7] Zhang H, Ning R, Zhao Y, Yan Z, Chen Y. The mechanism of the Shuang Bai Su Qing recipe in treating periodontitis based on network pharmacology and molecular docking technology. Medicine 2023;102:44(e35139).
[8] Kariu T, Hamada N, Lakshmyya K. Luteolin inhibits Porphyromonas gingivalis growth and alleviates alveolar bone destruction in experimental murine periodontitis. Biosci Biotechnol Biochem 2024;88:37-43.
[9] Sharma MH, Deepika PC, Venkatesh MP, Chandan S, Shashikumar P. Efficacy of 3% Psidium guajava local drug delivery in the treatment of chronic periodontitis: A randomized controlled trial. J Int Oral Health 2021;13:17-23.
[10] Luque-Bracho A, Rosales Y, Vergara-Buenaventura A. The benefits of propolis in periodontal therapy. A scoping review of preclinical and clinical studies. J Ethnopharmacol 2023;303:115926.
[11] Arampatzis AS, Pampori A, Droutsa E, Laskari M, Karakostas P, et al. Occurrence of luteolin in the Greek flora, isolation of luteolin and its action for the treatment of periodontal diseases. Molecules 2023;28:7720.
[12] Augusco MAC, Sarri DA, Panontin JF, Rodrigues MAM, Fernandes RdMN, et al. Extracts from the leaf of *Couroupita guianensis* (Aubl.): Phytochemical, toxicological analysis and evaluation of antioxidant and antimicrobial activities against oral microorganisms. Plants 2023;12:2327.
[13] Singh A, Yadav S, Pathak P, Verma A, Yadav JP. Harnessing luteolin's therapeutic potential in human disorders: Medicinal significance, biological, clinical properties and analytical aspects. Pharmacol Res Mod Chin Med 2024;10:100401.
[14] Muruganathan N, Dhanapal AR, Baskar V, Muthuramalingam P, Selvaraj D, et al. Recent updates on source, biosynthesis and therapeutic potential of natural flavonoid luteolin: A review. Metabolites 2022;12:1145.
[15] Aziz N, Kim MY, Cho JY. Anti-inflammatory effects of luteolin: A review of in vitro, in vivo, and in silico studies. J Ethnopharmacol 2018;225:342-358.
[16] Yang K, Song Y, Ge L, Su J, Wen Y, et al. Measurement and correlation of the solubilities of luteolin and rutin in five imidazole-based ionic liquids. Fluid Phase Equilib 2013;344:27-31.
[17] Huang L, Kim M-Y, Cho JY. Immunopharmacological activities of luteolin in chronic diseases. Int J Mol Sci 2023;24:2136.
[18] Liu L, Peng Z, Huang H, Xu Z, We X. Luteolin and apigenin activate the Oct-4/Sox2 signal via NFATc1 in human periodontal ligament cells. Cell Biol Int 2016;40:1094-1106.
[19] Gutiérrez-Venegas G, Contreras-Sánchez A. Luteolin and fisetin inhibit the effects of lipopolysaccharide obtained from Porphyromonas gingivalis in human gingival fibroblasts. Mol Biol Rep 2013;40:477-485.
[20] Quan H, Dai X, Liu M, Wu C, Wang D. Luteolin supports osteogenic differentiation of human periodontal ligament cells. BMC Oral Health 2019;19:229.
[21] Casili G, Ardizzone A, Lanza M, Gugliandolo E, Portelli M, et al. Treatment with luteolin improves lipopolysaccharide induced periodontal diseases in rats. Biomedicines 2020;8:442.
[22] Yuce BH, Toker H, Yildirim A, Tekin MB, Gevrek F, et al. The effect of luteolin in prevention of periodontal disease in Wistar rats. J Periodontol 2019;90:1481-1489.
[23] Yamamoto H, Ogawa T. Antimicrobial activity of Perilla seed polyphenols against oral pathogenic bacteria. Biosci Biotechnol Biochem 2002;66:921-924.
[24] Gutierrez-Venegas G, Gomez-Mora JA, Meraz-Rodríguez MA, Flores-Sanchez MA, Ortiz-Miranda LF. Effect of flavonoids on antimicrobial activity of microorganisms present in dental plaque. Heliyon 2019;5:e03013.
[25] Yoshizawa S, Meguro M, Ohyama H, Takeuchi-Hatanaka K, Matsushita S, et al. Focal adhesion kinase mediates human leukocyte histocompatibility antigen class II-induced signaling in gingival fibroblasts. J Periodont Res 2007;42:572-579.
[26] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Goffmann TC, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[27] Kostić M, Kitić D, Petrović MB, Jevtović-Stoimenov T, Jović M, et al. Anti-inflammatory effect of the *Salvia sclarea* L. ethanolic extract on lipopolysaccharide-induced periodontitis in rats. J Ethnopharmacol 2017;199:52-59.
[28] Gutiérrez-Venegas G, Luna OA, Arreguín-Cano JA, Hernández-Bermúdez C. Myricetin blocks lipoteichoic acid-induced COX-2 expression in human gingival fibroblasts. Cell Mol Biol Lett 2014;19:126-139.
[29] Gutiérrez-Venegas G, Kawasaki-Cárdenas P, Maldonado-Frías S. Luteolin inhibits lipopolysaccharide actions on human gingival fibroblasts. Eur J Pharmacol 2006;541:95-105.
[30] Gutiérrez-Venegas G, Jiménez-Estrada M, Maldonado S. The effect of flavonoids on transduction mechanisms in lipopolysaccharide-treated human gingival fibroblasts. Int Immunopharmacol 2007;7:1199-1210.
[31] Gutiérrez-Venegas G, Torras-Ceballos A, Gómez-Mora JA, Fernández-Rojas B. Luteolin, quercetin, genistein and quercetagetin inhibit the effects of lipopolysaccharide obtained from Porphyromonas gingivalis in H9c2 cardiomyoblasts. Cell Mol Biol Lett 2017;22:1-12.
[32] Gutiérrez-Venegas G, Giroshi Bando-Campos C. The flavonoids luteolin and quercetagetin inhibit lipoteichoic acid actions on H9c2 cardiomyocytes. Int Immunopharmacol 2010;10:1003-1009.
[33] Matsuta T, Sakagami H, Satoh K, Kanamoto T, Terakubo S, et al. Biological activity of luteolin glycosides and tricin from *Sasa senanensis* Rehder. In vivo 2011;25:757-762.
[34] Alhassani AA, Hu FB, Rimm EB, Li Y, Rosner BA, et al. Dietary flavonoid intake and risk of periodontitis. J Periodontol 2020;91:1057-1066.
[35] Sparrow TV, Dodington DW, Yumol JL, Fritz PC, Ward WE. Higher intakes of flavonoids are associated with lower salivary IL-1β and maintenance of periodontal health 3–4 years after scaling and root planing. J Clin Periodontol 2020;47:461-469.
[36] Rakoczy K, Kaczor J, Sołtyk A, Szymańska N, Stecko J, et al. Application of luteolin in neoplasms and nonneoplastic diseases. Int J Mol Sci 2023;24:15995.

[37] Jang CH, Moon N, Oh J, Kim JS. Luteolin shifts oxaliplatin-induced cell cycle arrest at G0/G1 to apoptosis in HCT116 human colorectal carcinoma cells. Nutrients 2019;11:770.

[38] Palko-Labuz A, Sroda-Pomianek K, Uryga A, Kostrzewa-Suslow E, Michalak K. Anticancer activity of baicalein and luteolin studied in colorectal adenocarcinoma LoVo cells and in drug-resistant LoVo/Dx cells. Biomed Pharmacother 2017;88:232-241.

[39] Hong J, Fristiohady A, Nguyen CH, Milovanovic D, Huttary N, et al. Apigenin and luteolin attenuate the breaching of MDA-MB231 breast cancer spheroids through the lymph endothelial barrier in vitro. Front Pharmacol 2018;9:317495.

[40] Huang L, Jin K, Lan H. Luteolin inhibits cell cycle progression and induces apoptosis of breast cancer cells through downregulation of human telomerase reverse transcriptase. Oncol Lett 2019;17:3842-3850.

[41] Tavsan Z, Kayali HA. Flavonoids showed anticancer effects on the ovarian cancer cells: Involvement of reactive oxygen species, apoptosis, cell cycle and invasion. Biomed Pharmacother 2019;116:109004.

[42] Chen PY, Tien HJ, Chen SF, Horng CT, Tang HL, et al. Response of myeloid leukemia cells to luteolin is modulated by differentially expressed pituitary tumor-transforming gene 1 (PTTG1) oncoprotein. Int J Mol Sci 2018;19:1173.

[43] Franco YE, de Lima CA, Rosa MN, Silva VA, Reis RM, et al. Investigation of U-251 cell death triggered by flavonoid luteolin: Towards a better understanding on its anticancer property against glioblastomas. Nat Prod Res 2021;35:4807-4813.

[44] You Y, Wang R, Shao N, Zhi F, Yang Y. Luteolin suppresses tumor proliferation through inducing apoptosis and autophagy via MAPK activation in glioma. Onco Targets Ther 2019;23:83-96.

[45] Ho HY, Chen PJ, Lo YS, Lin CC, Chuang YC, et al. Luteolin-7-O-glucoside inhibits cell proliferation and modulates apoptosis through the AKT signaling pathway in human nasopharyngeal carcinoma. Environ Toxicol 2021;36:2013-2024.

[46] Lee Y, Kwon YH. Regulation of apoptosis and autophagy by luteolin in human hepatocellular cancer Hep3B cells. Biochem Biophys Res Commun 2019;517:617-622.

[47] Velmurugan BK, Lin JT, Mahalakshmi B, Chuang YC, Lin CC, et al. Luteolin-7-O-glucoside inhibits oral cancer cell migration and invasion by regulating matrix metalloproteinase-2 expression and extracellular signal-regulated kinase pathway. Biomolecules 2020;10:502.

[48] Kou JJ, Shi JZ, He YY, Hao JJ, Zhang HY, et al. Luteolin alleviates cognitive impairment in Alzheimer's disease mouse model via inhibiting endoplasmic reticulum stress-dependent neuroinflammation. Acta Pharmacol Sin 2022;43:840-849.

[49] Qin L, Chen Z, Yang L, Shi H, Wu H, et al. Luteolin-7-O-glucoside protects dopaminergic neurons by activating estrogen-receptor-mediated signaling pathway in MPTP-induced mice. Toxicology 2019;426:152256.

[50] Du Y, Liu P, Xu T, Pan D, Zhu H, et al. Luteolin modulates SERCA2a leading to attenuation of myocardial ischemia/reperfusion injury via sumoylation at lysine 585 in mice. Cell Physiol Biochem 2018;45:883-898.

[51] Zhu S, Xu T, Luo Y, Zhang Y, Xuan H, et al. Luteolin enhances sarcoplasmic reticulum Ca2+-ATPase activity through p38 MAPK signaling thus improving rat cardiac function after ischemia/reperfusion. Cell Physiol Biochem 2017;41:999-1010.

[52] Davella R, Mamidala E. Luteolin: A potential multiple targeted drug effectively inhibits diabetes mellitus protein targets. J Pharm Res Int 2021;33:161-171.

[53] Lv J, Zhou D, Wang Y, Sun W, Zhang C, et al. Effects of luteolin on treatment of psoriasis by repressing HSP90. Int Immunopharmacol 2020;79:106070.

[54] Palombo R, Savini I, Avigliano L, Madonna S, Cavani A, et al. Luteolin-7-glucoside inhibits IL-22/STAT3 pathway, reducing proliferation, acanthosis, and inflammation in keratinocytes and in mouse psoriatic model. Cell Death Dis 2016;7:e2344.

[55] Góngora L, Giner RM, Máñez S, del Carmen Recio M, Ríos JL. *Phagnalon rupestre* as a source of compounds active on contact hypersensitivity. Planta Medica 2002;68:561-564.

[56] Jo BG, Park NJ, Jegal J, Choi S, Lee SW, et al. *Stellera chamaejasme* and its main compound luteolin 7-O-glucoside alleviates skin lesions in oxazolone and 2, 4-dinitrochlorobenzene-stimulated murine models of atopic dermatitis. Planta Medica 2019;85:583-590.

[57] Kwon EY, Kim SY, Choi MS. Luteolin-enriched artichoke leaf extract alleviates the metabolic syndrome in mice with high-fat diet-induced obesity. Nutrients 2018;10:979.

[58] Park HS, Lee K, Kim SH, Hong MJ, Jeong NJ, et al. Luteolin improves hypercholesterolemia and glucose intolerance through LXRα-dependent pathway in diet-induced obese mice. J Food Biochem 2020;44:e13358.

[59] Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. Biofactors 2020;46:306-308.

[60] Dai LM, Cheng H, Li WP, Liu SQ, Chen MZ, et al. The influence of luteolin on experimental inflammatory models in rats. Acta Anhui Med Univ 1985;20:1-3.

[61] B Fiszer-Szafaraz. The oral LD50 of luteolin in mice. Analyt Biochem 1984;143:76-84.