REVIEW ARTICLE

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The role of flavonoids in the treatment of periodontal diseases – literature review

Jakub Adamczyk[1,A-D], Martyna Chwałowska[1,A-D], Natalia Gębka[2,A-D], Krzysztof Stós[3,A-D], Natalia Jakubowicz[4,A-D], Agnieszka Gabryś-Kwolek[1,A-D], Rafał Rój[1,D-F]

[1] *Academic Centre for Dentistry and Specialised Medicine in Bytom, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland*
[2] *Dr. B. Hager Multispecialty County Hospital, Tarnowskie Góry, Poland*
[3] *Regional Specialist Hospital No. 4, Bytom, Poland*
[4] *Academic Centre for Dentistry and Specialised Medicine, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. Periodontal disease is one of the many diseases of the oral cavit. Periodontium is defined as the tissues that surround and hold the tooth in the socket. Periodontitis may lead to the loss of hard and soft tissues, resulting in the loss of dentition. The current standards for the treatment of periodontal disease are based on both surgical treatment and non-surgical treatment. The subject of research among many scientists is the effect of flavonoids – substances of plant origin, on periodontal diseases. This literature review aims to present the possibility of using flavonoids as adjunctive treatment in periodontal diseases.

Review Methods. Articles in English were searched using PubMed databases to evaluate the effect of flavonoids in the prevention and treatment of periodontal disease. The bibliography was reviewed to eliminate duplicate works.

Brief description of the state of knowledge. The anti-inflammatory, antibacterial and antiresorptive properties of flavonoids are the main factors influencing their use in the prevention of periodontal disease. Thanks to these three properties, the risk of periodontal disease is significantly reduced, which is why extracts from plants with a high flavonoid content are increasingly used in products for daily oral hygiene.

Summary. The antibacterial, anti-inflammatory and antiresorptive effects of flavonoids make them an important factor in the treatment of periodontal disease. Further research in the use of natural medicinal substances of plant origin is an important aspect for the development of modern medicine.

Key words

periodontal disease, periodontium, flavonoids, periodontology

INTRODUCTION

Periodontal disease is a significant problem today. It is estimated that, depending on the country surveyed, between 1–25.7% of the population already suffer from periodontitis,. These differences are likely due to different research methodologies in the various centres where the studies are conducted, as well as varying access to diagnostics, treatment techniques, and the level of hygiene of the population [1].

Periodontitis is an oral disease with microorganisms at its root, mainly *Actinobacillus actinomycetemcomitans*, the virulence of which is due to the presence of a lipopolysaccharide (LPS) molecule that play a key role in the development of periodontal disease [2]. During the course of the disease, the connective tissue of the gums and alveolar bone supporting the teeth are destroyed. Host immune and inflammatory reply associated with specific periodontal pathogens and their metabolic products, mediate the destruction of local tissue [3].

Address for correspondence: Jakub Adamczyk, Academic Centre for Dentistry and Specialised Medicine, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Plac Akademicki 17, 41-902 Bytom, Poland
E-mail: jakub.adamczyyk@gmail.com

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The most common periodontal diseases include gingivitis and periodontitis associated with the presence of bacterial biofilm on the surface of teeth. Long-term presence of plaque leads to local inflammation manifested by reddening of the gums and bleeding during tooth brushing. The most important differences between those two disease entities are that in gingivitis there is only deepening of gingival pockets, while in periodontitis there is also connective tissue attachment and alveolar bone loss.

Treatment of periodontitis can be divided into surgical and non-surgical treatments. Non-surgical methods include scaling, sandblasting, full mouth disinfection (FMD), local drug delivery (LDD), and photodynamic therapy. The most common surgical procedures include open/closed curettage, gingival or connective tissue grafting, and guided bone regeneration [4].

Combination treatments of periodontal disease, including surgical or non-surgical periodontal therapy, have provento be only partially effective [4]. Moreover, the widespread development of antibiotic resistance in pathogenic bacteria and the negative impact on the natural intestinal flora, is forcing the search for newer strategies to control periodontitis. Modern dentistry is looking for newer solutions in the prevention and treatment of periodontitis, focusing its

attention on medications containing flavonoids, compounds of plant origin, in their composition [3]. The potential profitable effects of flavonoids have been demonstrated on varied periodontal cells, including gingival epithelial cells, gingival fibroblasts and periodontal ligament fibroblasts, as well as osteoblasts supporting alveolar bone [5]. The most important properties of flavonoids are antioxidant, anti-inflammatory and antimicrobial activity [2].

Flavonoids are found in vascular and spore-bearing plants and in bryophytes and algae. They are commonly present in the bark, wood, fruits, flowers, seeds and leaves of plants [6].

They are also an important element in the human diet. According to studies, on average, a person consumes about 1 g of flavonoid compounds per day. The daily intake of flavonoids in the form of glycosides ranges from 230–1,000 mg/day. In contrast, the intake of aglycones ranges from 23–170 mg/day and are mainly flavonols, flavanones and flavones. As of today, there is no information on the content of the compounds in question in the diet of the Polish population, although it is known that the main sources of flavenoids are onions, tea and apples. Data on flavonoid intake vary. Western societies have been shown to provide between 50–800 mg of flavonoids daily in the diet. Eastern countries, on the other hand, up to 2 g due to their significant intake of plant products, mainly from legumes which are a rich source of isoflavones [6].

Flavonoids can also be found in dental products for daily oral hygiene, such as mouthwashes: Perio Plus Citrox (Curaprox), Oroben (Aboca), ALFA MED Professional (Atos), or toothpastes: Professional ULTRACOMPLEX (Splat), ADS720 (Curasept), Vilcacora (A-Z Medica).

OBJECTIVE

The aim of the review is to summarize the literature on the use of flavonoids in the prevention and treatment of periodontal disease.

METHOD AND MATERIALS

To narrow down the search for articles, only one database was examined. Articles in English published in the PubMed database from 2014–2022 were searched to assess the newest research about the function of flavonoids in the treatment of periodontitis. Key words used in this search were: flavonoids, periodontology, periodontium, and periodontal disease. A manual search was also used to include all matching articles. The bibliography of selected studies and other literature reviews were checked to include other studies suitable for the review. Duplicate papers were eliminated.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Articles in English	Articles other than in English
Clinical trials (original research) and *in vivo, in vitro,* clinical cases	Studies without a control group, literature reviews, systematic reviews, meta-analyses
Articles published between 2014–2022	Research prior 2014

RESULTS

Initially, 331 articles were obtained from the Pubmed search engine. The focus was on articles published after 2014, written in English. After removing duplicate articles and an initial evaluation using titles and abstracts – 292 articles were excluded. Of the remaining 39 publications, 10 misclassified studies were rejected. From 29 selected articles, 20 literature reviews were removed. In the end, 9 studies were obtained that largely focus on animal models and meet inclusion criteria.

REVIEW AND DISCUSSION

Definition and action of flavonoids. Flavonoids are derivatives of 2-phenylbenzo-pirone. Selected groups of flavonoids differ in the type and number of substituents, with the differences between compounds in each class usually due to the different structure of only one outermost ring. They are divided into numerous subsets involving flavonols, flavanones, flavanones, isoflavans, isoflavones, flavones, dihydroflavonols, chalcones, and anthocyanidins. The most common and best-studied flavonoid is quercetin and its glycosides [7].

Table 1. Division of flavonoids

Group of flavonoids	Examples of chemical compounds
Flavonols	quercetin, kaempferol, myricetin, morine, fisetin
Flavones	luteolin, apigenin
Flavanones	hesperidin, naringenin, eriodoctiol
Isoflavones	daidzein, genistein, glycitein
Catechins	catechin, tefalvin
Anthocyanidins	cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin

Flavonoids in periodontal diseases. *In vivo* studies in animal models have revealed multiple effects of flavonoids on periodontal cells and tissues, including adjustment of inflammatory responses in periodontal components, and potential preservative effects in periodontal ligament tissues and alveolar bone [5]. Conclusions from the study by Fernández-Rojas et al. [5] mention that flavonoids are highly promising clinical agents for the prevention and decreasing of periodontal disease. In addition, they are readily available to patients and are included in mouthwashes and toothpastes, as well as many food products.

The ability of various flavonoids to adjust nitric oxide production by LPS-stimulated human gingival fibroblasts has been assessed by the authors of another study [2]. They investigated the mechanism of action by which luteolin inhibits LPS, and concluded that luteolin interferes with LPS signalling paths by activating several mitogen-activated protein kinases, and inhibiting the expression of inflammatory mediators. Alfonso Varela-López et al. [2] in the first phase of *in vitro* studies, confirmed that luteolin restrains the expression of inflammatory mediators in human fibroblasts.

The authors of another study [8] discovered that a diet supplemented with eriocitrin and eriodictyol could modify the inflammatory response associated with (LPS)-induced

periodontitis in mice. The results of a study by Carvalho JS. [8] suggest that a diet supplemented with the citrus flavonoids eriocitrin or eriodictyol may help prevent periodontitis, providing a potential method of enhancing local immunity and host defence. Mooney EC et al. [9] showed that orally-administered quercetin helps maintain the health of periodontal tissues by alleviating inflammation, and promotes the development of symbiotic bacterial flora. This may prove to be an efficient treatment option due to its high tolerability and safety profile, as an inexpensive and feasible long-term supplement in patient populations with chronic diseases, including those prone to periodontal disease.

Quercetin is an efficient anti-microbial and anti-inflammatory agent in periodontal disease. The anti-inflammatory effect of quercetin on human gingival fibroblasts (HGF) stimulated with LPS by *Porphyromonas Gingivalis,* showed that quercetin attenuates the formation of inflammatory mediators: IL-1β, IL-6, IL-8 and Tumour Necrosis Factor-α (TNF-α) in HGFs treated with LPS of *P. gingivalis.* A study by Xiong G. et al. [10] suggests the promising therapeutic possibilities of quercetin in the treatment of periodontitis. Similarly, a study by Gloria Gutiérrez-Venegas et al. [11] described the effects of flavonoids (quercetin, genistein, luteolin and quercetagetin) on the regulation of the LPS-activated transduction action in HGF. Based on these studies, quercetagetin showed the highest anti-inflammatory activity among the flavonoids tested.

Cultures of *Staphylococcus Epidermidis* and primary HGF in the study by Gomez-Florit M. et al. [12] were treated with various doses of chrysin, diosmetin, galangin, quercitrin and taxifolin. According to the findings of this study, quercitrin could contribute to the protection and restoration of gingival tissue integrity, thereby demonstrating a potential application in the treatment of periodontal disease or to improve soft tissue integration after implant placement.

Exposure to puerarin may stimulate the proliferation and differentiation of periodontal cells and affect alkaline phosphatase activity. This was the conclusion by Li J. et al. [13] who studied the effect of puerarin on the osteogenic differentiation of Human Periodontal Ligament Stem Cells (PDLSCs). They demonstrated that the plane of Alkaline Phosphatase (ALP) activity is highly enhanced by boosting the concentrations of puerarin.

On the other hand, Ming J. et al. [14] summarized the effectiveness of baicalein in the treatment of periodontal diseases. Baicalin is a pharmacologically-active substance in periodontal tissues, although its essential mechanisms of action have not been completely defined. Further studies are needed to establish their clinical efficacy in the treatment of periodontal disease.14].

A study by Shigeru Matsumoto et al. [15] checked the anti-inflammatory effects of nobiletin and tangeretin on LPS-induced resorption of bone in mice. Nobiletin and tangeretin inhibited LPS-induced osteoclast formation, bone resorption, and inhibited the osteoclastogenesis activation of receptors. It was shown that nobiletin, belonging to the polymethoxyflavones (PMFs), inhibited systemic bone resorption and maintained bone mass in mice with osteoporosis. In a mouse experimental model, the compound clearly restored alveolar bone mass and reduced periodontal disease by inhibiting LPS-induced bone resorption. Accordingly, PMFs may therefore represent a new therapeutic strategy in cases of bone loss caused by periodontitis. In another study, Gómez-Florit M. et al. [16] examined the ability of quercetin' to alter the production of biomarkers associated with periodontal recovery on primary HGF, and on primary human Mesenchymal Stem Cells (hMSCs) cultured in both basal and inflammatory environments. It was observed that quercetin reduced inflammatory mediator release and affected collagen metabolism, which may have applications in supporting periodontal soft and hard tissue regeneration. Wenjing Zhang et al. [17] investigated the effect of quercetin and its function in the osteogenic reply of human Periodontal Ligament Stem Cells (hPDLSCs) in TNF-α-induced inflammation. The authors showed that quercetin reduces impaired hPDLSC osteogenesis in TNF-α-induced inflammation. Thus, quercetin may prove to be a potential remedy against periodontal bone defects.

CONCLUSIONS

The potential use of flavonoids in the prevention and treatment of periodontitis is of growing interest to researchers worldwide. Plants rich in flavonoids show a number of activities that cannot only prevent the development of periodontal

Table 3. Review of selected flavonoids with therapeutic effects and side effects

Flavonoid	Natural occurrence	Names of commercial medications	Action in the prevention and treatment of periodontal disease	Interactions and contraindications
Quercetin	Apples, lime, oranges, lemons, grapefruit	Taxifolin (Kenay), Quercetin (Swanson)	- anti-inflammatory - regenerative - antibacterial	Product should not be used in people with coagulation disorders and in pregnant women.
Baicalin	Baikal Thyroid	Baikadent (Herbapol)	- antibacterial - anti-inflammatory - regenerative	Baicalein is not recommended for use in people suffering from liver disease, and taking drugs impairing liver function. The preparation may cause drowsiness.
Luteolin	Celery, parsley, broccoli, onions	Luteolin Complex (Swanson), Luteolina (Yango)	- anti-inflammatory - antibacterial	Should not be used in pregnant women, newborns and children.
Nobiletin	Mandarins	Sytrinol (Now), Nobiletin (Gingo)	- antiresorptive - blocks the formation of osteoclasts	Not recommended for use in pregnant and lactating women. If you are taking antiplatelet drugs, anti-coagulants and selected groups of NSAIDs, it is recommended to consult a doctor.
Naringina	Grapefruit, orange	Naringina (Swanson)	- antibacterial	Should not be used in pregnant and lactating women.
Genistein	Bean crops. Mainly soybeans.	Soyfem (Biofarm)	- anti-inflammatory	Not recommended for use in people with soy allergy. Genistein, like other phytoestrogens, can both potentiate and attenuate the effect of sex hormones through beta-estrogen receptor affinity.

disease, but also effectively treat it. From the studies reviewed, researchers indicate the following advantages of flavonoids: reducing inflammation, anti-microbial activity, stimulating regenerative processes in the periodontium, and blocking LPS which inhibits periodontal cell proliferation.

Increasing the diet to include vegetables and fruits rich in flavonoids may prove to be an important element in preventing the progression of periodontal disease, as well as supporting the healing process. Further scientific research is needed to provide definitive scientific evidence of the clinical efficacy of flavonoid compounds in the treatment of periodontitis. This will make it possible to understand the exact mechanisms of action and enable the implementation of novel methods of prevention and treatment of periodontal disease.

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