

The Particulars of Applying Odontoprotectors at Different Stages of Therapeutic Process of Periodontal Diseases (A Scoping Review)

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Abstract: Rational use of drugs underlies the development of a treatment strategy. In particular, it is important in dental practice to properly select odontoprotectors for the prevention, treatment and maintenance therapy of periodontal diseases. A methodological approach based on the Arskey & O'Malley's framework was applied to analyse the state of knowledge and previous studies on the use of odontoprotector drug group at different stages of the therapeutic process of periodontal disease. Of the 6 initial scientific databases, the research was conducted in 3 databases that best met the specified search conditions: Google (Google Scholar); PubMed; Wiley InterScience (The Cochrane Library). The literature was selected for the last 5 years (2016-2021). A total of 492 scientific papers were analysed. It is established that the available scientific information is divided into 4 main areas: the use of herbal remedies and folk remedies; antibiotic therapy in dental practice; prospects for the use of nanotechnology in dentistry; results of experimental researches and review articles on a particular active pharmaceutical ingredient.

Keywords: Antibiotics, Dentistry, Non-Traditional Medicine, Odontoprotector Drug Group, Periodontal Diseases.

1. INTRODUCTION

Periodontal diseases include a large group of pathologies that are common in all age groups. According to the WHO, more than 80% of school-age children in developed countries have periodontal disease, while the incidence of periodontal diseases reaches more than 95% among the adult population. So, a comprehensive study of prevention, detection, and treatment of periodontal diseases is an urgent task of modern medicine.

The use of drugs is one of the important components of the therapeutic process. The development of modern technologies, the search for new active pharmaceutical ingredients, and the study of all known drugs have created favourable conditions for a significant expansion of the range of drugs, including those used in dental practice.

This study aims to summarize and arrange the data of bibliographic and semantic analysis of the scientific literature on the use of odonto protector drug groups at different stages of the therapeutic process of periodontal diseases.

2. METHODS

2.1. Design

A methodological approach to determining the target literature was based on Arskey & O'Malley's framework [1]. This methodological framework is based on the literature survey, which involves studying the scope of research on the selected topic and identifying issues that are poorly covered in the literature. In particular, bibliographic and semantic research is conducted in 4 main areas: establishing the total volume of research on the selected topic; assessment of the completeness of the systematic review; generalization and dissemination of research results; identifying issues that are not covered or are poorly covered in the literature.

2.2. Search Strategy

The selection of electronic databases for the study was based on generally accepted recommendations, specialization, and international rankings for the search of medical literature, for which we developed the following decision tree.

Analysis of pre-selected 6 electronic databases (Embase (Elsevier); Google (Google Scholar); PubMed; ResearchGate; Wiley InterScience (The Cochrane Library), BioMed Central) according to the above decision tree allowed focusing on the following 3 sources of information: Google (Google Scholar); PubMed; Wiley InterScience (The Cochrane Library).

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Google Scholar electronic database provides a relatively large number of search results but covers both scientific literature, popular science and entertainment publications. Not all publications presented in this database have an adequate level of evidence. The electronic database PubMed provides the largest number of publications with a high level of evidence of scientific validity of the information material contained in the publications.

The literature was selected for the last 5 years (2016-2021).

Since the main objective of this work is to assess the completeness and quality of coverage of the use of odontoprotector drug group at different stages of the therapeutic process of periodontal diseases, we used the following keywords and phrases: odontoprotector; drug/medicine, AND periodontal disease; pharmacotherapy AND periodontal disease.

Figure 1 shows the distribution of search results by keywords and phrases in the studied electronic databases.

Analysis of the results of the survey of the established keywords and phrases showed 10 main categories:

- 1) particulars of applying certain categories of odontoprotectors;

- 2) features of the use of odontoprotectors in certain categories of patients;
- 3) study of the action mechanism of odontoprotectors;
- 4) methods of non-drug treatment of periodontal diseases;
- 5) therapeutic techniques of periodontal diseases;
- 6) the latest technologies in the treatment of periodontal diseases;
- 7) aspects of state regulation and legislation in the field of dentistry;
- 8) research on self-treatment of periodontal diseases;
- 9) study of the risk of drug-induced development, complication, or exacerbation of periodontal diseases (narcotic and hormonal drugs, ethanol, etc.);
- 10) development of a treatment strategy for the simultaneous treatment of periodontal diseases and such diseases as rheumatoid arthritis, diabetes, cancer, cardiovascular pathology.

As for directions 4-10 do not meet the established research criteria, such publications were not taken into account.

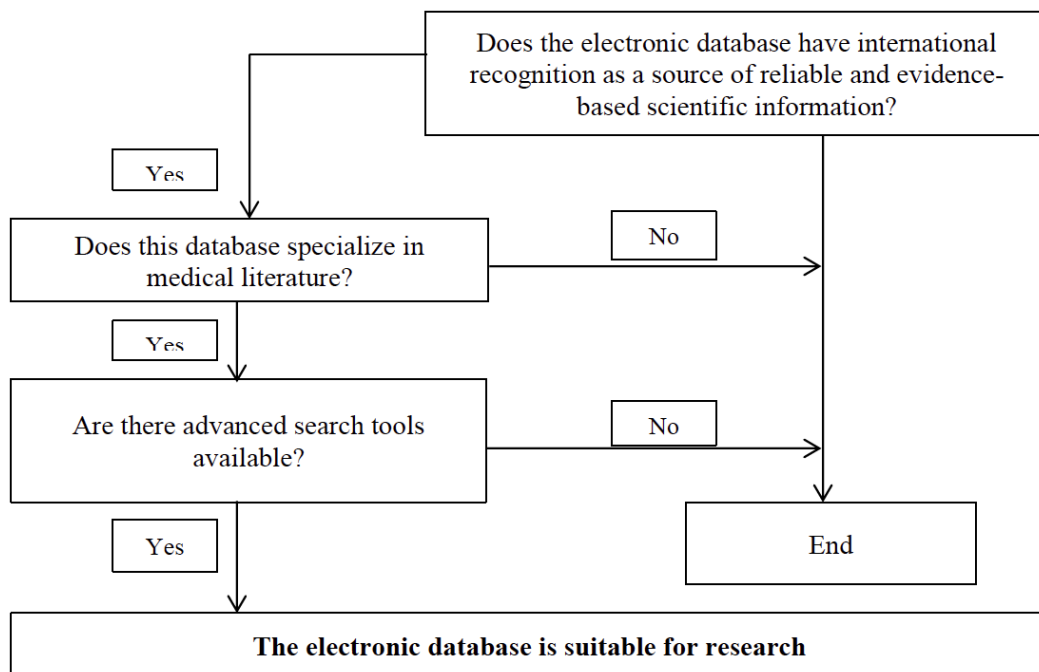


Figure 1: The decision tree on the choice of electronic databases for research on the selected topic.

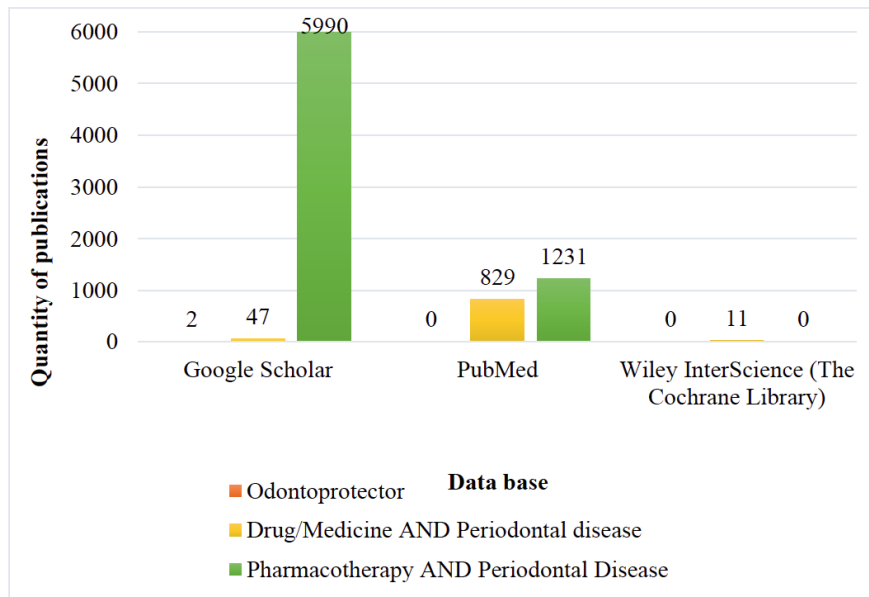


Figure 2: Distribution of search results by keywords and phrases in the studied electronic databases.

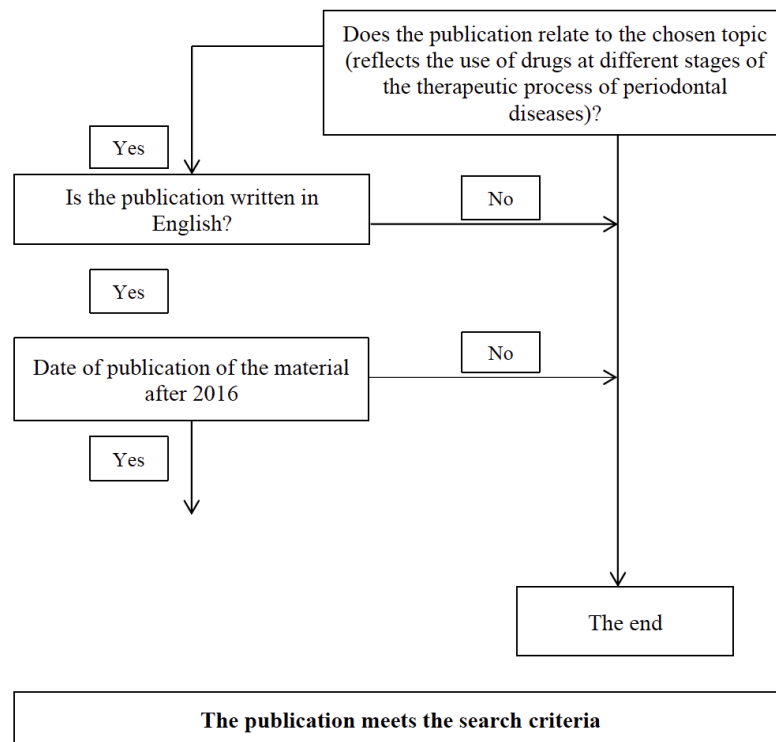


Figure 3: Decision tree for selecting publications on the topic.

To narrow the scope of information retrieval, we developed a decision tree to establish the compliance of publications with the set search criteria (Figure 2). Repeated articles were also excluded from the scoping review.

The final number of publications for analysis was 492.

3. RESULTS

A study of certain electronic databases for selected keywords and phrases showed that the term “odontoprotector” is new and rarely used by researchers as a keyword and in the text of scientific publications. According to the established evaluation criteria, 2 articles were found for the keyword “odontoprotector” in the Google Scholar database.

Search by the keyword phrase “Drug / Medicine AND Periodontal disease” contains the largest number of materials that best fit the established scope of the study.

The retrieval request for the keyword phrase “Pharmacotherapy AND Periodontal disease” has the largest number of publications, but requires specification and setting of additional retrieval parameters. This search category contains the most information in the form of review articles and descriptions of the use of certain drug categories.

The results were combined because the search categories for the key phrases “Drug/Medicine AND Periodontal disease” and “Pharmacotherapy AND Periodontal disease” contain quite a lot of repetitions.

The 4 main areas of research were established in the analysed volume of literature:

1. Research the herbal remedies, folk remedies, remedies provided in national medical systems at different stages of the therapeutic process of periodontal diseases.
2. Studies on the use of antibiotics at different stages of the therapeutic process of periodontal diseases.

3. Research on nanotechnology in dentistry.
4. Other categories of research describe the use of odontoprotectors at different stages of the therapeutic process of periodontal diseases.

The distribution of publications in the established areas is illustrated in Figure 4.

As Figure 4 shows, the largest share of scientific publications is related to the description of the use of particular drugs, both in the form of review articles and in the form of case studies.

4. DISCUSSION

4.1. Research on the Herbal Remedies, Folk Remedies, Remedies Provided in National Medical Systems at Different Stages of the Therapeutic Process of Periodontal Diseases

Studies have shown that a fairly wide range of studies deals with the use of herbal remedies and folk remedies. Most of these remedies are described by the authors as promising anti-inflammatory, antiseptic, antibacterial, and wound healing agents.

A significant proportion of publications provide the results of experimental studies of curcumin, berberine, and chitosan.

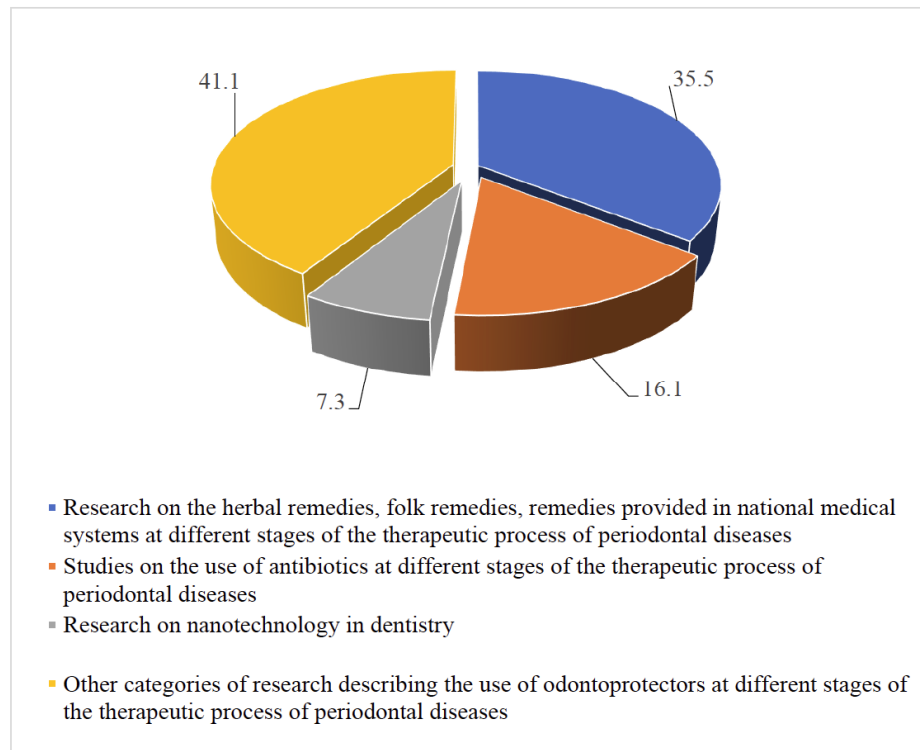


Figure 4: Distribution of publications in the established areas.

For example:

- In [2] the authors cover the prospect of using traditional herbal remedies as an adjunct or primary therapy for several periodontal diseases in Mexico. The authors concluded that the evidence base is mandatory for each such remedy.
- The researchers in [3] present the results of studying the viability of cells, anti-inflammatory activity and polarization properties of macrophages of various cranberry concentrates. It was established that cranberry-derived proanthocyanidins can act as an anti-inflammatory component in the treatment of periodontal and peri-implant diseases.
- Researchers in [4] offers the simultaneous use of curcumin as a prophylactic to prevent periodontitis, as well as a natural immunosuppressant for rheumatoid arthritis.
- The effect of *A. muciniphila* on inflammation caused by *Porphyromonas gingivalis* is described in [5]. It is established that the protective effects of the introduction of *A. muciniphila* are quite high and it is advisable to use it as an adjunct to the treatment of periodontal diseases.
- Bromelain as a potential adjunct in the non-surgical treatment of periodontitis, which reliably acts as an anti-inflammatory and antioxidant agent, is described in [6].
- The potential ability of psoralen and angelicin to act as new natural remedies for the prevention and treatment of periodontal diseases is emphasized in [7].
- The use of omega-3-enriched cranberry juice is proven to be useful as an adjunct in non-surgical periodontal therapy to reduce glycated hemoglobin, high-density lipoprotein cholesterol, and improve periodontal status in diabetic patients with periodontal diseases [8].
- In many studies, honey has shown significant antimicrobial activity against several periodontal pathogens [9].
- Quercetin's antimicrobial effect was proven. Molecular docking analysis also showed that quercetin can interact with gingipain and inhibit various virulence factors of *P. gingivalis* [10].
- Researchers also evaluated the antimicrobial activity of dichloromethane crude extract, dichloromethane-soluble fractions, subfractions of garden sage (*Salvia officinalis* L.), as well as pure substances (manool, salvigenin, and viridiflorogen) against periodontal pathogens [11].
- Neem leaf extract, which contains polyphenols that adhere to the surface of the oral cavity, is proven to be able to provide long-lasting antibacterial and synergistic antioxidant action in combination with bacteria, erythrocytes, and lysozyme. Therefore, it can be especially effective for periodontal diseases [12].
- 75% ethanolic extract of *Colocasia antiquorum* var. *esculenta* (CA) demonstrated antibacterial effect *in vitro*, while varnish and varnish with CA showed an increased diversity of the oral microbiome, indicating that CA has the potential to treat periodontal diseases [13].
- There is a literature review to examine the variety and extent of herbal products used to maintain oral health, including various areas of oral care such as dental caries, periodontal support, bacterial infections, oral cancer, and inflammatory disorders [14].
- There also are authors who continue a systemic review of proanthocyanidins and flavan-3-ols in the prevention and treatment of periodontal disease in their work, cover the immunomodulatory effect, as well as discuss the direct antibacterial properties [15].
- Mouthwash based on *Scrophularia striata* (Iranian traditional remedy) is effective in the treatment of chronic periodontitis and is more effective than the Iranian mouthwash *Irsha* [16].
- An analysis of the antibacterial activity of plant species used for sanitation of the oral cavity against *Porphyromonas gingivalis* is provided [17].
- Some papers describe the history of the Kampo medical system in the field of dentistry, its recognition and implementation at the state level in Japan, as well as recommendations for the integration of this system and its treatment methods, as well as drugs in practical dentistry in Western countries [18].

- There are studies devoted to the antibacterial effect of ethanolic extract of propolis, and compounds derived from it, against *Porphyromonas gingivalis*, a key periodontal pathogen [19].
- Scientists presented the results of comparing the clinical and microbiological benefits of routine root extension and alignment with the additional use of Triphala (Hiora GA, Indian drug system) as a local drug delivery agent in the treatment of periodontitis [20].
- Works are describing Hainosan (Painongsan), a traditional Japanese and Chinese remedy used to treat several purulent diseases, including gingivitis and periodontitis. The authors gave a positive assessment of the antibacterial action of the extract and extracts of its three components *in vitro* against *Porphyromonas gingivalis*, one of the pathogenic bacteria that causes periodontitis [21].
- Researchers describe the mechanism of odontoprotective effect of berberine (Chinese medicinal herbal extract). Berberine has been shown to increase odontoblast differentiation. The article presents experimental data confirming the accelerating effect of berberine on the odontoblast differentiation from dental pulp stem cells (DPSC), as well as the formation of mineralized nodules by real-time polymerase chain reaction. Berberine has been shown to function as a promoter of odontoblast differentiation by promoting the Wnt/ β -catenin pathway, suggesting that it may be useful in the treatment of dental caries [22].
- The reasonability of developing an enzyme-mediated periodontal membrane for targeted delivery of antibiotics to infected periodontal pockets was proven on the example of a chitosan membrane [25].
- The review contains an analysis of the prospects of phage therapy in dentistry, as well as the possibility of creating an oral microbiome [26].
- A multivariate meta-analysis of adjunctive therapy with Azithromycin in non-surgical treatment of chronic periodontitis [27].
- A review of the antibiofilm activity of phenolic compounds against bacteria, which play an important role in infections related to medical device biofilm, and the activity of polyphenols against bacterial agents that cause caries and periodontal diseases [28].
- In situ studies of the Levofloxacin- and Metronidazole-containing gel proved its thermal sensitivity, mucoadhesiveness, suitability for syringe application, as well as slow and controlled drug release with effectiveness against a wide range of bacteria [29].
- The review covers recently published scientific evidence on the use of professionally delivered local antimicrobial agents and provides an analysis of currently available drug delivery systems in periodontal disease treatment [30].
- Metformin is presented as a powerful stimulus to increase the effectiveness of photodynamic therapy for inducing microbial cell destruction [31].
- A study of the practice of prescribing antibiotics among general practicing dentists and specialists in the treatment of endodontic infections in the United Arab Emirates [32].

4.2. Studies on the Use of Antibiotics at Different Stages of the Therapeutic Process of Periodontal Diseases

Several studies and many review articles deal with the use of antibiotics and antibacterial agents in dentistry in general and periodontal disease treatment in particular. For example:

- A research on the reasonability of using antibiotics in pediatric dentistry [23].
- The data of an experimental study of a combination of hybrid gels for synergistic periodontal antibacterial treatment with long-term drug release and photothermal effect [24].

4.3. Research on Nanotechnology in Dentistry

A considerable volume of scientific literature studies the prospects and experimental results of the use of nanotechnology-based tools. For example:

- Researchers describe a new method of rational use of Doxycycline in the clinical treatment of periodontal diseases and a new direction to explain the mechanism of action of these and other nanoparticles that the drugs carry [33].

- Authors present the results of the use of Chitosan nanoparticles filled with Minocycline or Tetracycline for in situ delivery to the periodontal environment to improve drug efficacy [34].
- Studies demonstrate that 45 nm gold nanoparticles can not only directly modulate human periodontal cells, but also regulate the early inflammatory response of periodontal tissues by regulating macrophage phenotypes, and therefore generate a microenvironment with limited levels of inflammatory cytokines and reparative cytokines, which leads to the differentiation of periodontal ligament cells, regeneration of periodontal tissues and prevention of the progress of periodontitis [35].

4.4. Other Categories of Research Describing the Use of Odontoprotectors at Different Stages of the Therapeutic Process of Periodontal Diseases

Most of the analysed scientific publications are related to review articles and data of experimental studies of particular drugs. The results regarding the use of hyaluronic acid, Chlorhexidine, vitamins (C, A, E, D), inorganic substances at different stages of the therapeutic process of periodontal diseases are the most common.

For example:

The authors provide the results of the use of Pentoxifylline and Tocopherol for the treatment of the medication-related osteonecrosis of the jaw and experimentally prove the reasonability of this treatment strategy [36].

Papers demonstrate the importance of maintaining sufficient levels of vitamin D in the body to maintain oral health and overall health and point to a link between inadequate vitamin D status and the development of several periodontal diseases [37].

Data from an experimental study of the effect of vanilla acid on the prevention of inflammation and bone destruction in experimental periodontitis as an inflammatory bone disease is presented [38].

Treatment with α -Terpineol in combination with β -Cyclodextrin on the state of the oral cavity, blood, and liver in case of ligature-induced periodontitis is described as effective [39].

The team of authors describes the link between periodontal inflammation and atherosclerotic plaque destabilization. Studies show that some lipid mediators, including lipoxins and resolvins, are powerful in preventing and probably treating some inflammatory diseases, including periodontitis and vascular inflammation [40].

The results of a systemic literature review on the use of hyaluronic acid as an adjunct to the treatment of chronic inflammatory periodontal disease are presented, in addition to its use to improve healing after conventional dental procedures [41].

Both the basic concepts and recent advances are considered in the development of hyaluronic acid-based hydrogels for biomedical applications, including for the treatment of periodontal diseases [42].

The review described the equivalent or even higher efficacy of curcumin compared to widely used drugs for the treatment of periodontitis, such as Chlorhexidine. The authors review experimental and clinical results on the antiperiodontal effects of curcumin and the pharmacological mechanisms underlying these effects [43].

The study covers the therapeutic benefit of C3-targeted intervention (using locally introduced small peptide compound (Cp40/AMY-101) as an adjunct treatment for human periodontal disease [44].

An analysis of clinical trials, case reports, and a literature review evaluating the effects of licorice on oral microorganisms and oral diseases is provided [45].

The authors describe the anti-inflammatory and antioxidant effects of dietary polyphenols, which may affect various biological mechanisms to reduce the onset and progress of periodontitis [46].

Possibilities of an injectable local delivery system of odontoprotectors for personalized periodontal use are also observed [47].

The results of experimental studies on the use of xanthan-based Chlorhexidine gel prove it to be of great benefit in improving the condition of chronic periodontitis [48].

Studies proved that rinsing the oral cavity with Chlorhexidine helps reduce biofilm formation and gingivitis after surgery. However, no further reduction in

periodontal pocket depth compared to any placebo or control solution was found [49].

Studies showed that taking probiotic patients did not affect the development of inflammation in the gums and enamel decalcification [50].

The use of probiotics in the prevention and treatment of certain oral cavity diseases, as well as the possibility of developing designer probiotics for the next generation of complementary oral and throat medical care, is investigated [51].

The study showed that cinnamic acid reduced the number of osteoclasts and inflammation, as well as increased the number of osteoblasts and osteoprotegerin expression in the current model of periodontitis with bone lesions in animals [52].

Researchers present the results of the evaluation and comparison of the pharmacological effect of different drugs on pain relief after periodontal surgery [53].

The effectiveness of local and/or systemic use of statins as an adjunct to non-surgical and/or surgical periodontal therapy was evaluated [54].

The results of studies suggest that mTOR inhibition by rapamycin or other pharmacological agents may be useful in the treatment of a clinically significant condition for which there is no effective treatment yet [55].

Some authors emphasize the potential benefits of the local application of bisphosphonates. In orthodontics, bisphosphonates significantly reduce root resorption and have the advantage of maintaining fixation [56].

Therefore, examples are given that best characterize each of the 4 main areas. Areas 4.1 — 4.3 have a common search keyword that allows combining them into separate categories. Area 4.4 covers the largest number of publications, but it is impossible to choose a common search keyword for this category.

5. CONCLUSION

It was found in this scoping review that the largest number of scientific publications on the particulars of applying odontoprotectors at different stages of the therapeutic process of periodontal diseases is divided into 4 main areas: the use of herbal remedies and folk

remedies; antibiotic therapy in dental practice; remedies obtained with the use of nanotechnology in the treatment of periodontal diseases; results of experimental studies and review articles on a particular active pharmaceutical ingredient.

The smallest volume of scientific information is found in the following areas:

- combination of active pharmaceutical ingredients in the development of a periodontal disease treatment strategy;
- particulars of the use of odontoprotectors in different age groups;
- features of application of certain groups of odontoprotectors.

The obtained results allow concluding that it is important to continue studying the data of the scientific literature on the particulars of applying odontoprotectors at different stages of periodontal disease treatment. Further in-depth analysis should be performed on certain pharmacological groups or a particular active pharmaceutical ingredient.

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Received on 02-03-2022

Accepted on 01-04-2022

Published on 12-05-2022

<https://doi.org/10.6000/1929-6029.2022.11.05>

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