Literature Review

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Current Concepts of Non-Surgical Periodontal Therapy in Chronic Periodontitis

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Abstract

Background

Periodontitis is a chronic multifactorial inflammatory disease that is widespread worldwide and, when advanced, leads to tooth loss and reduced quality of life. The etiology of periodontitis is due to the occurrence of pathogenic lesions, inflammatory and immune states of the host and systemic risk factors. For effective prevention and treatment of periodontitis, a thorough diagnosis, elimination of causes and reduction of modifiable risk factors are of primary importance.

Objective

The objective this review is to provide current concepts of periodontitis treatment.

Materials and Methods

Inclusion Criteria: *included clinical trials that evaluated the effects of using new approaches to periodontitis therapy and written in English.*

Data Extraction: *A comprehensive electronic literature search was performed in the following databases: PubMed, PMC, Science Direct, and Scopus using the Medical Subject Heading (MeSH) terms: biofilm, oral microbiome, new treatments, essential oils, oral care products, and periodontitis.156 articles were found and 100 full-text articles of high methodological quality were selected.*

Results

This review focuses on non-surgical periodontal therapy (NSPT) (subgingival treatment, laser therapy and photodynamic therapy) and adjunctive chemotherapeutic approaches such as systemic and topical antibiotics and antiseptics, subgingival pocket irrigation.

Studies have demonstrated the effectiveness of non-surgical periodontal therapy in reducing clinical parameters such as probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP) and plaque index (PI). For successful prevention and treatment of periodontitis, the following are of primary importance: Careful diagnosis, elimination of causes and reduction of modifiable risk factor.

Conclusions

The long-term success of periodontal therapy depends on maintaining good oral hygiene and adhering to regular periodontal maintenance visits. This highlights the need for ongoing periodontal care even after initial treatment.

Keywords : periodontal disease, biofilm, dental plaque, oral hygiene, non-surgical periodontal therapy.

Introduction

Periodontal diseases are currently among the most common in dental practice and affect patients of all age groups.

Periodontitis is a common disease affecting 11% of adults worldwide in advanced cases (Kwon et al., 2021).
A sharp increase in the prevalence of periodontal diseases, the loss of a large number of teeth, disruption of the act of chewing and speech, the impact on the general condition of the body and a decrease in the quality of human life make it necessary to consider periodontal diseases as a special section of dental science, and the problem is made not only general medical, but also social (Nazir, 2017).
Several factors play a major role in the development of periodontitis (Genco & Borgnakke, 2013).

Periodontitis associated with the accumulation of dental plaque (which will be referred to as dental biofilm/biofilm), and characterised by progressive destruction of the teeth-supporting apparatus, including the periodontal ligament and alveolar bone (Kwon et al., 2021).

The common features of periodontitis include gingival inflammation, clinical attachment loss, radiographic evidence of alveolar bone loss, sites with deep probing depths, mobility, bleeding upon probing and pathologic migration (Abdulkareem et al., 2021).

Virulence factors from these periodontal pathogens stimulate the host macrophages, and other inflammatory and constituent cells, leading to the production of a range of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-1β and prostaglandin E2 (PGE2) (Santonocito et al., 2022; Gemmell et al., 1997; Luchian et al., 2022).

The presence of these pro-inflammatory cytokines and virulence factors stimulates the production of matrix metalloproteinases (MMPs) by macrophages, fibroblasts, junctional epithelial cells, and neutrophils (Checchi et al., 2020). The resulting MMPs then mediate the destruction of collagen fibres in periodontal tissues, especially periodontal ligaments. (Genco & Borgnakke, 2013). In addition, the pro-inflammatory cytokines induce the expression of receptor activator of nuclear factor κB ligand (RANK-L) on the osteoblasts and T helper cells (Cekici et al., 2014; Di Benedetto et al., 2013).

The resulting RANK-L on the osteoblasts and the T helper cells then interacts with receptor activator of nuclear factor κB (RANK) on osteoclast precursors, which results in the genesis of osteoclasts and their maturation. The mature osteoclasts mediate alveolar bone destruction (De Leon-Oliva et al., 2023).
It is well known that the treatment of periodontitis involves complex treatment, that is, the impact on both the etiological factors and the pathogenetic mechanisms of the inflammatory process, as well as the use of symptomatic treatment (Cekici et al., 2014).

The lack of early diagnosis and timely therapy in patients with this disease in a short time can lead to rapid destruction of periodontal tissues and tooth loss. If the disease is diagnosed at a late stage, successful treatment is a difficult task (Roshna & Nandakumar, 2012; Shaddox & Walker, 2010).

According to the 2017, World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions new periodontitis classification categorises the disease based on a multi-dimensional staging and grading system emphasized the need for identifying a standard mode of therapy for the treatment of Periodontal and Peri-Implant Diseases (Papapanou et al., 2018).

The European Federation of Periodontology (EFP) has published the first official evidence-based guidelines for the treatment of stage I, II and III periodontitis(fig.1) (Sanz et al., 2020).

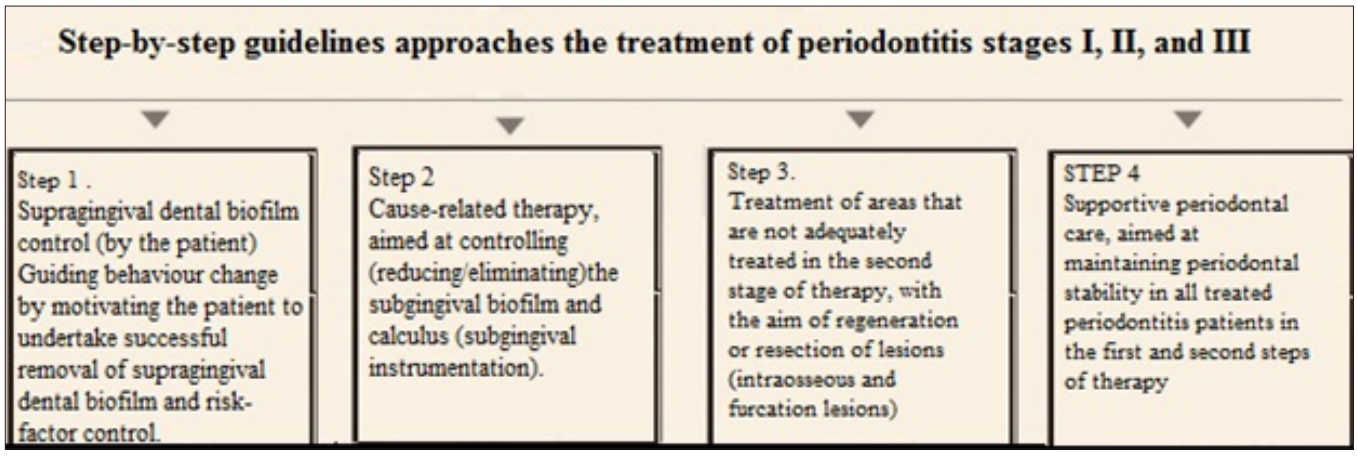

Figure 1: Guidelines for the treatment of stage I, II and III periodontitis

In the clinical practice guideline from the European Federation of Periodontology (EFP), a clear definition of the desired outcome after treatment of Stage I-II periodontitis has been established.

After completion of periodontal therapy, the effectiveness of treatment is determined by the health of the gums with a reduced periodontium (bleeding on probing in < 10% of areas; shallow probing depth of 4 mm or less and no areas of 4 mm with bleeding on probing).
Reduction in BOP and PI, PD and improvement in CAL are valuable indicators, reduction in these parameters means reduction in inflammation and improvement in oral hygiene respectively (Sanz et al., 2020; Tonetti et al., 2018;Papapanou et al., 2018).

The main risk indicators and risk factors for periodontitis are shown in fig2.

Etiologic factors include complex dynamic interactions between specific bacterial infections, destructive host immune responses, and environmental factors such as smoking (White et al., 2018; Grossi et al., 1994; Mealey & Oates, 2006).

Periodontitis is difficult to treat due to the etiology of the disease.

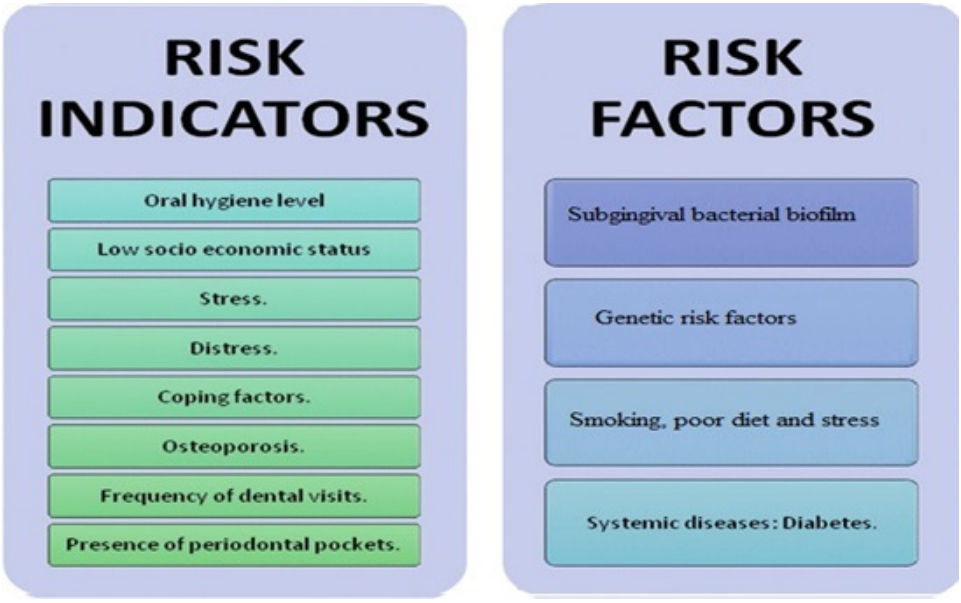

Figure 2: Risk factors for periodontitis

The aim of this review is to provide current concepts of periodontitis treatment. Both clinical and biological rationales will be discussed.

Various approaches applied for the treatment of periodontal disease include surgical intervention, mechanical therapy and use of pharmacological agents (Glickman & Smulow, 1965; Tariq et al., 2012; Kumar et al., 2012).

Medications are specifically used for better management of periodontitis and include antimicrobials that change microbial flora in periodontal milieu and host response modulating agents which modify host response like reduction of excessive enzymes level, cytokines, prostaglandins and osteoclast activity (Radu et al., 2024; Tariq et al., 2012).

In addition to regular dental checkups, proper oral hygiene practices, and the use of natural oral care products. Once adequate home care or biofilm control has been achieved, scaling and root planing should be performed in areas with a periodontal probing depth of 5 mm or more. This phase of treatment should be combined with correction of local factors, extraction of hopeless teeth, and treatment of active carious lesions, piezoelectric or ultrasonic scalers may be used in conjunction with hand instruments (Hatem Alassy, et al., 2021; Matia et al., 1986).

Occlusal adjustments should be considered to eliminate flutter, severe mobility, or excessive centric and lateral excursion contacts (Oosterwaal et al., 1987; Davies et al., 2001; Deas et al., 2006).

The status of subgingival irrigation in the management of periodontitis remains a topic of debate. Several studies indicated the impact of subgingival irrigation as a monotherapy and in combination with root planning and revealed that subgingival irrigation with a variety of agents reduced the amount of gingival microbial load (Harrel et al., 2006; de Andrade et al., 2017).

Subgingival irrigation helps to diminish gingival inflammation despite unchanged plaque levels by diluting plaque toxicity, interference with subgingival plaque maturation, or possibly by washing away unattached plaque. Pocket irrigation is able to reduce microbial load in the pocket and offers some better clinical parameters like pocket depth, bleeding of gum etc, but is associated with a major drawback of showing erratic results, which is probably attributed to short residence time of the drug

in the periodontal pocket (Stambaugh, et al., 1981; Abullais et al., 2015).

After mechanical debridement, the microbial load drops to 0.1%.However; it recolonizes within a week this time with less pathogenic composition. In this perspective, the concept of one stage, full-mouth disinfection was introduced in 1995 for the avoidance of re-infection from microbial reservoirs and showed potential results. Objective of this concept was to eliminate or at least suppress all periodontopathogens in a very short time period not only from the periodontal pockets but also from all intraoral niches such as tongue, tonsils and mucus membrane (Fine et al., 1994; Tariq et al., 2012).

Chlorhexidine is widely considered the gold standard of treatment due to its powerful antimicrobial properties (Shirmohammadi et al., 2013).

The use of lasers is also being investigated as a new technique for the treatment for periodontal disease (Poppolo Deus & Ouanounou, 2022; Richards, 2015; Elavarasu et al., 2012). Several features, such as ablation or vaporization, hemostasis, and sterilization effects, make this laser treatment technique as an adjunct or alternatives to conventional mechanical periodontal therapy. The CO_2 and Neodymium-doped: Yttrium-Aluminum-Garnet (Nd:YAG) lasers have been approved for soft tissue treatment and Erbium–doped: Yttrium–Aluminum-Garnet (Er:YAG) laser has been introduced which can be used for periodontal hard tissues treatment such as root surface debridement, as well as soft tissue management (Ciurescu et al., 2024; Laky et al., 2021; Gurpegui et al., 2022).

The authors feel that more extensive research has to be carried out to confirm the usefulness of laser as a technique for treatment of periodontal diseases, especially in terms of chances of recolonization of microorganisms after laser treatment as compared to other techniques used (Lopes et al., 2008; Munteanu et al., 2022; Bundidpun et al., 2018; Munteanu et al., 2017).

Since the most serious factor to consider in periodontal tissue inflammation is the persistence of periodontal tissue in the periodontal cavity, the normalization of the level of microflora in the periodontal cavity provides good treatment is the main task of the filling of teeth with the use of medicinal preparations of various types to create a spectrum of fast-acting agents. Thus, the most widespread use of various drugs in the treatment of chronic generalized periodontal disease has been obtained by antibacterial drugs, which are divided into two main groups (Amato et al., 2023; Addy & Martin, 2003).

1. **Antiseptics**: substances that have a small group of selective treatment activity. Interacting with enzymes and proteins of the cells of microorganisms, they cause coagulation, facilitating the elimination of pathogenic proteins of microflora in the areas of tissue;
2. **Antibiotics:** substances of blood natural problems or substances of semisynthetic origin, time also davtyn possessing enzymes direct polishing action improves again stgenopathogenic painful microflora procedure atsome inflammation section of the periodontium. A recent systematic review examining the benefits of systemic antibiotics as adjunctive therapy in the treatment of moderate to severe periodontitis found that systemic antibiotics might be considered as adjunctive therapy in the treatment of moderate to severe periodontitis.
3. Wides preadusere caption receive treatment metronidazole tissues drugs most list leaves basedon. In relation to polyurethane, recently in periodontology the basis of depth antimicrobial modern chemotherapy have become to use new antibacterial liquids, preparations from the group of biofluoroquinolones of the IV generation.

Local antibiotic treatment includes minocycline microspheres and doxycycline and systemic treatment includes amoxicillin, metronidazole, azithromycin and doxycycline regimen with dosages depending on the severity of the disease and other general aspects of the patient but they may not be effective for all strains especially P. gingivalis (fig.3) (Teughels et al., 2020;Patil et al., 2013; Sholapurkar et al., 2020; H R et al., 2019; Krayer et al., 2009; Nibali et al., 2019; Teughels et al., 2020; Bland et al., 2010; Herrera et al., 2002; Horz et al.,2007; Mombelli, 2018).

Single agent regimen dosage/duration	
Amoxicillin	500 mg, three times per day × 8 d
Azithromycin	500 mg, once daily × 4-7 d
Ciprofloxacin	500 mg, twice daily × 8 d
Clindamycin	300 mg, three times daily × 10 d
Doxycycline or minocycline	100-200 mg, once daily × 21 d
Metronidazole	500 mg, three times daily × 8 d
Combination therapy	
Metronidazole + amoxicillin	250 mg, of each three times daily × 8 d
Metronidazole + ciprofloxacin	500 mg of each twice daily × 8 d

Figure 3: Recommended systemic antibiotic dosing regimens.

Systemic antimicrobials used in combination with SRP are effective in terms of CAL and PPD changes. However, it should be remembered that systemic antibiotics are an adjunct to mechanical periodontal therapy and should not be used as monotherapy. The use of systemic antibiotics should be limited to, aggressive periodontitis and recurrent or refractory cases that cannot be cured by other therapeutic methods. Indiscriminate use of systemic antimicrobials may lead to the development of antibiotic resistance (Cuevas-Gonzalez et al., 2023; Slots & Ting, 2002).

To reduce the risks of adverse effects of systemic antimicrobial therapy, efforts have led to the development of local delivery of antimicrobial and antiseptic agents (LAD) directly into the periodontal pocket by placing high concentrations of antibiotic or antiseptic in direct contact with the root surface without significant systemic.

Among the first resorbable systems developed was AtridoxTM, a 10% doxycycline formulation (50 mg in a bioresorbable gel system). The polymer gel fills and conforms to the shape of the pocket, then hardens to a wax-like consistency when in contact with sulcular fluid (Hanes & Purvis, 2003).

The early success of Atridox™ led to the development of other absorbable systems such as minocycline microspheres (Arestin™), chlorhexidine gluconate chips (PerioChip™) and gel (Chlosite™), and metronidazole gel (Elyzol™) (Bonito et al., 2005; Bhansali, 2014).

Topical anti-infective agents have resulted in significant additional reductions in PPD or increases in CAL.

The etiopathogenesis of periodontal diseases consider not only specific periodontopathogens, but also synergistic and dysbiotic microbial communities that lead to unresolved inflammation due to changes in the host's immune-inflammatory response (Hajishengallis & Lamont 2012;Caton et al., 2001; Botero et al., 2013; Haas et al., 2012).

As a result, new treatments aimed at restoring a healthy oral microbiome and periodontal health are currently being studied, which may explain the beneficial effects of probiotics on periodontal health.

The World Health Organization (WHO) defined probiotics as "live microorganisms which, when administered in appropriate amounts, confer a health benefit on the host." Most probiotics currently in use are lactic acid bacteria of the genera Lactobacillus and Bifido bacterium, although fungi, Bacillus species, Clostridium, Propionibacterium, and Gram-negative bacteria such as Escherichia coli are probiotically involved in the host's immune-inflammatory response because they can induce the secretion of antimicrobial peptides or anti-inflammatory molecules (Food and Agriculture Organization of the United Nations (FAO), 2006; Foligné et al., 2013; Grenier, 1996; Teanpaisan et al., 2011; Zhao et al., 2012).

A recent systematic review assessed the effects of probiotics on clinical, microbial, and immunological outcomes when used as an adjunct to probiotics. Results showed significant benefits of probiotics in both PPD and CAL when baseline mean PPD values were ≥ 5 mm (Ho et al., 2020).

However, further studies are needed to evaluate the use of different therapeutic regimens of probiotics in the treatment of periodontitis.

Specialized pro-resolving mediators (Omega-3 polyunsaturated fatty acids). In general, act as receptor agonists, controlling the resolution of inflammation and promoting healing SMP).

The evidence for the use of pro-resolving mediators in the treatment of periodontitis is still in the preclinical stages. The main results showed that these mediators lead to an increase in bone tissue and, consequently, bone regeneration by reducing inflammatory cell infiltration and osteoclast activity (El-Sharkawy et al., 2010; Castro Dos Santos et al., 2020).

The results suggest that Omega-3 has potential benefit in reducing periodontal disease progression and improving outcomes that need to be confirmed by clinical studies (Van Dyke , 2011; Van Dyke, 2017; Balta et al., 2017; Serhan et al., 2008; Stańdo et al., 2020).

Regeneration of the alveolar bone support and attachment apparatus can be achieved by regenerative surgical procedures such as root biomodification, use of bone substitute grafts, guided tissue regeneration (GTR) and growth factors (Ramseier et al., 2012).

The use of platelet-rich plasma is currently one of the few ways to modulate and improve wound healing and fight infections without the use of drugs.

Platelet-rich plasma is a proven source of growth factors such as PDGF, TGF, IGF, VEGF, EGF, platelet-derived angiogenesis factor and platelet factor IV (Everts et al., 2020).

Autologous plasma enriched with platelets and fibrin is an endogenous source of growth factors obtained by separating whole blood by density gradients.

PRP therapy - injections of platelet-rich autologous plasma (PRP) yavlyetsya One of the methods of treating parodontit, since platelets contain numerous growth factors and cytokines that promote the regeneration of damaged tissues (Jalaluddin et al., 2017; Döri et al., 2007). Due to these factors, platelet-rich plasma injected into tissues leads to the formation of new capillaries, normalization of hemodynamics, tissue aeration and metabolism. Delivery of autologous platelets to periodontal wounds can increase the local concentration of growth factors, which may improve healing outcomes.

The positive effect of PRP on bone healing is attributed to the angiogenic, proliferative and differentiating effect of PDGF

and TGF present in high concentrations (Trombelli et al., 2002; Okuda et al., 2005).

The advantage of PRP therapy is that platelet-rich plasma can accelerate the regeneration of bones, cartilage and epithelium, since the regeneration process is universal and differs only in duration. Another advantage of PRP therapy is the improvement of microcirculation and metabolism, which stimulates local immunity (Döri et al., 2007; Yassibag-Berkman et al., 2007). PRP therapy eliminates the possibility of infection and allergic reactions.

Direct contraindications to the introduction of PRP injections are only problems with bleeding and/or consequences of bleeding, manifested by a decrease in the number of platelets below 100,000/µl and anemia (hemoglobin below 90 g/l), as well as intolerance to anticoagulants and coagulants.

In addition, it is recommended to exercise caution and a selective approach when prescribing the procedure to patients with blood clotting disorders, febrile patients, individuals with oncopathology, active herpes and other viral infections.
Plastic surgical therapy is used when non-surgical therapy is ineffective and Plastic surgical therapy includes removal of necrotic tissue and flap surgery, bone grafting, guided tissue regeneration and gingival grafting (Zucchelli & Mounssif, 2015; Carnevale & Kaldahl, 2000; Stavropoulos et al., 2021).

Periodical monitoring and assessment of the periodontal status are important to evaluate the outcome of treatment, These include regular dental examinations, periodontal examinations, radiographic assessments and comparison of clinical parameters such as pocket depth and attachment levels. There is a growing trend in the use of herbal medicine in the complex treatment of periodontal disease.

In the case of periodontal disease, various herbs such as turmeric, neem, aloe vera, pomegranate, catechu, tulsi, clove, lemon grass, green tea, tea tree oil, peppermint, garlic, pineapple, oak bark, babul, bakul, sage are currently used. Herbal medicine, coriander, moringa, amla, guava and grape seed extract have been shown to have a number of therapeutic effects including anti-inflammatory, antipruritic, antihalitosis, antiresorptive, antioxidant, antibacterial, antifungal, antiviral and antimicrobial properties. However, they should be used under the supervision of a dentist to ensure optimal results and effectiveness (Gawish et al., 2023; Tidke et al., 2022; Al-Maweri et al., 2020; Boyapati et al., 2024).

Plant compounds with antibacterial properties are used in mouthwashes and other dental care products to reduce bacterial adhesion and plaque formation, and reduce inflammation associated with periodontal disease, as shown in the ONI table. They are available as mouthwashes, gels, or as an adjunct to scaling procedures.

Periodontitis can be treated with various nanomaterials such as liposomes, lipid and polymer nanoparticles, and dendrimers.

Another emerging area of interest is immune modulatory therapy, this approach involves the use of biologics such as monoclonal antibodies and cytokine inhibitors to target specific immune pathways involved in periodontal pathogenesis.

Regenerative therapy aims to promote the regeneration of periodontal tissues, may include the use of growth factors, stem cells, tissue engineering techniques and scaffolds to stimulate repair.

Declaration

Declaration of competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. None of the authors has any relevant financial relationship(s) with a commercial interest.

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References

1. Kwon, T., Lamster, I., B., & Levin, L. (2021). Current Concepts in the Management of Periodontitis. *Int Dent J, 71*(6), 462-476. DOI: 10.1111/idj.12630
2. Nazir, M. A. (2017). Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int J Health Sci (Qassim), 11*(2), 72-80. https://pubmed.ncbi.nlm.nih.gov/28539867/
3. Genco, R. J., & Borgnakke, W. S. (2013). Risk factors for periodontal disease. *Periodontol 2000, 62*(1), 59-94. DOI: 10.1111/j.1600-0757.2012.00457.x
4. Abdulkareem, A. A., Imran, N. K., Abdulraheam, R. H., & Gul, S. S. (2021). Prevalence and factors influencing reporting of true periodontal chief complaints: A retrospective analysis. *Clin Exp Dent Res. 7*(4), 443-449. DOI:10.1002/cre2.385
5. Santonocito, S., Ferlito, S., Polizzi, A., Ronsivalle, V., Sclafani, R., Valletta, A., Lo Giudice, A., Cavalcanti, R., Spagnuolo, G., & Isola, G. (2022). Therapeutic and Metagenomic Potential of the Biomolecular Therapies against Periodontitis and the Oral Microbiome: Current Evidence and Future Perspectives. *Int J Mol Sci, 23*(22), 13708. DOI: 10.3390/ijms232213708
6. Gemmell, E., Marshall, R. I., & Seymour, G. J. (1997). Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. *Periodontol* 2000, 14, 112-43. DOI: 10.1111/j.1600-0757.1997.tb00194.x
7. Luchian, I., Goriuc, A., Sandu, D., & Covasa, M. (2022). The Role of Matrix Metalloproteinases (MMP-8, MMP-9, MMP-13) in Periodontal and Peri-Implant Pathological

Processes. *Int J Mol Sci, 23*(3), 1806. DOI: 10.3390/ijms23031806
8. Checchi, V., Maravic, T., Bellini, P., Generali, L., Consolo, U., Breschi, L., & Mazzoni, A. (2020). The Role of Matrix Metalloproteinases in Periodontal Disease. *Int J Environ Res Public Health, 17*(14), 4923. DOI: 10.3390/ijerph17144923
9. Cekici, A., Kantarci, A., Hasturk, H., & Van Dyke, T. E. (2014). Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontol 2000, 64*(1), 57-80. DOI: 10.1111/prd.12002
10. Di Benedetto, A., Gigante, I., Colucci, S., & Grano, M. (2013). Periodontal disease: linking the primary inflammation to bone loss. *Clin Dev Immunol*, 2013, 503754. DOI: 10.1155/2013/503754
11. De Leon-Oliva, D., Barrena-Blázquez, S., Jiménez-Álvarez, L., Fraile-Martinez, O., García-Montero, C., López-González, L., Torres-Carranza, D., García-Puente, L. M., Carranza, S. T., Álvarez-Mon, M. Á., Álvarez-Mon, M., Diaz, R., & Ortega, M. A. (2023). The RANK-RANKL-OPG System: A Multifaceted Regulator of Homeostasis, Immunity, and Cancer. *Medicina, 59*(10), 1752. https://www.mdpi.com/1648-9144/59/10/1752
12. Roshna, T., & Nandakumar, K. (2012). Generalized aggressive periodontitis and its treatment options: case reports and review of the literature. *Case Rep Med*, 2012, 535321. DOI: 10.1155/2012/535321
13. Shaddox, L. M., & Walker, C. B. (2010). Treating chronic periodontitis: current status, challenges, and future directions. *Clin Cosmet Investig Dent*, 2, 79-91. https://pubmed.ncbi.nlm.nih.gov/23662085/
14. Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman, K. S., Kumar, P. S., Loos, B. G., Machtei, E., Meng, H., Mombelli, A., Needleman, I., Offenbacher, S., Seymour, G. J., Teles, R., & Tonetti, M.,S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol, 89*(Suppl 1), S173-S182. DOI: 10.1002/JPER.17-0721
15. Sanz, M., Herrera, D., Kebschull, M., Chapple, I., Jepsen, S., Beglundh, T., Sculean, A., & Tonetti, M. S. (2020). Treatment of stage IIII periodontitis-The EFP S3 level clinical practice guideline. *J Clin Periodontol, 47*(Suppl 22), 4–60. DOI: 10.1111/jcpe.13290
16. Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: framework and proposal of a new classification and case definition. *J Periodontol*, 89 Suppl 1, S159-72. DOI: 10.1002/JPER.18-0006
17. White, P. C., Hirschfeldm, J., Milward, M. R., Cooper, P. R., Wright, H. J., Matthews, J. B., & Chapple, I. L. C. (2018). Cigarette smoke modifies neutrophil chemotaxis, neutrophil extracellular trap formation and inflammatory response-related gene expression. *J Periodontal Res, 53*(4), 525–535. DOI: 10.1111/jre.12542
18. Grossi, S. G., Zambon, J. J., Ho, A. W., Koch, G., Dunford, R. G., Machtei, E. E., Norderyd, O. M., & Genco, R. J. (1994). Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *J Periodontol, 65*(3), 260–267. DOI: 10.1902/jop.1994.65.3.260
19. Mealey, B. L., & Oates, T. W. (2006). American Academy of Periodontology. Diabetes mellitus and periodontal diseases. *J Periodontol, 77*(8), 1289–1303. DOI: 10.1902/jop.2006.050459
20. Glickman, I., & Smulow, J. B. (1965). Effect of excessive occlusal forces upon the pathway of gingival inflammation in humans. *J Periodontol* (1930), 36, 141–147. DOI: 10.1902/jop.1965.36.2.141
21. Tariq, M., Iqbal, Z., Ali, J., Baboota, S., Talegaonkar, S., Ahmad, Z., & Sahni, J. K. (2012). Treatment modalities and evaluation models for periodontitis. *Int J Pharm Investig. 2*(3), 106-22. DOI: 10.4103/2230-973X.104394
22. Kumar, A. J., Anumala, N., & Avula, H. (2012). Novel and often bizarre strategies in the treatment of periodontal disease. *J Indian Soc Periodontol, 16*(1), 4-10. DOI:10.4103/0972-124X.94595.
23. Radu, C. M., Radu, C. C., Arbănaşi, E. M., Hogea, T., Murvai, V. R., Chiș, I. A., & Zaha, D. C. (2024). "Exploring the Efficacy of Novel Therapeutic Strategies for Periodontitis: A Literature Review" Life (Basel) 14(4), 468. DOI: 10.3390/life14040468
24. Alassy, H., Pizarek, J. A., Kormas, I., Pedercini, A., & Wolf, L. F. (2021). Antimicrobial adjuncts in the management of periodontal and peri-implant diseases and conditions: a narrative review. *Front Oral Maxillofac Med*, 3, 1-18. DOI:10.21037/fomm-20-84.
25. Matia, J. I., Bissada, N. F., Maybury, J. E., & Ricchetti, P. (1986). Efficiency of scaling of the molar furcation area with and without surgical access. *Int J Periodontics Restorative Dent. 6*(6), 24-35. https://pubmed.ncbi.nlm.nih.gov/3542872/
26. Oosterwaal, P. J., Matee, M. I., Mikx, F. H., van 't Hof, M. A., & Renggli, H. H. (1987).The effect of subgingival debridement with hand and ultrasonic instruments on the subgingival microflora. *J Clin Periodontol, 14*(9), 528-33. DOI: 10.1111/j.1600-051x.1987.tb00995.x
27. Davies, S. J., Gray, R. J., Linden, G. J., & James, J. A. (2001). Occlusal considerations in periodontics. *Br Dent J, 191*(11), 597-604. DOI: 10.1038/sj.bdj.4801245
28. Deas, D. E., & Mealey, B. L. (2006). Is there an association between occlusion and periodontal destruction? : Only in limited circumstances does occlusal force contribute to periodontal disease progression, *J Am Dent Assoc, 137*(10), 1381-1389. DOI: 10.14219/jada.archive.2006.0050
29. Harrel, S. K., Nunn, M. E., & Hallmon, W. W. (2006). Is there an association between occlusion and periodontal destruction? Yes—occlusal forces can contribute to periodontal destruction. *J Am Dent Assoc,137*(10), 1380-1392. DOI: 10.14219/jada.archive.2006.0049
30. De Andrade, D. P., Carvalho, I. C. S., Gadoi, B. H., Rosa, L. C. L., Barreto, L. M. R. C., & Pallos, D. (2017). Subgingival irrigation with a solution of 20% propolis extract as an adjunct to non-surgical periodontal treatment:

a preliminary study. *J Int Acad Periodontol, 19*(4), 145–151. https://pubmed.ncbi.nlm.nih.gov/31473730/
31. Stambaugh, R. V., Dragoo, M., Smith, D. M., & Carasali, L. (1981).The limits of subgingival scaling. *Int J Periodontics Restorative Dent, 1*(5), 30–41. https://pubmed.ncbi.nlm.nih.gov/7047434/
32. Abullais, S. S., Dani, N., Hamiduddin, I., Priyanka, N., Kudyar, N., & Gore, A. (2015). Efficacy of irrigation with different antimicrobial agents on periodontal health in patients treated for chronic periodontitis: A randomized controlled clinical trial. *Ayu 36*(4):380-386. DOI: 10.4103/0974-8520.190702
33. Fine, J. B., Harper, D. S., Gordon, J. M, Hovliaras, C. A., & Charles, C. H. (1994). Short-term microbiological and clinical effects of subgingival irrigation with an antimicrobial mouthrinse. *J Periodontol, 65*(1), 30-6. DOI: 10.1902/jop.1994.65.1.30
34. Shirmohammadi, A., Babaloo, Z., Eskandari, A., Purabbas, R., & Babaloo, A. (2013). The Effects of One-Stage Full-Mouth Disinfection and Qua-drant-Wise Scaling and Root Planing on Serum Levels of IL-17 and IL-1β and Clinical Parameters (A randomized Controlled Trial Study). *J Dent (Tehran), 10*(3), 248-55. https://pubmed.ncbi.nlm.nih.gov/25512752/
35. Poppolo Deus, F., & Ouanounou, A. (2022). Chlorhexidine in Dentistry: Pharmacology, Uses, and Adverse Effects. *Int Dent J, 72*(3), 269-277. DOI: 10.1016/j.identj.2022.01.005
36. Richards, D. 92015). Chlorhexidine mouthwash more effective than dentifrice or gel. *Evid Based Dent, 16*(2), 59. DOI: 10.1038/sj.ebd.6401102
37. Elavarasu, S., Naveen, D., & Thangavelu, A. (2012). Lasers in periodontics. *J Pharm Bioallied Sci, 4*(Suppl 2), S260-3. DOI: 10.4103/0975-7406.100245
38. Ciurescu, C. E., Dima, L., Ciurescu, V. A., Noja, G. G., Istodor, A. V., Moga, M. A., Ardelean, L. C., Rusu, L-C., & Leretter, M. T. (2024). Laser Therapy Effects on Periodontal Status: A Randomized Study Using Gaussian Network Analysis and Structural Equation Modeling Approach. *Medicina, 60*(3), 437. DOI: 10.3390/medicina60030437
39. Laky, M., Müller, M., Laky, B., Arslan, M., Wehner, C., Husejnagic, S., Lettner, S., Moritz, A., & Rausch-Fan, X. (2021). Short-term results of the combined application of neodymium-doped yttrium aluminum garnet (Nd: YAG) laser and erbium-doped yttrium aluminum garnet (Er: YAG) laser in the treatment of periodontal disease: a randomized controlled trial. *Clin Oral Investig, 25*(11), 6119-6126. DOI: 10.1007/s00784-021-03911-x
40. Gurpegui Abud, D., Shariff, J. A., Linden, E., & Kang, P. Y. (2022). Erbium-doped: yttrium-aluminum-garnet (Er:YAG) versus scaling and root planing for the treatment of periodontal disease: A single-blinded split-mouth randomized clinical trial. *J Periodontol, 93*(4), 493-503. DOI: 10.1002/JPER.21-0133
41. Lopes, B. M., Marcantonio, R. A., Thompson, G. M., Neves, L. H., & Theodoro, L. H. (2008). Short-term clinical and immunologic effects of scaling and root planing with Er: YAG laser in chronic periodontitis. *J Periodontol, 79*(7), 1158-67. DOI: 10.1902/jop.2008.070600
42. Munteanu, I. R., Luca, R. E., Mateas, M., Darawsha, L. D., Boia, S., Boia, E. R., & Todea, C. D. (2022). The Efficiency of Photodynamic Therapy in the Bacterial Decontamination of Periodontal Pockets and Its Impact on the Patient. *Diagnostics (Basel), 12*(12), 3026. DOI: 10.3390/diagnostics12123026
43. Bundidpun, P., Srisuwantha, R., Laosrisin, N. (2018). Clinical effects of photodynamic therapy as an adjunct to full-mouth ultrasonic scaling and root planing in treatment of chronic periodontitis. *Laser Ther, 27*(1), 33-39. DOI: 10.5978/islsm.18-OR-03
44. Munteanu, I. R., Todea, C., Luca, R. E., & Mocuta, D. E. (2018, August 10). Photodynamic therapy in periodontology: A systematic review; Proceedings of the Proc. SPIE 10831, Seventh International Conference on Lasers in Medicine, *Timisoara, Romania,* 13–15 July 2017, 108310B. https://www.researchgate.net/publication/326961569_Photodynamic_therapy_in_periodontology_a_systematic_review
45. Amato, M., Santonocito, S., Polizzi, A., Tartaglia, G. M., Ronsivalle, V., Viglianisi, G., Grippaudo, C., & Isola, G. (2023). Local Delivery and Controlled Release Drugs Systems: A New Approach for the Clinical Treatment of Periodontitis Therapy. *Pharmaceutics, 15*(4), 1312. DOI: 10.3390/pharmaceutics15041312
46. Addy, M., Martin, M. V. (2003). Systemic antimicrobials in the treatment of chronic periodontal diseases: a dilemma. *Oral Dis, 9*(Suppl 1), 38-44. DOI: 10.1034/j.1601-0825.9.s1.7.x
47. Teughels, W., Feres, M., Oud, V., Martín, C., Matesanz, P., & Herrera, D. (2020). Adjunctive effect of systemic antimicrobials in periodontitis therapy: a systematic review and meta-analysis. *J Clin Periodontol, 47*(Suppl 22), 257-281.DOI: 10.1111/jcpe.13264
48. Patil, V., Mali, R., & Mali, A. (2013). Systemic anti-microbial agents used in periodontal therapy. *J Indian Soc Periodontol, 17*(2), 162-8. DOI:10.4103/0972-124X.113063
49. Sholapurkar, A., Sharma, D., Glass, B., Miller, C., Nimmo, A., & Jennings, E. (2020). Professionally Delivered Local Antimicrobials in the Treatment of Patients with Periodontitis-A Narrative Review. *Dent J (Basel), 9*(1), 2. DOI: 10.3390/dj9010002
50. H, R. R., Dhamecha, D., Jagwani, S., Rao, M., Jadhav, K., Shaikh, S., Puzhankara, L., & Jalalpure, S. (2019). Local drug delivery systems in the management of periodontitis: A scientific review. *J Control Release*, 307, 393-409. DOI: 10.1016/j.jconrel.2019.06.038
51. Krayer, J. W., Leite, R. S., & Kirkwood, K. L. (2010). Non-surgical chemotherapeutic treatment strategies for the management of periodontal diseases. *Dent Clin North Am, 54*(1), 13-33. DOI: 10.1016/j.cden.2009.08.010
52. Nibali, L., Koidou, V. P., Hamborg, T. & Donos, N. (2019). Empirical or microbiologically guided systemic antimicrobials as adjuncts to nonsurgical periodontal therapy? A systematic review. *J Clin Periodontol, 46*(10), 999–1012. DOI: 10.1111/jcpe.13164

53. Bland, P. S., Goodson, J. M., Gunsolley, J. C., Grossi, S. G., Otomo-Corgel, J., Doherty, F., & Comiskey, J. L. (2010). Association of antimicrobial and clinical efficacy: periodontitis therapy with minocycline microspheres. *J Int Acad Periodontol, 12*(1), 11–19. https://pubmed.ncbi.nlm.nih.gov/20593634/
54. Herrera, D., Sanz, M., Jepsen, S., Needleman, I., & Roldán, S. (2002). A Systematic Review on the Effect of Systemic Antimicrobials as an Adjunct to Scaling and Root Planing in Periodontitis Patients. *J. Clin. Periodontol, 29*(Suppl 3), 136–159. DOI: 10.1034/j.1600-051x.29.s3.8.x
55. Horz, H.-P., & Conrads, G. (2007). Diagnosis and Anti-Infective Therapy of Periodontitis. *Expert Rev. Anti-Infect. Ther, 5*(4), 703–715. DOI: 10.1586/14787210.5.4.703
56. Mombelli, A. (2018). Microbial Colonization of the Periodontal Pocket and Its Significance for Periodontal Therapy. *Periodontol 2000, 76*(1), 85–96. DOI: 10.1111/prd.12147
57. Cuevas-Gonzalez, M.V., Cuevas-Gonzalez, J. C., Espinosa-Cristóbal, L. F., Donohue-Cornejo, A., Reyes López, S.Y., Saucedo Acuña, R. A., García Calderón, A. G., & Guzmán Gastelum, D. A. (2023). Use or Abuse of Antibiotics as Prophylactic Therapy in Oral Surgery: A Systematic Review. *Medicine, 102*(37), e35011. DOI: 10.1097/MD.0000000000035011
58. Slots, J., & Ting, M. (2002). Systemic antibiotics in the treatment of periodontal disease. *Periodontol* 2000. 28, 106-176. DOI: 10.1034/j.1600-0757.2002.280106.x
59. Hanes, P. J., & Purvis, J. P. (2003). Local anti-infective therapy: pharmacological agents. A systematic review. *Ann Periodontol, 8*(1), 79-98. DOI: 10.1902/annals.2003.8.1.79
60. Bonito, A. J., Lux, L., & Lohr, K. N. (2005). Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. *J Periodontol, 76*(8), 1227-1236. DOI: 10.1902/jop.2005.76.8.1227
61. Bhansali, R. S. (2014). Non-surgical periodontal therapy: An update on current evidence. *World J Stomatol, 3*(4), 38-51. DOI:10.5321/wjs.v3.i4.38
62. Hajishengallis, G., & Lamont, R. J. (2012). Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Mol Oral Microbiol, 27*(6), 409-19. DOI: 10.1111/j.2041-1014.2012.00663.x
63. Caton, J. G., Ciancio, S. G., Blieden, T. M., Bradshaw, M., Crout, R. J., Hefti, A. F., Massaro, J. M., Polson, A. M., Thomas, J., & Walker, C. (2001). Subantimicrobial dose doxycycline as an adjunct to scaling and root planing: post-treatment effects. *J Clin Periodontol, 28*(8), 782–789. DOI: 10.1034/j.1600-051x.2001.280810.x
64. Botero, J. E., Yepes, F. L., Ochoa, S. P., Hincapie, J. P., Roldan, N., Ospina, C. A., Castrillon, C. A., & Becerra, M. A. (2013). Effects of periodontal non-surgical therapy plus azithromycin on glycemic control in patients with diabetes: a randomized clinical trial. *J Periodontal Res, 48*(6), 706–712. DOI: 10.1111/jre.12058
65. Haas, A. N., Seleme, F., Segatto, P., Susin, C., Albandar, J., Oppermann, R. V., Fontanella, V. R., & Rösing, C. K. (2012). Azithromycin as an adjunctive treatment of aggressive periodontitis: radiographic findings of a 12-month randomized clinical trial. *Am J Dent 25*(4), 215–219. https://pubmed.ncbi.nlm.nih.gov/23082385/
66. Food and Agriculture Organization of the United Nations (FAO) (2006). World Health Organization. Probiotics in food, health and nutritional properties and guidelines for evaluation. *Rome*, https://openknowledge.fao.org/server/api/core/bitstreams/382476b3-4d54-4175-803f-2f26f3526256/content
67. Foligné, B., Daniel, C., & Pot, B. (2013). Probiotics from research to market: the possibilities, risks and challenges. *Curr Opin Microbiol, 16*(3), 284-92. DOI: 10.1016/j.mib.2013.06.008
68. Grenier, D. (1996). Antagonistic effect of oral bacteria towards Treponema denticola. *J Clin Microbiol, 34*(5), 1249-52. DOI: 10.1128/jcm.34.5.1249-1252.1996
69. Teanpaisan, R., Piwat, S., & Dahlén, G. (2011). Inhibitory effect of oral Lactobacillus against oral pathogens. *Lett Appl Microbiol, 53*(4), 452-9. DOI: 10.1111/j.1472-765X.2011.03132.x
70. Zhao, J. J., Feng, X. P., Zhang, X. L., & Le, K. Y. (2012). Effect of Porphyromonas gingivalis and Lactobacillus acidophilus on secretion of IL1B, IL6, and IL8 by gingival epithelial cells. *Inflammation, 35*(4), 1330-7. DOI: 10.1007/s10753-012-9446-5
71. Ho, S. N., Acharya, A., Sidharthan, S., Li, K. Y., Leung, W. K., McGrath, C., & Pelekos, G. (2020). A systematic review and meta-analysis of clinical, immunological, and microbiological shift in periodontitis after nonsurgical periodontal therapy with adjunctive use of probiotics. *J Evid Based Dent Pract, 20*(1), 101397. DOI: 10.1016/j.jebdp.2020.101397
72. El-Sharkawy, H., Aboelsaad, N., Eliwa, M., Darweesh, M., Alshahat, M., Kantarci, A., Hasturk, H., Van Dyke, T. E. (2010). Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 Fatty acids and low-dose aspirin. *J Periodontol, 81*(1), 1635–1643. DOI: 10.1902/jop.2010.090628
73. Castro Dos Santos, N. C., Andere, N. M. R. B., Araujo, C. F., de Marco, A. C., Kantarci, A., Van Dyke, T. E., & Santamaria, M. P. (2020). Omega3 PUFA and aspirin as adjuncts to periodontal debridement in patients with periodontitis and type 2 diabetes mellitus: randomized clinical trial [published online ahead of print Feb 26, 2020]. *J Periodontol, 91*(10), 1318-1327. https://doi.org/10.1002/JPER.19- 0613
74. Van Dyke, T. E. (2011). Proresolving lipid mediators: potential for prevention and treatment of periodontitis. *J Clin Periodontol, 38* (Suppl 11), 119-25. DOI: 10.1111/j.1600-051X.2010.01662.x
75. Van Dyke, T. E. (2017). Pro-resolving mediators in the regulation of periodontal disease. *Mol Aspects Med*, 58, 21-36. DOI: 10.1016/j.mam.2017.04.006
76. Balta, M. G., Loos, B. G., Nicu, E. A. (2017). Emerging concepts in the resolution of periodontal inflammation: a role for Resolvin E1. *Front Immunol*, 8, 1682. DOI: 10.3389/fimmu.2017.01682

77. Serhan, C. N., Chiang, N., & Van Dyke, T. E. (2008). Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol, 8*(5), 349-61. DOI: 10.1038/nri2294
78. Stańdo, M., Piatek, P., Namiecinska, M., Lewkowicz, P., Lewkowicz, N. (2020). Omega-3 Polyunsaturated fatty acids EPA and DHA as an ADJUNCT TO NON-SURGICAL TREATMENT OF PERIODONTITIS: A RANDOMIZED CLINICAL TRIAL. *Nutrients, 12*(9), 2614. DOI: 10.3390/nu12092614
79. Ramseier, C. A., Rasperini, G., Batia, S., Giannobile, W. V. (2012). Advanced reconstructive technologies for periodontal tissue repair. *Periodontol 2000, 59*(1), 185-202. DOI: 10.1111/j.1600-0757.2011.00432.x
80. Everts, P., Onishi, K., Jayaram, P., Lana, J. F., Mautner, K. (2020). Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. *Int J Mol Sci. 21*(20), 7794. DOI: 10.3390/ijms21207794
81. Jalaluddin, M., Singh, D. K., Jayanti, I., Kulkarni, P., Faizuddin, M., & Tarannum, F. (2017). Use of Platelet Rich Plasma in the Management of Periodontal Intra-Osseous Defects: A Clinical Study. *J Int Soc Prev Community Dent, 7*(2), 105-115. DOI: 10.4103/jispcd.JISPCD_28_17
82. Döri, F., Kovács, V., Arweiler, N. B., Huszár, T., Gera, I., Nikolidakis, D. (2007). Effect of platelet rich plasma on the healing of intrabony defects treated with an an organic bovine bone mineral and expanded poly tetrafluroethylene membranes. *J Periodontol, 78*(6), 983–90. DOI:10.1902/jop.2007.060349
83. Trombelli, L., Heitz-Mayfield, L. J., Needleman, I., Moles, D., & Scabbia, A. (2002). A systemic review of graft materials and biological agents for periodontal intra osseous defects. *J Clin Periodontol, 29*(Suppl 3), 117–35. DOI: 10.1034/j.1600-051x.29.s3.7.x
84. Okuda, K., Tai, H., Tanabe, K., Suzuki, H., Sato, T., Kawase, T., Saito, Y., Wolff, L. F., & Yoshiex, H. (2005). Platelet Rich Plasma combined with porous hydroxyapatite graft for the treatment of intrabony periodontal defect in humans. A comparative controlled clinical study. *J Periodontol, 76*(6), 890–8. DOI: 10.1902/jop.2005.76.6.890
85. Yassibag-Berkman, Z., Tuncer, O., Subasioglu, T., Kantarci, A. (2007). Combined use of platelet rich plasma and bone grafting with or without guided tissue regeneration in the treatment of anterior interproximal defects. *J Periodontol, 78*(5), 801–9. DOI: 10.1902/jop.2007.060318
86. Zucchelli, G., & Mounssif, I. (2015). Periodontal plastic surgery. *Periodontol 2000, 68*(1), 333-68. DOI: 10.1111/prd.12059
87. Carnevale, G., & Kaldahl, W. B. (2000). Osseous resective surgery. *Periodontol 2000*, 22, 59-87. DOI: 10.1034/j.1600-0757.2000.2220106.x
88. Stavropoulos, A., Bertl, K., Spineli, L. M., Sculean, A., Cortellini, P., Tonetti, M. (2021). Medium- and long-term clinical benefits of periodontal regenerative/reconstructive procedures in intrabony defects: Systematic review and network meta-analysis of randomized controlled clinical studies. *J Clin Periodontol, 48*(3), 410-430. DOI: 10.1111/jcpe.13409 Epub 2021 Jan 21.
89. Gawish, A. S., ElMofty, M. S., Jambi, S., Felemban, D., Ragheb, Y. S., & Elsayed, S. A. (2023). Phytotherapy in periodontics as an effective and sustainable supplemental treatment: a narrative review. *J Periodontal Implant Sci*, 11. DOI: 10.5051/jpis.2301420071
90. Tidke, S., Chhabra, G. K., Madhu, P. P., Reche, A., Wazurkar, S., Singi, S. R. (2022). The Effectiveness of Herbal Versus Non-Herbal Mouthwash for Periodontal Health: A Literature Review. *Cureus, 14*(8), e27956. DOI: 10.7759/cureus.27956
91. Al-Maweri, S. A., Nassani, M. Z., Alaizari, N., Kalakonda, B., Al-Shamiri, H. M., Alhajj, M. N., Al-Soneidar, W. A., & Alahmary, A. W.(2020). Efficacy of aloe vera mouthwash versus chlorhexidine on plaque and gingivitis: A systematic review. *Int J Dent Hyg, 18*(1), 44-51. DOI: 10.1111/idh.12393
92. Boyapati, R., Peeta, J., Dhulipalla, R., Kolaparthy, L., Adurty, C., Cheruvu, R. N. S. (2024). Comparative evaluation of the efficacy of probiotic, Aloe vera, povidine-iodine, and chlorhexidine mouthwashes in the treatment of gingival inflammation: A randomized controlled trial. *Dent Med Probl, 61*(2), 181-190. DOI: 10.17219/dmp/156425