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Resolution of Inflammation in Periodontitis: A Comprehensive Review

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Abstract

Inflammation, a natural defence mechanism against injury or infection, can become problematic when it fails to resolve, as observed in conditions like periodontitisThis review explores how inflammation is resolved in periodontitis and seeks potential treatments for this chronic condition, which damages the periodontium, including the gingival tissue, periodontal ligament, and alveolar bone. The pathogenesis of this disease is initiated by the inflammatory response triggered by resident leukocytes and endothelial cells upon exposure to bacterial biofilms, resulting in vasodilation and immune cell recruitment. The review stresses the importance of researching targeted approaches for periodontitis treatment, such as inducing neutrophil apoptosis, shifting from M1 to M2 macrophages, and exploring M2-based tissue engineering. Additionally, investigating lymphangiogenesis and Treg cell recruitment at the inflammation site offers promising avenues. In conclusion, further studies are needed to refine lymphangiogenesis and assess the potential of pro-resolving lipid mediators and anti-inflammatory cytokines in managing periodontitis. Ongoing research aims to uncover the underlying biomolecular mechanisms governing immune cells and resolving mediators, with the ultimate goal of restoring tissue equilibrium and promoting healing.

Keywords: *Periodontitis; inflammation; resolution of inflammation; Macrophages; Apoptosis; periodontal diseases*

1. Introduction

"Periodontal disease (PD) is a chronic inflammation leading to the breakdown of tooth-supporting tissues, including the gums, periodontal ligament, and alveolar bone (Trowbridge et al., 1997)" [1]. "According to Könönen E et al., (2019), periodontal diseases result from an inflammatory response involving resident leukocytes and endothelial cells against bacterial biofilm. Bacterial metabolites trigger cytokine and neuropeptide release by junctional epithelium cells, leading to local blood vessel dilation. Neutrophils move from blood vessels to the inflamed area in response to chemokines, transitioning from innate to acquired immune responses. Macrophages, plasma cells, and T & B lymphocytes enter the inflammatory site to clear cellular debris via phagocytosis, ultimately resolving the inflammation [2]." Chronic and pathological inflammation can occur when the protective inflammatory response falters in clearing harmful substances produced by neutrophils and delays the removal of apoptotic inflammatory cells. This condition is often seen in susceptible individuals, leading to chronic diseases and fibrosis when acute inflammation remains unresolved. Yucel-Lindberg et al., (2013) highlighted that the inability to resolve inflammation and restore tissue balance can lead to

chronic inflammation, contributing to conditions like arthritis, asthma, cancer, cardiovascular diseases, and periodontal diseases. Efficiently initiating and resolving acute inflammation is crucial for overall health. Traditionally, it was thought that stopping pro-inflammatory mediators served as the 'off switch' for inflammation, ending subsequent responses passively [3].

2. Materials And Methods

Resolution of inflammation in periodontitis has been the subject of a comprehensive electronic literature search from 2003 to 2022 using PubMed and Google Scholar databases with relevant MeSH terms and keywords. Combinations of the following keywords were used for the identification of the studies to be considered in this review: “periodontics,” “resolution of inflammation”. To broaden the search for relevant articles, selected article references were reviewed.

This study is to find similar topics from several articles that will be reviewed and summarized. PICO was used as a strategy to find the articles:

A. Problem: Patients in needs of resolution of inflammation in periodontitis

B. Intervention: Medication-aided periodontal inflammation resolution.

C. Comparison: Spontaneous inflammation resolution in periodontal disease

D. Outcome: Innovative treatment methods for resolving periodontal inflammation

The criteria for eligibility were as listed below.

Inclusion criteria:

• Research encompassing the natural resolution of inflammation, neutrophil apoptosis, macrophage reprogramming, lipid mediator involvement, and drug-induced resolution of inflammation

Exclusion criteria:

• Case reports, case series, review articles, systematic reviews, and meta-analysis.

Study Selection

Eligibility criteria, databases, and search strategies were utilized to identify pertinent studies. Reviewers independently evaluated study titles and abstracts, selecting those that met the criteria. The search resulted in 60 titles, from which 20 articles adhering to the inclusion criteria were included in the qualitative analysis. These chosen articles underwent a comprehensive examination to elucidate the pathobiology of inflammation resolution in periodontitis. (FIGURE 1)

Data Analysis

The following characteristics were considered for data extraction:

- Qualitative analysis was done for evidence synthesis.

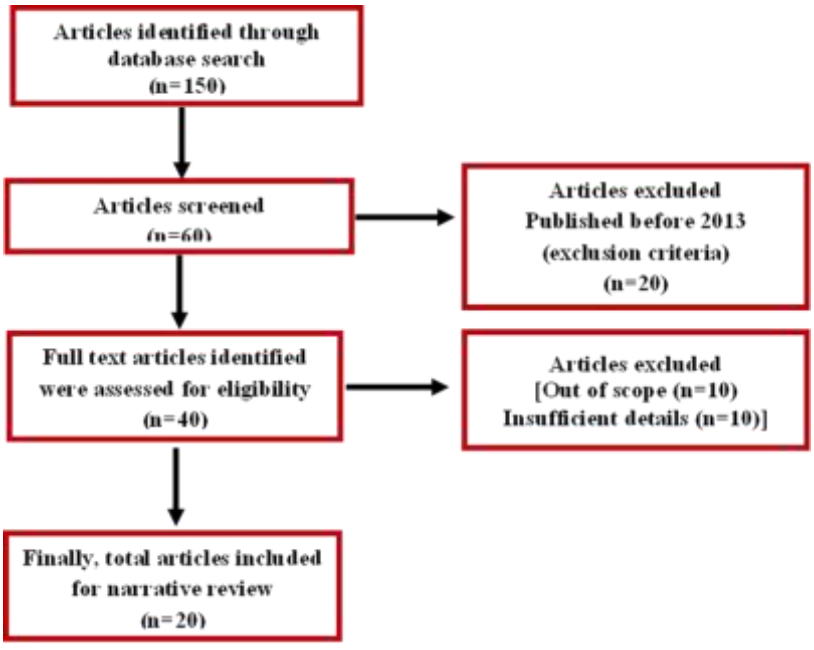

FIGURE 1: PRISMA flow diagram of articles screening and selection

3. Results and Discussion

Out of the 40 articles identified, 20 were especially relevant to understanding inflammation resolution in chronic periodontitis. This review's findings indicate that effectively managing periodontal disease in humans relies on recognizing shared pathways, which can enhance our comprehension of the disease and foster the creation of innovative treatment approaches. We extracted and organized detailed information from both animal and human studies, including their outcomes and results, into tables (TABLE 1 & 2).

Table 1: *Animal Studies for Resolution of Inflammation*

REFERENCES	TITLE	YEAR	FINDINGS
Arita *et al* [4]	Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2, 4, 6-trinitrobenzene sulfonic acid-induced colitis.	2005	Aspirin initiates the production of Resolvin E1, offering a targeted treatment approach for intestinal inflammation.
Oguma *et al* [5]	In vitro effect of recombinant human tumor necrosis factor-α on canine neutrophil apoptosis.	2006	TNF-α initiates divergent PMN apoptotic pathways and inhibits their cell death.
Kesavalu. L *et al* [6]	Omega-3 fatty acid effect on alveolar bone loss in rats.	2006	Omega-3 fatty acid supplementation reduces alveolar bone loss in P. gingivalis infection, making it a valuable addition to periodontal disease treatment.
Scannell *ET AL* [7]	Annexin-1 and peptide derivatives are released by apoptotic cells and stimulate phagocytosis of apoptotic neutrophils by macrophages.	2007	Annexin-1 and its peptide derivatives enhance inflammation resolution, expanding annexin-1's anti-inflammatory potential.
Serhan *et al* [8]	Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions.	2009	Maresin is crucial for DHA and macrophage's positive contributions to tissue balance, inflammation resolution, wound healing, and host defense.
Recchiuti *et al* [9]	MicroRNAs in resolution of acute inflammation: identification of novel resolvin Dl-miRNA circuits.	2011	Resolvin-regulated miRNAs target genes in the resolution process, creating a new circuit where RvD1 receptors control these specific miRNAs.
Flesher *et al* [10]	Resolvin E1 promotes resolution of inflammation in a mouse model of an acute exacerbation of allergic asthma.	2014	Resolvin E1 supports airway inflammation resolution in an asthma model by affecting activated pulmonary macrophages.
Hasturk *et al* [11]	Resolvin E1 regulates inflammation at the cellular and tissue level and restores tissue homeostasis.	2015	Treating a rabbit model with Resolvin E1 completely healed the local lesion and reduced systemic inflammation markers, including C-reactive protein and IL-1.
Alqahtani *et al* [12]	Enhanced silver nanoparticle-induced pulmonary inflammation in a metabolic syndrome mouse model and resolvin D1 treatment.	2022	Metabolic syndrome mice exposed to silver nanoparticles initially experience increased pulmonary inflammation. Subsequently, they are treated with resolution mediators like Resolvin D1 to aid in resolving the inflammation.

Table 2- *Human Studies For Resolution Of Inflammation.*

REFERENCES	TITLE	YEAR	FINDINGS
H Hasturk *et al* [13]	Resolvin E1 protects from local inflammation and osteoclast-mediated bone destruction in periodontitis.	2006	Resolvin E1's distinct binding pattern on human neutrophils, separate from the lipoxin receptor, highlights its protective role in countering inflammation and preventing osteoclast-induced bone loss in periodontitis.
El-Sharkawy *et al* [14]	Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 Fatty acids (PUFAs) and low-dose aspirin.	2010	Salivary RANKL and MMP-8 levels decreased significantly in the omega-3 group compared to the control group, suggesting that incorporating ω-3 PUFAs and 81 mg aspirin into the diet is a cost-effective way to enhance periodontal therapy.
Zein Elabdeen *et al* [15]	Ratio of pro-resolving and pro-inflammatory lipid mediator precursors as potential markers for aggressive periodontitis.	2013	The study analyzed the ratios of pro-resolving lipid mediator precursors associated with resolvins and protectins versus pro-inflammatory lipid mediators. These ratios consistently indicated a decrease in aggressive periodontitis patients' gingival crevicular fluid (GCF) and saliva compared to healthy controls, implying their potential as a valuable marker for this condition.
Deore *et al* [16]	Omega 3 fatty acids as a host modulator in chronic periodontitis patients: a randomised, double-blind, palcebo-controlled, clinical trial.	2014	Omega-3 fatty acids alleviate gingival inflammation, reduce pocket depth, and enhance attachment level gain, making them valuable host modulators for preventing and managing chronic periodontitis.
Dogan *et al* [17]	Lipoxin A4 and neutrophil/lymphocyte ratio: a possible indicator in achieved systemic risk factors for periodontitis.	2015	Hyperlipidemic patients demonstrate elevated Lipoxin A4 levels and an elevated Neutrophil/Lymphocyte ratio, serving as systemic risk indicators for periodontitis.
Wang *et al* [18]	Maresin 1 biosynthesis and proresolving anti-infective functions with human-localized aggressive periodontitis leukocytes. *Infection and Immunity.*	2016	patients with localised aggressive periodontitis (LAP), Maresin1 levels and macrophage phagocytic activity were diminished compared to healthy controls. However, the administration of 1 nM Maresin1 enhanced macrophage phagocytic activity in LAP patients, underscoring the clinical potential of therapies targeting the Maresin1 pathway for LAP treatment.
Umrania *et al* [19]	Polyunsaturated fatty acids as an adjunct to scaling and root planing on salivary interleukin-1β levels in patients with chronic periodontitis: A clinico-immunological study.	2017	Omega-3 PUFAs manage cytokines, demonstrating pro-resolution characteristics and functioning as adjuncts in chronic periodontitis treatment.

Tobón-Arroyave *et al* [20]	Salivary levels of specialized pro-resolving lipid mediators as indicators of periodontal health/disease status.	2019	Independent connection is observed, showing reduced Lipoxin A4 levels and increased salivary levels of Protectin 1 and Maresin 1 in periodontitis, signifying an SPM imbalance within the disease.
Castro dos Santos *et al* [21]	Omega-3 (PUFA) and aspirin as adjuncts to periodontal debridement in patients with periodontitis and type 2 diabetes mellitus: randomized clinical trial.	2020	Enhancing periodontal debridement with omega-3 and aspirin enhances periodontitis treatment in individuals with type 2 diabetes, providing both clinical and immunological advantages.
Onal *et al* [22]	Salivary levels of last generation specific pro-resolving lipid mediators (SPMs) (protectin and maresin) in patients with cardiovascular and periodontal disease: A case-control study.	2021	Protectin and Maresin's involvement may lead to the development of cardiometabolic and periodontal issues, serving as early indicators for the transition from a healthy state to a diseased one, potentially encompassing cardiovascular disease and periodontitis.
Maybodi *et al* [23]	Effects of omega-3 supplementation as an adjunct to non-surgical periodontal therapy on periodontal parameters in periodontitis patients: a randomized clinical trial.	2022	Omega-3 supplements, when added to a three-month non-surgical periodontal treatment, led to significant improvements in chronic periodontitis patients.

Bacterial biofilm triggers the onset of periodontal inflammation as a protective response. In those vulnerable to it, this inflammation becomes chronic, characterizing periodontal pathology. Excessive inflammation gives rise to periodontitis, indicating a breakdown in resolution processes. Neutrophils, the most abundant white blood cells, swiftly arrive at injury or infection sites during inflammation to combat invading microorganisms (Chen L et al., 2017 [24]. Huang et al., (2018) emphasized that during the resolution phase, specific mechanisms, such as the reduced production of pro-inflammatory chemokines, lead to their depletion, preventing further neutrophil infiltration [25]. The authors also stressed the significance of phagocytic cells, like macrophages, recognizing and engulfing apoptotic cells to successfully resolve inflammation. Furthermore, Huang and colleagues proposed that dying neutrophils themselves have an anti-inflammatory effect by influencing nearby cells, particularly in regulating the release of inflammatory cytokines by macrophages. As mentioned by Huang et al., the timing and extent of apoptosis can be impacted by microorganisms, depending on their strategies to evade the immune system and the overall health of the host [25].

The exploration of apoptosis in periodontitis has a long history spanning several decades. In a study from 2002 by M. Perretti et al., the combined influence of aspirin and dexamethasone on the control of polymorphonuclear neutrophil recruitment to inflamed sites was investigated. Administering both substances into murine air pouches notably reduced PMN infiltration [26]. Various techniques are available to regulate neutrophil apoptosis, including the use of pharmacological inhibitors that target cyclin-dependent kinases. In a study from 2006, Rossi et al., examined the CDK inhibitor R-roscovitine, which significantly enhanced the resolution of inflammation involving neutrophils in mouse models. Their research revealed that R-roscovitine stimulates PMN apoptosis by reducing the levels of the anti-apoptotic protein Mcl-1. This has sparked substantial research in understanding the control of PMN apoptosis and its potential as a therapeutic focus in inflammatory and infectious diseases (Rossi et al., 2006) [27].

Polyunsaturated fatty acids are released from cell membranes during pathogen invasion and inflammation, and they are transported to the inflamed area. Lipoxin (LX), resolvin (Rv)-D, resolvin-E, protectin, and maresin are among the promising pro-resolution mediators. These lipid derivatives help resolve tissue inflammation by stopping neutrophil recruitment, promoting macrophage differentiation, and aiding in the removal of inflammatory cells and tissue debris. This process restores tissue balance, supports vascular integrity, and facilitates tissue regeneration and repair. Lipoxins are

generated in various human organs and can boost macrophage phagocytosis of apoptotic neutrophils (Freire MO & Van Dyke TE., 2013) [28]. In a 2017 study, Tarannum et al. explored how ALOX15 gene variations impact chronic periodontitis and lipoxin levels in patients' GCF. Their research found that ALOX15 gene polymorphisms are linked to an increased risk of chronic periodontitis and affect both GCF LXA4 levels and the release of essential lipoxins for periodontal resolution. Moreover, resolvins and protectins, derived from omega-3 polyunsaturated fatty acids, come in two forms: RvD and RvE. Notably, RvE1 can induce apoptosis in activated CD4+ T cells, a crucial step in resolving inflammation [29].

Multiple studies have underscored the pivotal role of Resolvin and Protectin in addressing periodontitis. In a 2014 study led by Flesher et al., RvE1's efficacy was assessed in a mouse model of acute exacerbation of chronic allergic asthma. Administering RvE1 during allergen-induced asthma inflammation led to a decrease in inflammatory cell count and cytokine levels in airway lavage fluid, validating RvE1's pro-resolving effects [10]. Another investigation in 2006 by H. Hasturk et al. delved into Resolvin E1's (RvE1) actions in regulating neutrophil-mediated tissue damage and resolving inflammation in patients with localized aggressive periodontitis. Their findings showed that RvE1 specifically binds to human neutrophils at a distinct site from the LX receptor, offering protection against inflammation-induced tissue and bone loss associated with periodontitis [13].

Derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), Protectin (PDs) and Maresin (MaRs) are the latest pro-resolving lipid mediators actively engaged in resolving inflammation. In a 2019 study by Tobón-Arroyave et al., they investigated salivary levels of lipoxin A4 (LXA4), protectin D1 (PD1), resolvin E1 (RvE1), and maresin 1 (MaR1) in periodontitis patients. Their findings revealed an imbalance in specialized pro-resolving lipid mediators (SPMs) in periodontal disease, with reduced LXA4 and increased PD1/MaR1 salivary levels [20]. In 2021, Onal, Mehmet Artuğ et al. assessed salivary levels of protectin (PD) and maresin (MaR) in patients with cardiovascular disease (CVD) and periodontal disease. Their results suggested that lower salivary PD levels and higher salivary MaR levels in CVD patients could potentially predict the transition from a healthy to a diseased state [22].

The fact is clear: the resolution of inflammation is controlled by protective mediators. These mediators comprise lipoxins derived from arachidonic acid, aspirin-triggered lipoxins, E-series resolvins from ω3-eicosapentaenoic acid, D-series resolvins from docosahexaenoic acid, protectins, and maresins [30]. Back in 2008, Anderson P and Delgado M underscored the vital role of protective agents in managing the resolution of inflammation. These agents include lipoxins, aspirin-triggered lipoxins, E-series, and D-series resolvins, protectins, and maresins [30]. In 2010, G and Serhan CN provided details on the specific interaction between lipid compounds and G protein-coupled receptors found on innate immune cells. This interaction impedes the infiltration of white blood cells, reinstates the normal permeability of blood vessels, triggers the programmed cell death of neutrophils, promotes the non-inflammatory arrival of monocytes/macrophages, and aids macrophages in disposing of dying neutrophils, foreign intruders (bacteria), and decaying remains. These coordinated procedures collectively result in the resolution of inflammation and the reinstatement of the pre-disease state [31].

4. Conclusion

Future research should focus on inducing neutrophil apoptosis selectively, exploring M1 to M2 macrophage transitions, and considering M2-based tissue engineering for treating periodontitis. Translational studies in complex areas like lymphangiogenesis are essential through clinical trials. Attracting Treg cells to inflammation sites holds potential for resolving periodontitis. Pro-resolving lipid mediators and anti-inflammatory cytokines are effective in treating the condition. This field is constantly studying biomolecular mechanisms for healing and maintaining homeostasis.

References:

1. Trowbridge, H. O., Emling, R. C., & Fornatora, M. (1997). Inflammation. A review of the process. Implant dentistry, 6(3), 238.
2. Könönen, E., Gursoy, M., & Gursoy, U. K. (2019). Periodontitis: a multifaceted disease of tooth-supporting tissues. Journal of clinical medicine, 8(8), 1135.
3. Yucel-Lindberg, T., & Båge, T. (2013). Inflammatory mediators in the pathogenesis of periodontitis. Expert reviews in molecular medicine, 15, e7.
4. Arita, M., Yoshida, M., Hong, S., Tjonahen, E., Glickman, J. N., Petasis, N. A., ... & Serhan, C. N. (2005). Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2, 4, 6-trinitrobenzene sulfonic acid-induced colitis. Proceedings of the National Academy of Sciences, 102(21), 7671-7676.
5. Oguma, K., Sano, J., Kano, R., Watari, T., & Hasegawa, A. (2006). In vitro effect of recombinant human tumor necrosis factor-α on canine neutrophil apoptosis. Research in veterinary science, 80(2), 162-166.

6. Kesavalu, L., Vasudevan, B., Raghu, B., Browning, E., Dawson, D., Novak, J. M., ... & Ebersole, J. L. (2006). Omega-3 fatty acid effect on alveolar bone loss in rats. Journal of dental research, 85(7), 648-652.
7. Scannell, M., Flanagan, M. B., destefani, A., Wynne, K. J., Cagney, G., Godson, C., & Maderna, P. (2007). Annexin-1 and peptide derivatives are released by apoptotic cells and stimulate phagocytosis of apoptotic neutrophils by macrophages. The Journal of Immunology, 178(7), 4595-4605.
8. Serhan, C. N., Yang, R., Martinod, K., Kasuga, K., Pillai, P. S., Porter, T. F., ... & Spite, M. (2009). Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. Journal of Experimental Medicine, 206(1), 15-23.
9. Recchiuti, A., Krishnamoorthy, S., Fredman, G., Chiang, N., & Serhan, C. N. (2011). MicroRNAs in resolution of acute inflammation: identification of novel resolvin D1-miRNA circuits. The FASEB Journal, 25(2), 544.
10. Flesher, R. P., Herbert, C., & Kumar, R. K. (2014). Resolvin E1 promotes resolution of inflammation in a mouse model of an acute exacerbation of allergic asthma. Clinical science, 126(11), 805-818.
11. Vivo, T. H. I. (2007). Resolvin E1 Regulates Inflammation at the. J Immunol, 179, 7021-7029.
12. Alqahtani, S., Xia, L., & Shannahan, J. H. (2022). Enhanced silver nanoparticle-induced pulmonary inflammation in a metabolic syndrome mouse model and resolvin D1 treatment. Particle and Fibre Toxicology, 19(1), 54.
13. Hasturk, H., Kantarci, A., Ohira, T., Arita, M., Ebrahimi, N., Chiang, N., ... & Van Dyke, T. E. (2006). RvE1 protects from local inflammation and osteoclastmediated bone destruction in periodontitis. The FASEB journal, 20(2), 401-403.
14. El-Sharkawy, H., Aboelsaad, N., Eliwa, M., Darweesh, M., Alshahat, M., Kantarci, A., ... & Van Dyke, T. E. (2010). Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 fatty acids and low-dose aspirin. Journal of periodontology, 81(11), 1635-1643.
15. Zein Elabdeen, H. R., Mustafa, M., Szklenar, M., Rühl, R., Ali, R., & Bolstad, A. I. (2013). Ratio of pro-resolving and pro-inflammatory lipid mediator precursors as potential markers for aggressive periodontitis. PloS one, 8(8), e70838.
16. Deore, G. D., Gurav, A. N., Patil, R., Shete, A. R., NaikTari, R. S., & Inamdar, S. P. (2014). Omega 3 fatty acids as a host modulator in chronic periodontitis patients: a randomised, double-blind, palcebo-controlled, clinical trial. Journal of periodontal & implant science, 44(1), 25-32.
17. Doğan, B., Fentoğlu, Ö., Kırzıoğlu, F. Y., Kemer, E. S., Köroğlu, B. K., Aksu, O., ... & Orhan, H. (2015). Lipoxin A4 and neutrophil/lymphocyte ratio: a possible indicator in achieved systemic risk factors for periodontitis. Medical science monitor: international medical journal of experimental and clinical research, 21, 2485.
18. Wang, C. W., Colas, R. A., Dalli, J., Arnardottir, H. H., Nguyen, D., Hasturk, H., ... & Serhan, C. N. (2016). Maresin 1 biosynthesis and proresolving anti-infective functions with human-localized aggressive periodontitis leukocytes. Infection and Immunity, 84(3), 658-665.
19. Umrania, V. V., Deepika, P. C. R., & Kulkarni, M. (2017). Evaluation of dietary supplementation of omega-3 polyunsaturated fatty acids as an adjunct to scaling and root planing on salivary interleukin-1β levels in patients with chronic periodontitis: A clinico-immunological study. Journal of Indian Society of Periodontology, 21(5), 386.
20. Tobón-Arroyave, S. I., Isaza-Guzmán, D. M., Gómez-Ortega, J., & Flórez-Alzate, A. A. (2019). Salivary levels of specialized pro-resolving lipid mediators as indicators of periodontal health/disease status. Journal of Clinical Periodontology, 46(10), 978-990.
21. Castro dos Santos, N. C., Andere, N. M., Araujo, C. F., de Marco, A. C., Kantarci, A., Van Dyke, T. E., & Santamaria, M. P. (2020). Omega-3 PUFA and aspirin as adjuncts to periodontal debridement in patients with periodontitis and type 2 diabetes mellitus: randomized clinical trial. Journal of periodontology, 91(10), 1318-1327.
22. Önal, M. A., Fentoğlu, Ö., Aksoy, F., Calapoğlu, M., Varol, E., & Orhan, H. (2021). Salivary levels of last generation specific pro-resolving lipid mediators (SPMs)(protectin and maresin) in patients with cardiovascular and periodontal disease: A case-control study. Journal of Periodontal Research, 56(3), 606-615.
23. Önal, M. A., Fentoğlu, Ö., Aksoy, F., Calapoğlu, M., Varol, E., & Orhan, H. (2021). Salivary levels of last generation specific pro-resolving lipid mediators (SPMs)(protectin and maresin) in patients with cardiovascular and periodontal disease: A case-control study. Journal of Periodontal Research, 56(3), 606-615.
24. Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., ... & Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204.
25. Huang, J., Cai, X., Ou, Y., Zhou, Y., & Wang, Y. (2018). Resolution of inflammation in periodontitis: A review. International Journal of Clinical and Experimental Pathology, 11(9), 4283.
26. Perretti, M., Chiang, N., La, M., Fierro, I. M., Marullo, S., Getting, S. J., ... & Serhan, C. N. (2002). Endogenous lipid-and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A4 receptor. Nature medicine, 8(11), 1296-1302.
27. Rossi, A. G., Sawatzky, D. A., Walker, A., Ward, C., Sheldrake, T. A., Riley, N. A., ... & Haslett, C. (2006). Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. Nature medicine, 12(9), 1056-1064.

28. Freire, M. O., & Van Dyke, T. E. (2013). Natural resolution of inflammation. Periodontology 2000, 63(1), 149-164.
29. Tarannum, F., & Faizuddin, M. (2017). Effect of Alox-15 polymorphism on GCF levels of Lipoxin-A4 in chronic periodontitis: A preliminary study. Brazilian Dental Journal, 28, 140-147.
30. Anderson, P., & Delgado, M. (2008). Endogenous anti-inflammatory neuropeptides and pro-resolving lipid mediators: a new therapeutic approach for immune disorders. Journal of cellular and molecular medicine, 12(5b), 1830-1847.
31. Bannenberg, G., & Serhan, C. N. (2010). Specialized pro-resolving lipid mediators in the inflammatory response: An update. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1801(12), 1260-1273.