B-Dent: Jurnal Kedokteran Gigi Universitas Baiturrahmah, Vol 11, No.1: page 63-71
ISSN 2301-5454, e-ISSN 2654-7643
Available online at https://jurnal.unbrah.ac.id/index.php/bdent/index
(filled by editorial board after manuscript accepted)

THE EFFECTIVENESS OF PROCYANIDIN ON RED GRAPE SEED EXTRACT IN TREATMENT OF PERIODONTITIS INDUCED BY DIABETES MELLITUS

Ranny Rachmawati[*], Monica Annasthasia Handoko[**], Isabella Avrilia[**], Angela Latisha Wisnawati[**]

*Departement of Periodontics, Faculty of Dentistry, Universitas Brawijaya, Indonesia
** Faculty of Dentistry, Universitas Brawijaya, Indonesia
Email: rannyperio.fk@ub.ac.id

KEYWORDS

Diabetes Mellitus, Periodontitis, Procyanidin, Red Grape Seed

ABSTRACT

Introduction*: Periodontal disease, including periodontitis, ranks as the 6th complication for Diabetes Mellitus. Research has found an increase of inflammation and higher alveolar bone loss in the periodontal of diabetes mellitus patients. One of the components which exhibited multiple bio-activities like anti oxidative, anti-inflammatory, antidiabetic antimicrobial cardioprotective, neuroprotective, immunomodulatory, and anti-obesity activities is procyanidin. Procyanidin can be found in various natural ingredients and one of the most abundant compositions is found in red grape seeds.* ***Methods:*** *The method used in this study is a literature review from several academic databases including : Google Scholar, PubMed, Mendeley, Wiley, and the university's online library with boolean searching method.* ***Results:*** *The several articles used in this literature review show that the protective effect of grape seed procyanidin plays a role in attenuating the increase of MFG-E8, suppressing the increase of IL-1beta protein level, improving HOMA-IR and insulin levels in diabetes, increasing IL-10 and TGF-beta accumulation in the gingival epithelium of periodontitis condition, and MMP- and HIF-1alpha immunohistochemistry showed an increase in its levels for periodontitis with diabetes rats, but decreased as grape seed procyanidin extract (GSPE) was administered.* ***Conclusion:*** *The present study suggested that procyanidin in grape seed extract played a role in treating periodontitis in diabetes patients through its anti- inflammatory role and its ability to decrease alveolar bone loss. There are still very few studies regarding this topic, therefore further studies that are more specific to this topic is required*

INTRODUCTION

Periodontitis, one of the most common and universal human diseases worldwide. It affects more than 743 million people worldwide, ranks as the 6th most common chronic inflammatory disease in the world.[1] Periodontitis is a chronic multifactorial inflammatory disease 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.[2,3]

Diabetes mellitus (DM) is also a chronic disease that is very common in the world. The International Diabetes Federation (IDF) 2022 reports that 537 million adults worldwide have diabetes in 2021, with a projected increase of 45% or the equivalent of 783 million patients by

2045. Diabetes mellitus (DM) and its related complications are a serious threat to global health. Periodontitis, considered as the sixth complication of diabetes, is negatively affected by metabolic disorders and related pathological status in DM.[4,5]

Diabetes mellitus (DM) and periodontal disease are both considered amalgamate types of diseases. Although they have different determining factors, they share many common environmental and genetic factors that trigger and regulate the diseases.[6,7] Epidemiologic studies have proved that periodontitis in diabetic patients suffer more severe and extensive loss of periodontal tissue.[8,9] Excessive level of blood glucose in DM individuals often induces the formation of excessive reactive oxygen species (ROS) as well as the production and release of multiple pro-inflammatory cytokines.[9] The homeostatic imbalance between ROS and antioxidant defense systems can result in an oxidative stress response, which plays a pivotal role in the pathogenesis of periodontitis in diabetics.[1,10,11]

The conventional clinical therapies for periodontitis (mainly mechanical debridement and surgical periodontal treatment) do not consider the specific microenvironment of diabetes, and are limited in achieving satisfactory therapeutic effects.[12,13,14] Therefore, there is an urgent need to develop a novel strategy to implement personalized measures to treat periodontitis under diabetic conditions.[4]

One of the strategy ideas is by utilizing red grape (*Vitis vinifera*) seed (RGS). Red grape seed (RGS) has several advantages, such as its ability to stimulate certain tissue growth factors that play a role in wound healing, stimulate brain function, maintain healthy blood vessels, enhance the function of the immune system, and counteract the effects of exposure to free radicals. In the medical field, RGS extract can be utilized for healthcare related to bone strength, metabolic diseases, cancer, heart disease, atherosclerosis, and accelerates wound healing.[15,16,17] Red grape seed (RGS) extract contains procyanidin. Procyanidin can be found in various natural ingredients and one of the most abundant compositions is found in red grape seeds.[17,18]

From an industrial point of view, grape seeds are one of the most important natural renewable resources of catechins and procyanidins, because of their relative abundance and low cost.[19] Procyanidin is gaining traction in the fields of nutrition and medicine.[20] Grape seed procyanidin B2 (GSPB2) is a dimeric form of grape seed procyanidin extract (GSPE), more powerful than other water- soluble polyphenos in biological activities.[21]

Several studies have recently begun to report the various health benefits of consuming polyphenols like procyanidin that may reduce chronic diseases and metabolic disorders.[20] According to a comprehensive review of procyanidins, procyanidins exhibited multiple bio-activities like anti-oxidative, anti-inflammatory[22], antidiabetic, antimicrobial[23], cardioprotective, neuroprotective, immunomodulatory, and lipid-lowering and

anti-obesity activities.[4,24] Procyanidins also affect glycolytic homeostasis by lowering blood glucose levels and increasing the production of coenzyme A for binding and raising lipoproteins.[25]

From gathering all available observations, the aim of literature review is to present the recent data on periodontitis and DM in light of new findings and understand the two-way relationship between these diseases in order to provide effective treatment for patients. Finally, our goal is to determine the impact of the effectiveness of procyanidin on red grape seed extract in the healing process of periodontitis induced by DM.

METHODS

This literature review research on the effectiveness of procyanidin in red grape seed (RSG) extract in the treatment of periodontitis due to diabetes mellitus was carried out for one month in April 2023. Literature that was published in the span of 10 years from 2013 to 2023, were obtained from several academic databases such as: Google Scholar, PubMed, Mendeley, Wiley, and the university's online library. The keywords “grape seed”, “procyanidin”, “periodontitis”, and “diabetes mellitus” were used in this journals and articles search with the “boolean searching” method (ex: grape seed AND procyanidin AND periodontitis AND diabetes mellitus). The inclusion criterias for this research are: original research articles, published in the last 10 years, and contain materials regarding the association between procyanidin and periodontitis induced by diabetes mellitus. Whereas the exclusion criterias for this research are: duplicate articles, case report articles, review articles and articles with no full text manuscript.

RESULTS

The literature that discusses the effectiveness of procyanidin on red grape seed extract in treatment of periodontitis induced by diabetes mellitus were obtained from academic databases in a total of 55 articles. The number that passes the screening about suitability between the title of the articles or journals and the research theme so that it must be issued and remaining 21 journals or articles. The next stage is to do a feasibility test with a full text content assessment articles/ journal, in the same way as an abstract assessment. At this stage 17 articles and journals were issued, so that only 4 journals were included in further studies.

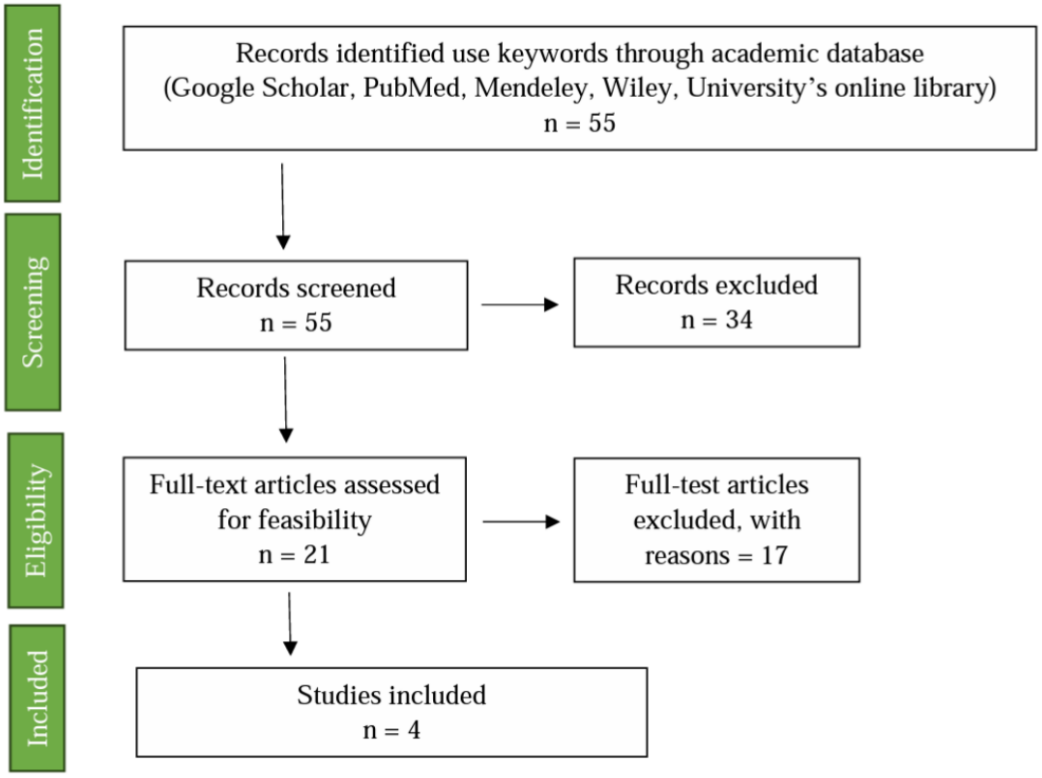

Figure 1. Prisma Flow Diagram

Table 1. Summary of Literature Review

No	Author	Title	Methods	Result	Database
1.	Yin *et al*., 2015[25]	Anti-inflammatory effects of grape seed procyanidin B2 on a diabetic pancreas	**Sample:** Diabetes (db/db) mice aged 7 weeks and non-diabetes (db/m) mice as the control group. **Instrument:** db/db mice were treated with grape seed procyanidin b2 (GSPB2) by administration. Body weights, food intake, fasting blood glucose (FBG), advanced glycation end products (AGEs), serum insulin and homeostasis model assessment of insulin resistance (HOMA-IR) were measured. Pancreas morphology and islet size were then analyzed. The statistical data was also analyzed.	GSPB2 attenuated the elevated body weights, food intake, and advanced glycation end-product levels in db/db mice. It also improved HOMA-IR, treatment also down-regulated the protein level of milk fat globule epidermal growth factor-8 (MFG-E8). Proinflammatory cytokines IL-1beta and NLRP3 were high in diabetic pancreas, but GSPB2 treatment attenuated these alterations.	PubMed Central

2.	Ozden *et al.*, 2016[26]	Effects of grape seed extract on periodontal disease : an experimental study in rats	**Design :** experimental study **Sample:** forty male Sprague Dawley rats with average weight of 150-200 g. **Instrument:** Periodontitis was created in seed extract (GSE) additionally each with different period of time, while the other one group acted as the control group. Histology, immunohisto chemical, and statistics data were analyzed. Inflammatory cell number (ICN), connective tissue attachment level (CAL), osteoclast density (OD), IL-10 and TGF-beta stainings in gingival epithelium (GE), connective tissue (GC), and periodontal ligament (PL) were used as the study parameters. GSE was administered via gavage feeding once a day.	Groups treated by GSE showed lower ICN, higher CAL, and lower OD. The IL-10 was also more intensive in the GEs. The group which received GSE 2 weeks before weeks) showed the highest IL-10 for PL. TGF-beta was higher in the GEs of all groups. Proanthocyanidin from grape seed played an anti-inflammatory role as a suppressor of proinflammatory cytokines, aligning with the result which showed an increased production of IL-10 due GSE intake.	PubMed Central
3.	Rayyan *et al.*, 2018[27]	Efficacy of grape seed extract gel in the treatment of Chronic periodontitis: A randomized clinical study	**Design:** randomized, double-blinded ,and parallel group clinical trial with one control and one test group. **Sample**: twenty- four patients were screened and examined, five patients with a mean age 43.5 ± 7.9 years, with the study inclusion criteria (a non smoker, a clinical diagnosis of chronic periodontitis with pocket depth ≥5 mm with evident radiographic bone loss, and willing to provide informed consent). **Instrument:** Eighty-six sites with pocket depth (PD) >4 mm were selected from were given, a week earlier. PD, gingival index (GI), plaque index (PI), and bleeding on probing (BOP) were measured, and sites were then divided into the control group (N = 38) and GSE group (N = 48). Four doses of formulated 2% mucoadhesive GSE gel were applied to GSE group sites at baseline visit (T0), and 3, 6, and 9 days after	Paired t test for both the control and GSE groups showed a significant reduction for all variables after 6 months of gel application (P < 05). The independent t test showed a significant difference (P< .05) only in the reduction of gingival index (mean: 0.85 ±0.77 for control and 1.3 ± 0.8 for GSE) and plaque index (mean: 0.75 ± 0.71 for control and 1.12 ± 0.7 for GSE). It can be concluded that the subgingival application of the formulated 2% mucoadhesive GSE gel showed significant improvement in the PI and GI only.	Wiley Online Library

			T0. Similarly, a control gel was applied to the control sites. PD, PI, GI and BOP were re-evaluated after 4 weeks and 6 months of first gel application.		
4.	Toker *et al*., 2018[28]	Morphometric and histopathological evaluation of the effect of grape seed proanthocyanidin on alveolar bone experimental	**Design:** Samples were divided into 6 groups, with 1 control group. **Sample:** Forty old, weighing around 270-350 g) **Instrument:** Diabetes mellitus was induced by intraperitoneal injection of a single dose of streptozotocin (60mg/kg). Periodontitis was induced via ligation method. Silk ligatures were placed at the mandibular right first molars. GSPE was administered by oral gavage. After 30 days, all rats were killed. Alveolar bone loss was measured morphometrically via a stereomicroscope. For Histopathological analyses, Alizarin red staining, and matrix factor (HIF)-1α immunohistochemistry were performed. Tartrate-resistant acid phosphatase-positive osteoclast cells and relative total inflammatory cells were also determined.	It was shown that the highest bone loss was in group with diabetes and periodontitis received 100 mg/kg/day grape seed procyanidin (GSPE-100) exhibited a decrease in the alveolar bone loss. D+P group also had the highest osteoclast counts but the difference was not significant compared to periodontitis (P), GSPE-100, and GSPE-200 groups. The inflammation is the highest in D+P group. GSPE-100 and GSPE-200 had an increase in osteoblast numbers, higher that shown to decrease these levels.	Wiley Online Library

DISCUSSION

A research conducted by Yin *et al*. 2015 showed an increase in milk fat globule epidermal growth factor (MFG-E8), a glycoprotein which is involved in inflammatory response, in diabetic mice specifically in its pancreas. Interleukin 1-beta (IL-1beta) also showed an increase in its protein levels.[25] The mice were treated with grape seed procyanidin b2 (GSPB2) by intragastric administration every morning. After analyzing its pancreas morphology, islet size, and statistical data, it was shown that GSPB2 has an anti-inflammatory effect in the diabetic mice. The suggestion was made for after being treated by GSPB2, the increase of MFG-E8 was attenuated, the increase of IL-1beta protein level was suppressed, HOMA-IR and insulin levels were improved.[29]

As for periodontitis, Ozden *et al*. 2017 conducted an experimental study in rats with periodontitis while being treated with grape

seed extract (GSE). The results suggested that GSE showed anti-inflammatory activities.[26] Histology assessment showed a lower inflammatory cell number (ICN), higher connective tissue attachment level (CAL), and lower osteoclast density (OD), after administering GSE via gavage feeding in rats with periodontitis (GSE groups). Immunohistochemical analysis exhibited higher IL-10 accumulation in the gingival epithelium (GE) of the periodontitis rats which received GSE treatment 2 weeks before periodontitis induction and continued for 6 weeks (for a period of 8 weeks). Transforming growth factor-beta (TGF-beta), the other immunohistochemical parameter which has anti-inflammatory effects due to its role in suppressing collagenase production and in enhancing the tissue inhibitors of matrix metalloproteinases, was also higher in the gingival epithelium of GSE groups. It was suggested that the GSPE in grape seed extract played an anti-inflammatory role as a suppressor of pro-inflammatory cytokines.[30]

Another randomized clinical study conducted by Rayyan *et al.*2018 did research regarding the effect of GSE in the form of a gel as treatment for chronic periodontitis. After applying the formulated 2% mucoadhesive GSE gel in periodontal pockets of chronic periodontitis patients, there was a significant reduction in the plaque index (PI), gingival index (GI), but no significant improvement in the pocket depth (PD). It was suggested that the antioxidant properties in GSE were to be related with the result and the proanthocyanidin component could inhibit the formation of plaque and the progression of periodontitis.[27]

Toker *et al*. 2018 suggested that GSPE may decrease periodontal inflammation and alveolar bone loss in diabetic rats. Periodontitis in diabetic rats showcased the highest alveolar bone loss compared to the one without diabetes, but administration of GSPE via oral gavage in rats with diabetes and periodontitis resulted in lower alveolar bone loss compared to the group in which GSPE was not administered. Histopathological analysis showed that the osteoblast cell counts were the lowest in periodontitis of diabetic rats, compared to periodontitis without diabetes. Administration of GSPE significantly increased the number of osteoblasts. The inflammatory cell was also analyzed and it showed that GSPE reduced inflammation in periodontitis of diabetic mice which inflammation was the highest, but the reduction did not reach the same level of the control group. Evaluation of matrix metalloproteinase-8 (MMP-8) and hypoxia inducible factor-1 alpha (HIF-1alpha) immunohistochemistry showed an increase in its levels for periodontitis with diabetes rats, but decreased as GSPE was administered.[28,]

Present study suggested that procyanidin in grape seed extract played an anti-inflammatory role in both periodontitis and diabetes. Administration of procyanidin in grape seed extract proved to decrease MFG-E8 and IL-1beta protein level, which played a role in causing inflammation in diabetes. In

periodontitis procyanidin in grape seed extract could inhibit the progression of periodontitis, and it may be related to procyanidin's effect in increasing IL-10 and TGF-beta counts in the gingival epithelium, which both played role as an anti-inflammatory. Whereas in a condition where periodontitis happened in diabetes patients, procyanidin in grape seed also helped in decreasing periodontal inflammation and alveolar bone loss through the decrease of MMP-8 and HIF- 1alpha levels, and increase osteoblast activity, although the study about grape seed procyanidin's effect towards periodontitis in diabetes patients is still very limited, therefore further studies are required.[30,31]

CONCLUSION

In conclusion, the present study suggested that procyanidin in grape seed extract played a role in treating periodontitis in diabetes patients through its anti-inflammatory role and its ability to decrease alveolar bone loss. There are still very few studies regarding this topic, therefore further studies that are more specific to this topic is required.

REFERENCES

1. Zhao, X., Yang, Y., Yu, J., Ding, R., Pei, D., Zhang, Y. & Li, A. (2022). Injectable hydrogels with high drug loading through B–N coordination and ROS-triggered drug release for efficient treatment of chronic periodontitis in diabetic rats. *Biomaterials*, 282, 121387.
2. Kwon, T., Lamster, I. B., & Levin, L. (2021). Current concepts in the management of periodontitis. *International dental journal*, 71(6),462-476.
3. Kumar, S. (2019). Evidence-based update on diagnosis and management of gingivitis and periodontitis. *Dental Clinics*, *63*(1), 69-81.
4. Wang, L., Li, Y., Ren, M., Wang, X., Li, L., Liu, F., & Song, J. (2022). pH and lipase-responsive nanocarrier-mediated dual drug delivery system to treat periodontitis in diabetic rats. *Bioactive materials*, 18, 254-266.
5. Kocher, T., König, J., Borgnakke, W. S., Pink, C., & Meisel, P. (2018). Periodontal complications of hyperglycemia/diabetes mellitus: epidemiologic complexity and clinical challenge. *Periodontology 2000*, *78*(1), 59-97.
6. Abdellatif, H. M., Binshabaib, M. S., Shawky, H. A., & ALHarthi, S.S. (2021). Association between periodontitis and genetic polymorphisms in interleukins among patients with diabetes mellitus. *Dentistry Journal*, *9*(4), 45.
7. Basu, A., Masek, E., & Ebersole, J. L. (2018). Dietary polyphenols and periodontitis—A mini-review of literature. *Molecules*, *23*(7), 1786.
8. Păunică, I., Giurgiu, M., Dumitriu, A. S., Păunică, S., Pantea Stoian, A. M., Martu, M. A., & Serafinceanu, C. (2023). The Bidirectional Relationship between Periodontal Disease and Diabetes Mellitus—A Review. *Diagnostics*, 13(4), 681.
9. D'Aiuto, F., Gkranias, N., Bhowruth, D., Khan, T., Orlandi, M., Suvan, J., ... & Mellor, T. (2018). Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *The lancet Diabetes & endocrinology*, *6*(12), 954-965.
10. Chen, M., Cai, W., Zhao, S., Shi, L., Chen, Y., Li, X. & Huang, S. (2019). Oxidative stress-related biomarkers in saliva and gingival crevicular fluid associated with chronic periodontitis: A systematic review and meta-analysis. *Journal of clinical periodontology*, *46*(6), 608-622.
11. Rajakumari, R., Volova, T., Oluwafemi, O. S., Rajesh Kumar, S., Thomas, S., & Kalarikkal, N. (2020). Grape seed extract-soluplus dispersion and its antioxidant activity. *Drug development and industrial pharmacy*, *46*(8), 1219-1229.
12. Bartold, P. M. (2018). Lifestyle and periodontitis: The emergence of personalized periodontics. *Periodontology 2000*, *78*(1), 7-11.
13. Bian, Y., Liu, C., & Fu, Z. (2021). Application value of combination therapy of periodontal curettage and root planning on moderate-to-severe chronic periodontitis in patients with type 2 diabetes. *Head & face medicine*, *17*(1), 1-9.
14. Graziani, F., Karapetsa, D., Alonso, B., & Herrera, D. (2017). Nonsurgical and surgical treatment of periodontitis: how many options for one disease?, *Periodontology 2000*, *75*(1), 152-

188.

15. Bell, L., Whyte, A. R., Lamport, D. J., Spencer, J. P., Butler, L. T., & Williams, C. M. (2022). Grape seed polyphenol extract and cognitive function in healthy young adults: a randomised, placebo-controlled, parallel-groups acute-on-chronic trial. *Nutritional Neuroscience*, *25*(1), 54-63.
16. Chatzopoulos, G. S., Karakostas, P., Kavakloglou, S., Assimopoulou, A., Barmpalexis, P., & Tsalikis, L. (2022). Clinical Effectiveness of Herbal Oral Care Products in Periodontitis Patients: A Systematic Review. *International Journal of Environmental Research and Public Health*, *19*(16), 10061.
17. Chen, H., Wang, W., Yu, S., Wang, H., Tian, Z., & Zhu, S. (2022). Procyanidins and their therapeutic potential against oral diseases. *Molecules*, *27*(9), 2932.
18. Delimont, N. M., & Carlson, B. N. (2020). Prevention of dental caries by grape seed extract supplementation: a systematic review. *Nutrition and health*, *26*(1), 43-52
19. Silvan, J. M., Gutiérrez-Docio, A., Moreno-Fernandez, S., Alarcón-Cavero, T., Prodanov, M., & Martinez-Rodriguez, A. J. (2020). Procyanidin-rich extract from grape seeds as a putative tool against Helicobacter pylori. *Foods*, 9(10), 1370
20. Dasiman, R., Nor, N. M., Eshak, Z., Mutalip, S. S. M., Suwandi, N.R., & Bidin, H. (2022). A review of procyanidin: Updates on current bioactivities and potential health benefits. *Biointerface Res. Appl. Chem*, 12(5), 5918-5940.
21. Zhang, Z., Li, B. Y., Li, X. L., Cheng, M., Yu, F., Cai, Q., & Shen, L. (2013). Proteomic analysis of kidney and protective effects of grape seed procyanidin B2 in db/db mice indicate MFG-E8 as a key molecule in the development of diabetic nephropathy. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 1832(6), 805- 816.
22. Galarraga-Vinueza, M. E., Dohle, E., Ramanauskaite, A., Al-Maawi, S., Obreja, K., Magini, R., & Schwarz, F. (2020). Anti-inflammatory and macrophage polarization effects of Cranberry Proanthocyanidins (PACs) for periodontal and peri-implant disease therapy. *Journal of Periodontal Research*, *55*(6), 821-829.
23. Nawrot-Hadzik, I., Matkowski, A., Hadzik, J., Dobrowolska-Czopor, B., Olchowy, C., Dominiak, M., & Kubasiewicz-Ross, P. (2021). Proanthocyanidins and flavan-3-ols in the prevention and treatment of periodontitis—Antibacterial effects. *Nutrients*, *13*(1), 165.
24. Bunte, K., Hensel, A., & Beikler, T. (2019). Polyphenols in the prevention and treatment of periodontal disease: A systematic review of in vivo, ex vivo and in vitro studies. *Fitoterapia*, *132*, 30-39.
25. Yin, W., Li, B., Li, X., Yu, F., Cai, Q., Zhang, Z., & Gao, H. (2015). Anti- inflammatory effects of grape seed procyanidin B2 on a diabetic pancreas. *Food & Function*, *6*(9), 3065-3071.
26. Özden, F. O., Sakallioğlu, E. E., Sakallioğlu, U., Ayas, B., & Erişgin, Z. (2017). Effects of grape seed extract on periodontal disease: An experimental study in rats. *Journal of Applied Oral Science*, 25, 121-129.
27. Rayyan, M., Terkawi, T., Abdo, H., Abdel Azim, D., Khalaf, A., AlKhouli, Z.,& Abu Naim, H. (2018). Efficacy of grape seed extract gel in the treatment of chronic periodontitis: A randomized clinical study. *Journal of Investigative and Clinical Dentistry*, *9*(2), e12318.
28. Toker, H., Balci Yuce, H., Lektemur Alpan, A., Gevrek, F., & Elmastas, M. (2018). Morphometric and histopathological evaluation of the effect of grape seed roanthocyanidin on alveolar bone loss in experimental diabetes and periodontitis. *Journal of periodontal research*, *53*(3), 478-486.
29. Da Silva Júnior, F. L., de Araújo Silva, D. N., da Silva Azevedo, M.L., da Silva, N. T., Almeida, H. C., da Silva, R. C. M.,& de Aquino Martins, A. R. L. (2022). Efficacy of ILIB on periodontal clinical parameters and glycemic control in patients with periodontitis and type II diabetes—randomized clinical trial. *Lasers in Medical Science*, *37*(3), 1945-1952.
30. Cirelli, T., Nepomuceno, R., Rios, A. C. S., Orrico, S. R., Cirelli, J.A., Theodoro, L. H., & Scarel-Caminaga, R. M. (2020). Genetic polymorphisms in the Interleukins IL1B, IL4, and IL6 are associated with concomitant periodontitis and type 2 diabetes mellitus in Brazilian patients. *Journal of Periodontal Research*, *55*(6), 918-930.
31. Wang, Q. Q., Gao, H., Yuan, R., Han, S., Li, X. X., Tang, M., & Yang, S. (2020). Procyanidin A2, a polyphenolic compound, exerts anti-inflammatory and anti-oxidative activity in lipopolysaccharide-stimulated RAW264. 7 cells.