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SIRT1 As A Novel Therapeutic Target For Periodontitis: A Rapid Review

Faisal Kuswandani[1*], Felisha Febriane Balafif[2], Nuroh Najmi[3], Anggun Rafisa[4]

[1]Pharmacy, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia. [2]Microbiology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia. [3]Anatomy Pathology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia. [4]Physiology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia

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ABSTRACT

SIRT1 plays a pivotal role in regulating a multitude of biological processes, including cellular metabolism, aging, DNA repair, inflammation, and oxidative stress. evidence suggesting a potential association between SIRT1 activity and periodontal health including periodontitis. This article aims to explore the immunobiological functions of SIRT1 in the initiation and progression of periodontitis. This comprehensive review utilized the PubMed and Cochrane Library databases to collate studies from December 2024 to December 2024. Arround 53 studies were screened and 5 studies were deemed suitable for analyses. Evidence based revealed that, SIRT1 levels elevated after periodontal treatment and its involvement in anti-inflammatory pathways suggest its beneficial role in managing periodontitis. Conclussion, clinical studies shows that SIRT1's potential as a biomarker and therapeutic target. Elevated SIRT1 levels after periodontal treatment and its involvement in anti-inflammatory pathways suggest its beneficial role in managing periodontitis. However, Prospective studies are necessary to deepen our understanding of their role in the pathophysiology of periodontitis and their potential clinical applications.

Corresponding Author:
Faisal Kuswandani
Pharmacy, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia
faisal.kuswandani@unpad.ac.id

INTRODUCTION

Periodontal disease is a chronic inflammatory disorder of periodontal tissues, characterized by the progressive destruction of the supporting structures of the teeth, including the periodontal ligament and alveolar bone.(Correâ et al., 2018; Kriaučiūnas et al., 2022) The pathogenesis of periodontal disease is primarily caused by a complex of oral pathogens, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Prevotella intermedia*, which form organized biofilms. These biofilms, in turn, activate the host immune system, triggering an inflammatory response that leads to soft tissue inflammation, progressive loss of periodontal support structures, and, ultimately, tooth loss.(Dascalu et al., 2022; Tamaki et al., 2014; Yang et al., 2021) Effective management of inflammation to alleviate periodontal inflammation and prevent bone destruction is crucial in the treatment of periodontitis. (Ye et al., 2022)

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SIRT1 (Silent Information Regulator 2 Homolog 1) is a NAD+-dependent deacetylase that is widely expressed in various tissues.(Kriaučiūnas et al., 2022) It plays a pivotal role in regulating a multitude of biological processes, including cellular metabolism, aging, DNA repair, inflammation, and oxidative stress.(Sun et al., 2024) SIRT1 regulates inflammatory responses by modulating transcription factors including NF-κB and decreasing the generation of pro-inflammatory cytokines.(Sun et al., 2024) SIRT1, with its ability to inhibit inflammatory pathways, has been identified as a crucial modulator in the resolution of inflammation in periodontitis.(Caribé, Villar, Romito, Takada, et al., 2020a; Correâ et al., 2018; Tamaki et al., 2014)

Despite evidence suggesting a potential association between SIRT1 activity and periodontal health, a comprehensive analysis of its role in the pathophysiology of periodontitis remains lacking. This article aims to explore the immunobiological functions of SIRT1 in the initiation and progression of periodontitis, with the goal of elucidating its potential as a therapeutic target for future treatment strategies.

METHOD

This comprehensive review utilized the PubMed and Cochrane Library databases to collate studies from December 2024 to December 2024. This review were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(Moher et al., 2015a) Boolean operators and keywords (periodontitis or periodontal disease) AND ("Sirtuin 1," or "Sirt1," or "Silent Mating Type Information Regulation 2 Homolog 1,") used to identify studies and search of the literature.

The inclusion criteria for this studies were : [1] Patients diagnosed with periodontitis conditions along with a control group for comparison. [2] An observational study design. [3] Measurement of SIRT1 levels via laboratory methods, specifically using ELISA for detection. [4] The study must be published in English. Studies were excluded based on the following criteria: [1] Lack of necessary data for analysis. [2] Research involving animal subjects. [3] Reviews article. [4] Articles not composed in English. [7] Studies focusing on non-periodontitis conditions.

The literature compilation process was divided between two investigators, who extracted data from the selected studies separately and then cross-verified their findings. When disagreements emerged, a third investigator was consulted to arbitrate and obtain a resolution. The research procedure is briefly shown in Figure 1.

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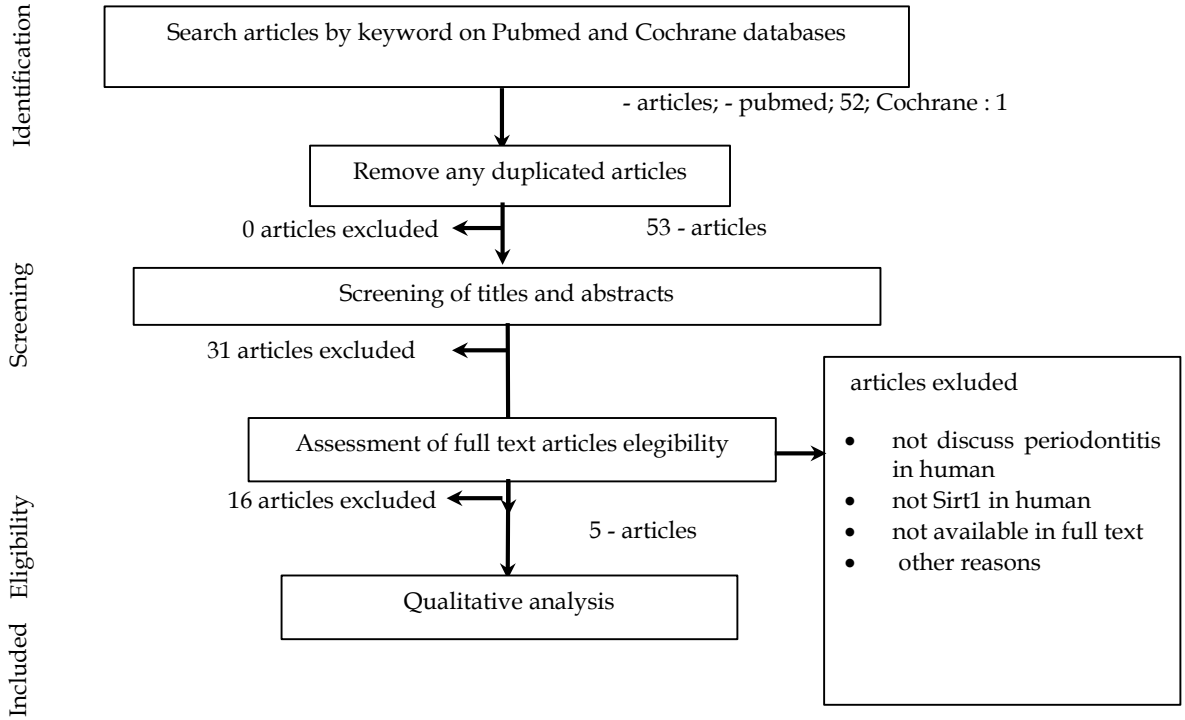

Figure 1 Flowchart of article search based on the PRISMA method(Moher et al., 2015b)

RESULT

Arround 53 studies were screened, from which 31 were excluded after a review of titles and abstracts due to duplication, irrelevance, or non-original research forms such as reviews and letters. This left 21 studies for detailed review. Ultimately, 5 studies were deemed suitable for analyses. The specifics of these studies are provided in table 1.

Table 1. Summary of the Results from Selected Article

No	Author	Study design	Treatment	Detail of patient, procedure, and evaluation	Important Result (conclusions)
1	Kriaučiūnas A, et al., 2022(Kriaučiūnas et al., 2022)	case-control study	Group 1 = 201 patient with periodontitis	Patients aged ≥ 18 years were included.	The genotypes and allele distributions of SIRT1 rs3818292 and rs7895833 were statistically significantly different between the
			Group 2 = 500 healty subject	Serum SIRT1 levels in patients from periferal venous blood were determined using the commercial enzyme-linked	

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No	Author	Study design	Treatment	Detail of patient, procedure, and evaluation	Important Result (conclusions)
				immunosorbent assay (ELISA) kit	periodontitis and the control group. SIRT1 serum levels of periodontitis patients is higher than control group subject but not statistically significantly (0.984 (5159) ng/mL vs. 0.514 (7705) ng/mL, p = 0.792)
2	Kudo, et al, 2018(Kudo et al., 2018)	case-control study	Group 1 = 34 periapical periodontitis patient Group 2 = 10 healty control group	Patients aged 20-74 years (13 males, 21 females) Control aged 20-57 (3 males, 7 females) Patient were treated endodontically for more than 6 month. Periapical lesional and healthy gingival tissues used for further analysis. Dual-colour immunofluorescence imaging was used to identify SIRT1 VEGF and VE-cadherin ßexpression	significantly elevated expression levels of SIRT1, VEGF, and VE-cadherin mRNA in periapical granulomas compared to healthy gingival tissues
3	Caribe, et al., 2020(Caribé, Villar, Romito,	prospective clinical trial	Group 1 = 40 periodontitis patient	Participant aged ≥ 45 years with at	Periodontal treatment was

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No	Author	Study design	Treatment	Detail of patient, procedure, and evaluation	Important Result (conclusions)
	Pacanaro, et al., 2020)		Group 2 = 38 healty control group	least 15 teeth were included. Patients in the periodontitis group underwent supra and subgingival mechanical scaling and root planing. also received 500 mg amoxicillin and 400 mg metronidazole three times a day for 14 days. Individual without periodontal disease did not receive any treatment. A 10 ml of blood from the peripheral vein was collected as a sample SIRT1 and MBL concentrations were determined in duplicate using an ELISA	associated with decreased serum concentrations of MBL and CRP and increased serum levels of SIRT1.
4	**Kluknavská, et al. 2021**(Kluknavská et al., 2021)	descriptive	Group 1 = 43 healty control group Group 2 = 17 gingivitis patient Group 3 = 23 chronic periodontitis patient Group 4 = 16 aggressive periodontitis patient	saliva collected between 7:00-9:00 Sirt1 concentration in saliva were determined by ELISA	SIRT-1 levels in the saliva of control and patient group showed no differences

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No	Author	Study design	Treatment	Detail of patient, procedure, and evaluation	Important Result (conclusions)
5	Caribe, et al., 2020(Caribé, Villar, Romito, Takada, et al., 2020b)	case-controlled studies	Group 1 = 20 healty control group Group 2 = 18 CAD patient Group 3 = 20 periodontitis patient Group 4 = 20 periodontitis patient + CAD	Participant aged 45-79 years (40 males, 38 females) Patients in the periodontitis group underwent supra and subgingival mechanical scaling and root planing. also received 500 mg amoxicillin and 400 mg metronidazole three times a day for 14 days. Individual without periodontal disease did not receive any treatment. A 10 ml of blood from the peripheral vein was collected as a sample Serum MBL and SIRT1 concentration were analyzed by ELISA	PD tretment increased MBL serum concentration and decreased SIRT1 serum concentration in control group. Conversely, PD tretment reduced MBL serum concentration and increased SIRT1 serum concentration in periodontitis patients with and without CAD and CAD patient without periodontitis

mannose binding lectin (MBL), coronary artery disease (CAD)

Discussion

Sirtuins modulate various cellular processes essential for maintaining homeostasis. They play an important role in counteracting oxidative stress and inflammation by regulating the expression and activation of downstream transcriptional factors, such as FOXO3a, Nrf2, and NF-κB, as well as antioxidant enzymes through epigenetic and post-translational modifications. Thereby sirtuin safeguarding cellular integrity in response to stress.(Pan et al., 2022) SIRT1 deacetylate FOXO3a, promoting the expression of genes associated with mitochondrial function, anti-apoptotic pathway, and oxidative stress resistance. Additionally, SIRT1 suppresses NF-κB signalling via deacetylating the p65 subunit at the K310 residue, which downregulates the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α (TNF-α). Moreover, SIRT1 modulates the AP-1

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transcription factor complex by interacting with c-Fos and c-Jun through its deacetylase activity, effectively downregulating cyclooxygenase-2 (COX-2) expression. This regulatory activity highlights the potential of SIRT1 as a therapeutic target in managing inflammatory conditions. Further investigations have identified a pivotal role for SIRT1, SIRT6, and SIRT7 in osteoblastogenesis and bone formation. Specifically, SIRT1 promotes the proliferation and differentiation of osteoblast progenitors through enhanced deacetylation of FOXO transcription factors. This activity underscores the significance of sirtuins in skeletal health and their potential in addressing bone-related pathologies.(Pan et al., 2022)

Clinical studies have also linked sirtuins to periodontal health. Research by Kriaučiūnas et al. revealed elevated serum levels of SIRT1 in patients with periodontitis compared to controls, although the difference was not statistically significant. The average SIRT1 serum level was 0.984 ng/mL in periodontitis patients versus 0.514 ng/mL in healthy individuals. Moreover, the SIRT1 rs3818292 AA and rs7895833 AA genotypes were significantly less frequent in the periodontitis group, suggesting a potential genetic association between SIRT1 and periodontal disease.(Kriaučiūnas et al., 2022)

In another study, SIRT1 was implicated in the AMPK/SIRT1/NF-κB signaling pathway, influencing glycolysis regulation and macrophage pyroptosis during bacterial infection in periodontal tissues. Glycolysis is an essential metabolic phase in bacterial infection that modulates pyroptosis activity, including macrophages as the most common immune cell during periodontal infection. Whereas, macrophage is important in the periodontitis resolution of infected periodontal tissue. (He et al., 2023) Glycolysis suppression mediated by SIRT1 activation via the AMP-activated protein kinase (AMPK) pathway inhibited macrophage pyroptosis and reduced the expression of pro-inflammatory cytokines, such as IL-1β and TNF-α, thereby mitigating periodontal tissue destruction. These findings emphasize the anti-inflammatory and cytoprotective roles of SIRT1 in periodontal disease resolution.(Chin et al., 2016)

Moreover, studies by Kudo et al. demonstrated significantly elevated expression levels of SIRT1, VEGF, and VE-cadherin mRNA in periapical granulomas compared to healthy gingival tissues. The fact that the patient with periapical granulomas has been receiving endodontic treatment for the previous six months may have an impact on this outcome. Treatment with resveratrol, a known SIRT1 activator, further enhanced SIRT1, VEGF, and VE-cadherin expression in human umbilical vein endothelial cells (HUVECs). This suggests that SIRT1 may promote angiogenesis in periapical granulomas by stimulating endothelial cell proliferation and VEGF/VE-cadherin expression, highlighting its role in wound healing and tissue regeneration. VEGF stimulates endothelial cell proliferation, differentiation, migration, and angiogenesis. While, angiogenesis is important in wound healing.(Kudo et al., 2018)

Research by Caribe et al. corroborated these findings by demonstrating a significant increase in SIRT1 levels following periodontal treatment. SIRT1 concentrations rose from 1.06 ± 1.03 ng/mL to 1.66 ± 1.64 ng/mL ($p < 0.001$) post-treatment, suggesting a beneficial role for SIRT1 in inflammation resolution and oxidative stress reduction during periodontal healing.(Caribé, Villar, Romito, Pacanaro, et al., 2020) SIRT1 activation has been shown to suppress the expression of pro-inflammatory cytokines, such as IL-1β and TNF-α, by

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downregulates Nf-KB activity as key mediators to the inflammatory response.(Chin et al., 2016; Sun et al., 2024)

These outcomes are further supported by studies examining scaling and root planing treatments, which consistently showed elevated SIRT1 levels in patients with and without coronary artery disease (CAD) after periodontal treatment. Collectively, these findings highlight the therapeutic potential of SIRT1 activation in managing periodontal diseases and enhancing systemic health.(Caribé, Villar, Romito, Takada, et al., 2020b)

Conversely, Kluknavská and collegues study reported no significant differences between SIRT-1 level in the saliva of control groups compared to patients with gingivitis, chronic periodontitis, and aggressive periodontitis. This discrepancy may be attributed to the intracellular localization of SIRT1, which might limit its detectability in saliva. These findings underscore the need for additional research to clarify the role of SIRT1 in periodontal disease pathogenesis. (Kluknavská et al., 2021)

Further long-term and prospective studies are essential to investigate the dynamic changes in SIRT1 and other related biomarkers, as well as their prognostic and therapeutic implications in periodontal disease. These studies should address limitations such as small sample sizes and focus on elucidating the molecular mechanisms underlying the involvement of sirtuins in periodontal health and disease.

CONCLUSSION

Clinical studies shows that SIRT1's potential as a biomarker and therapeutic target. Elevated SIRT1 levels after periodontal treatment and its involvement in anti-inflammatory pathways suggest its beneficial role in managing periodontitis. However, Prospective studies are necessary to deepen our understanding of their role in the pathophysiology of periodontitis and their potential clinical applications.

REFERENCE

Caribé, P. M. V., Villar, C. C., Romito, G. A., Pacanaro, A. P., Strunz, C. M. C., Takada, J. Y., Cesar, L. A. M., & Mansur, A. de P. (2020). Influence of the treatment of periodontal disease in serum concentration of sirtuin 1 and mannose-binding lectin. *Journal of Periodontology*, *91*(7), 900–905. https://doi.org/10.1002/JPER.19-0236

Caribé, P. M. V., Villar, C. C., Romito, G. A., Takada, J. Y., Pacanaro, A. P., Strunz, C. M. C., César, L. A. M., & Mansur, A. de P. (2020a). Prospective, case-controlled study evaluating serum concentration of sirtuin-1 and mannose-binding lectin in patients with and without periodontal and coronary artery disease. *Therapeutic Advances in Chronic Disease*, *11*, 2040622320919621. https://doi.org/10.1177/2040622320919621

Chin, Y. T., Hsieh, M. T., Lin, C. Y., Kuo, P. J., Yang, Y. C. S. H., Shih, Y. J., Lai, H. Y., Cheng, G. Y., Tang, H. Y., Lee, C. C., Lee, S. Y., Wang, C. C., Lin, H. Y., Fu, E., Whang-Peng, J., & Liu, L. F. (2016). 2,3,5,4'-Tetrahydroxystilbene-2-O-β-glucoside Isolated from Polygoni Multiflori Ameliorates the Development of Periodontitis. *Mediators of Inflammation*, *2016*, 6953459. https://doi.org/10.1155/2016/6953459

Correâ, M. G., Pires, P. R., Ribeiro, F. V., Pimentel, S. P., Cirano, F. R., Napimoga, M. H., Casati, M. Z., & Casarin, R. C. V. (2018). Systemic treatment with resveratrol reduces the progression of experimental periodontitis and arthritis in rats. *PLoS ONE*, *13*(10), e0204414. https://doi.org/10.1371/JOURNAL.PONE.0204414

Dascalu, L. M., Moldovan, M., Sarosi, C., Sava, S., Dreanca, A., Repciuc, C., Purdoiu, R., Nagy, A., Badea, M. E., Paun, A. G., Badea, I. C., & Chifor, R. (2022). Photodynamic Therapy with Natural Photosensitizers in the Management of Periodontal Disease Induced in Rats. *Gels 2022, Vol. 8, Page 134*, *8*(2), 134. https://doi.org/10.3390/GELS8020134

He, Y., Wang, Y., Jia, X., Li, Y., Yang, Y., Pan, L., Zhao, R., Han, Y., Wang, F., Guan, X., & Hou, T. (2023). Glycolytic reprogramming controls periodontitis-associated macrophage pyroptosis via AMPK/SIRT1/NF-κB signaling pathway. *International Immunopharmacology*, *119*. https://doi.org/10.1016/J.INTIMP.2023.110192

Kluknavská, J., Krajčíková, K., Bolerázska, B., Mašlanková, J., Ohlasová, J., Timková, S., Drotárová, Z., & Vašková, J. (2021). Possible prognostic biomarkers of periodontitis in saliva. *European Review for Medical and Pharmacological Sciences*, *25*(8), 3154–3161. https://doi.org/10.26355/EURREV_202104_25724

Kudo, H., Takeichi, O., Hatori, K., Makino, K., Himi, K., & Ogiso, B. (2018). A potential role for the silent information regulator 2 homologue 1 (SIRT1) in periapical periodontitis. *International Endodontic Journal*, *51*(7), 747–757. https://doi.org/10.1111/IEJ.12894

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., & Stewart, L. A. (2015a). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*(1), 1–9. https://doi.org/10.1186/2046-4053-4-1

Pan, Z., Dong, H., Huang, N., & Fang, J. (2022). Oxidative stress and inflammation regulation of sirtuins: New insights into common oral diseases. *Frontiers in Physiology*, *13*. https://doi.org/10.3389/FPHYS.2022.953078

Sun, H., Li, D., Wei, C., Liu, L., Xin, Z., Gao, H., & Gao, R. (2024). The relationship between SIRT1 and inflammation: a systematic review and meta-analysis. *Frontiers in Immunology*, *15*, 1465849. https://doi.org/10.3389/FIMMU.2024.1465849/BIBTEX

Tamaki, N., Cristina Orihuela-Campos, R., Inagaki, Y., Fukui, M., Nagata, T., & Ito, H. O. (2014). Resveratrol improves oxidative stress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defense pathways in a rat periodontitis model. *Free Radical Biology & Medicine*, *75*, 222–229. https://doi.org/10.1016/J.FREERADBIOMED.2014.07.034

Yang, B., Pang, X., Li, Z., Chen, Z., & Wang, Y. (2021). Immunomodulation in the Treatment of Periodontitis: Progress and Perspectives. *Frontiers in Immunology*, *12*, 781378. https://doi.org/10.3389/FIMMU.2021.781378/BIBTEX

Ye, Q., Xu, H., Liu, S., Li, Z., Zhou, J., Ding, F., Zhang, X., Wang, Y., Jin, Y., & Wang, Q. (2022). Apoptotic extracellular vesicles alleviate Pg-LPS induced inflammatory responses of macrophages via AMPK/SIRT1/NF-κB pathway and inhibit osteoclast formation. *Journal of Periodontology*, *93*(11), 1738–1751. https://doi.org/10.1002/JPER.21-0657

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