BUKTI KORESPONDENSI
ARTIKEL JURNAL NASIONAL BEREPUTASI

Judul Artikel	:	Exploring IL-1β and IL-17 in Periodontitis-Associated Oral Aging Pathways
Jurnal	:	Sound of Dentistry, 2024, Volume 9 | No.2 | Maret 2025 | https://doi.org/10.28932/sod.v9i2.11446
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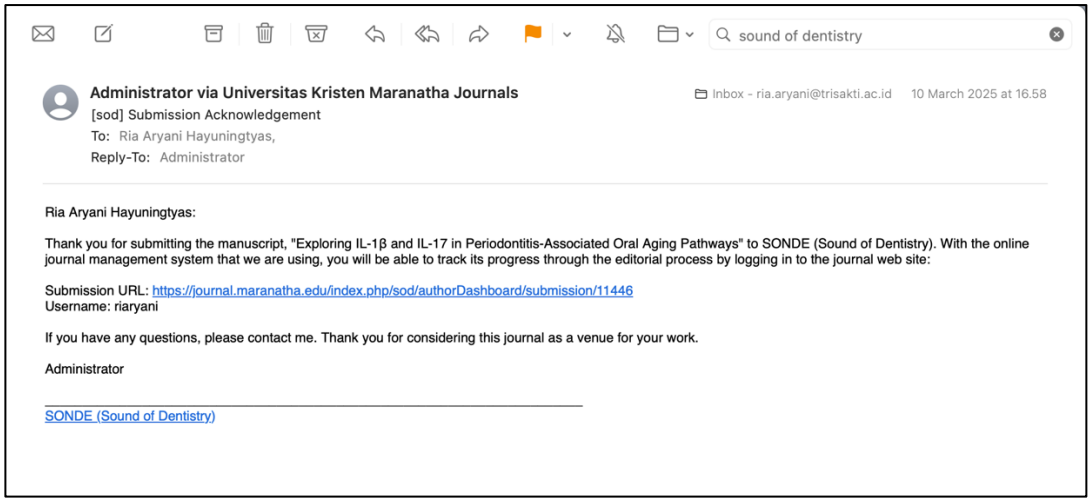
NO	PERIHAL	TANGGAL
1	Bukti pengajuan artikel	10 Maret 2025
2	Bukti permintaan revisi artikel	10 Maret 2025
3	Bukti pengiriman hasil revisi artikel	24 Maret 2025
4	Bukti artikel terpublikasi online	25 Maret 2025

1. Bukti pengajuan artikel – 10 Maret 2025



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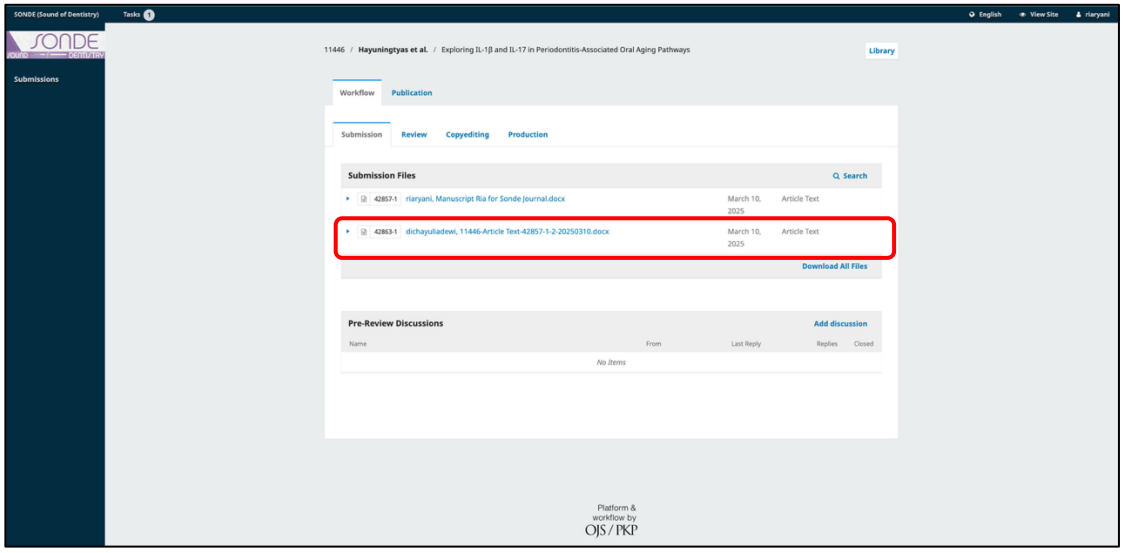
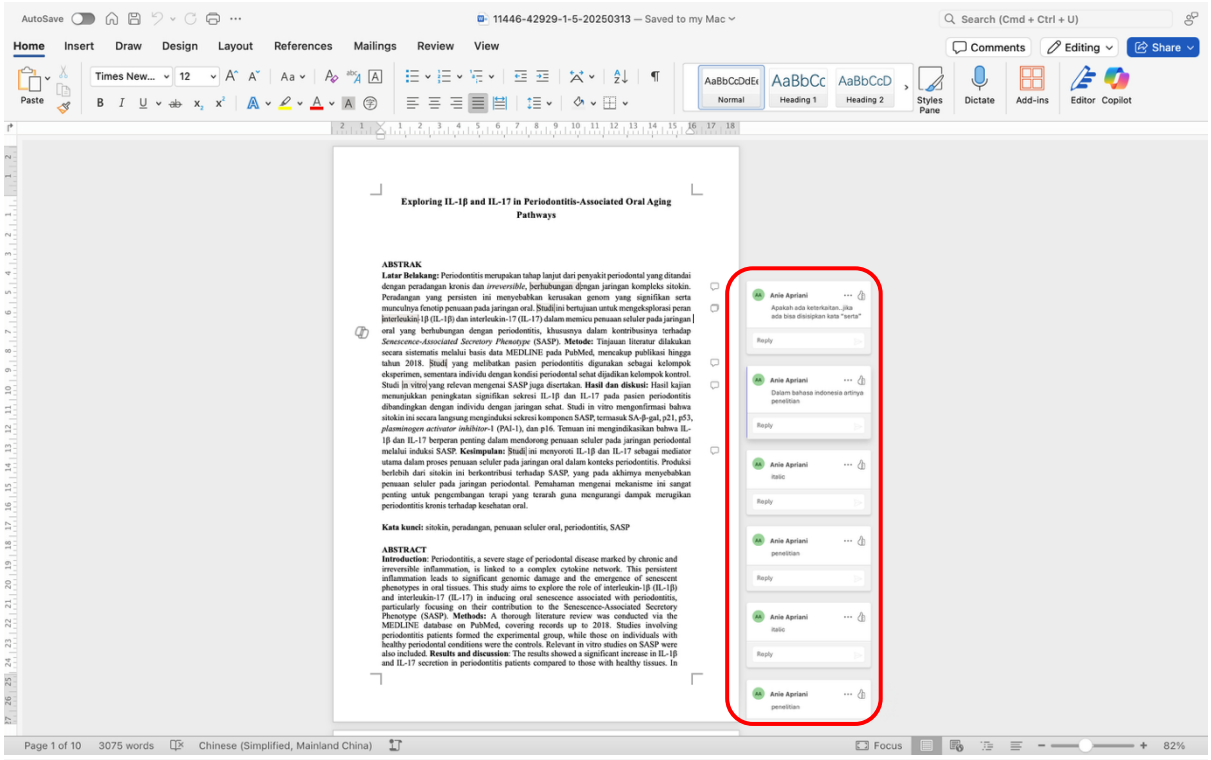




Exploring IL-1β and IL-17 in Periodontitis-Associated Oral Aging Pathways

ABSTRAK

Latar Belakang: Periodontitis merupakan tahap lanjut dari penyakit periodontal yang ditandai dengan peradangan kronis dan *irreversible*, berhubungan dengan jaringan kompleks sitokin. Peradangan yang persisten ini menyebabkan kerusakan genom yang signifikan serta munculnya fenotip penuaan pada jaringan oral. Studi ini bertujuan untuk mengeksplorasi peran interleukin-1β (IL-1β) dan interleukin-17 (IL-17) dalam memicu penuaan seluler pada jaringan oral yang berhubungan dengan periodontitis, khususnya dalam kontribusinya terhadap *Senescence-Associated Secretory Phenotype* (SASP). **Metode:** Tinjauan literatur dilakukan secara sistematis melalui basis data MEDLINE pada PubMed, mencakup publikasi hingga tahun 2018. Studi yang melibatkan pasien periodontitis digunakan sebagai kelompok eksperimen, sementara individu dengan kondisi periodontal sehat dijadikan kelompok kontrol. Studi in vitro yang relevan mengenai SASP juga disertakan. **Hasil dan diskusi:** Hasil kajian menunjukkan peningkatan signifikan sekresi IL-1β dan IL-17 pada pasien periodontitis dibandingkan dengan individu dengan jaringan sehat. Studi in vitro mengonfirmasi bahwa sitokin ini secara langsung menginduksi sekresi komponen SASP, termasuk SA-β-gal, p21, p53, *plasminogen activator inhibitor*-1 (PAI-1), dan p16. Temuan ini mengindikasikan bahwa IL-1β dan IL-17 berperan penting dalam mendorong penuaan seluler pada jaringan periodontal melalui induksi SASP. **Kesimpulan:** Studi ini menyoroti IL-1β dan IL-17 sebagai mediator utama dalam proses penuaan seluler pada jaringan oral dalam konteks periodontitis. Produksi berlebih dari sitokin ini berkontribusi terhadap SASP, yang pada akhirnya menyebabkan penuaan seluler pada jaringan periodontal. Pemahaman mengenai mekanisme ini sangat penting untuk pengembangan terapi yang terarah guna menguranggi dampak merugikan periodontitis kronis terhadap kesehatan oral.

Kata kunci: sitokin, peradangan, penuaan seluler oral, periodontitis, SASP

ABSTRACT

Introduction: Periodontitis, a severe stage of periodontal disease marked by chronic and irreversible inflammation, is linked to a complex cytokine network. This persistent inflammation leads to significant genomic damage and the emergence of senescent phenotypes in oral tissues. This study aims to explore the role of interleukin-1β (IL-1β) and interleukin-17 (IL-17) in inducing oral senescence associated with periodontitis, particularly focusing on their contribution to the Senescence-Associated Secretory Phenotype (SASP). **Methods:** A thorough literature review was conducted via the MEDLINE database on PubMed, covering records up to 2018. Studies involving periodontitis patients formed the experimental group, while those on individuals with healthy periodontal conditions were the controls. Relevant in vitro studies on SASP were also included. **Results and discussion**: The results showed a significant increase in IL-1β and IL-17 secretion in periodontitis patients compared to those with healthy tissues. In vitro studies confirmed that these cytokines directly induce the secretion of SASP components, including SA-β-gal, p21, p53, plasminogen activator inhibitor-1 (PAI-1), and p16. These findings suggest that IL-1β and IL-17 play a critical role in promoting cellular senescence in periodontal tissues by inducing SASP. **Conclusion**: This study highlights IL-1β and IL-17 as key mediators in oral senescence within the context of periodontitis. Their excessive production contributes to SASP, leading to cellular senescence in periodontal tissues. Understanding these mechanisms is crucial for developing targeted therapies to mitigate the detrimental effects of chronic periodontitis on oral health.

Keywords: cytokines, inflammation, oral senescence, periodontitis, SASP

INTRODUCTION

Periodontitis, initially a disease of the gingival tissue, can progress to deeper tissues if untreated, disrupting bone homeostasis and ultimately leading to tooth loss.[1] The development and progression of periodontitis are influenced by a combination of genetic predispositions, as well as environmental and behavioral factors.[2] In Indonesia, the 2018 Basic Health Research (Riskesdas) report revealed a notably high prevalence of periodontitis, affecting 74.1% of the population, with the highest rates observed among preelderly individuals (77.8%) and a gradual decline in prevalence among the elderly (66.0%).[3] Despite this decrease, elderly individuals remain particularly vulnerable to chronic inflammatory conditions, including periodontitis. This increased susceptibility in the elderly may be attributed to their prolonged exposure to periodontal pathogens, alongside alterations in the immuno-inflammatory status of their periodontal tissues.[4]

Periodontal disease arises from intricate interactions between pathogenic subgingival biofilm and the host's immune-inflammatory responses. A few key periopathogens, including *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*, are closely linked to periodontitis progression.[5] As periodontal pockets deepen, the microbiome becomes more diverse, dominated by Gram-negative anaerobes that produce virulence factors—such as fimbriae, LPS, proteinases, and enzymes—triggering strong immune responses and inflammatory mediator release. In advanced disease stages, immune cells contribute to a cytokine-rich environment, with cytokines like TNF-α, IL-1, IL-4, and IL-17 driving chronic inflammation.[6] Gingival fibroblasts, under these conditions, increase the secretion of enzymes and pro-inflammatory proteins, contributing to tissue destruction and bone resorption. IL-1β, the first cytokine specifically measured in chronic periodontitis, and IL-17, produced by Th17 cells, play critical roles in the immunopathogenesis of periodontitis.[7]

In individuals over 65, the risk of periodontitis is up to seven times higher than in adults aged 30 to 34, with its prevalence increasing among those aged 70 to 81 as the elderly population expands.[8] Aging is strongly associated with heightened susceptibility to periodontal disease, and recent research has identified periodontal pathogens as key factors in the etiology of Alzheimer's Disease (AD).[9] These pathogens not only contribute to periodontitis but are also linked to increased risks of diabetes, atherosclerosis, cardiovascular events, and cognitive decline. A cohort study revealed that patients with chronic periodontitis for over 10 years had a higher risk of developing AD and greater prevalence of comorbidities compared to those without periodontitis.[10] Additionally, severe periodontitis was associated with a higher incidence of mild cognitive impairment over a 5-year period in a community-dwelling population.[11]

Building on the established connection between periodontitis and systemic conditions, this paper aims to identify inflammatory markers associated with periodontitis that correlate with aging and dementia. Aging and dementia are characterized by the production of the Senescence-Associated Secretory Phenotype (SASP), a set of pro-inflammatory cytokines and related factors that contribute to cellular senescence. By elucidating the relationship between periodontal inflammation and the generation of SASP, this study seeks to uncover potential biomarkers linking periodontal disease with neurodegenerative processes. These findings could

inform future therapeutic strategies, where targeting specific cytokines and effectively managing periodontitis may serve as a preventative measure against the onset of dementia.

METHODS

A comprehensive literature review was conducted using the MEDLINE database on PubMed, covering studies published up to 2018. The selection criteria included research involving periodontitis patients, who were classified as the experimental group, while individuals with healthy periodontal conditions served as the control group. Relevant in vitro studies on the Senescence-Associated Secretory Phenotype (SASP) were also included to explore the molecular mechanisms underlying cellular senescence in periodontal tissues. The search strategy incorporated keywords such as "periodontitis," "IL-1β," "IL-17," "cellular senescence," and "SASP." Studies were screened based on their relevance to the role of inflammatory cytokines in periodontitis-induced cellular senescence. Data extraction focused on cytokine levels in patient samples, as well as experimental results from in vitro models assessing the effects of IL-1β and IL-17 on senescence markers, including SA-β-Gal, p21, p53, plasminogen activator inhibitor-1 (PAI-1), and p16. Statistical comparisons between cytokine levels in periodontitis patients and healthy controls were analyzed from the included studies. This methodological approach provided a comprehensive understanding of the contribution of IL-1β and IL-17 to periodontal inflammation and their potential role in cellular senescence.

RESULTS

The literature review identified key studies examining the relationship between periodontitis and cellular senescence. Research involving periodontitis patients, serving as the experimental group, was compared with data from individuals with healthy periodontal conditions. Additionally, in vitro studies on the Senescence-Associated Secretory Phenotype (SASP) were analyzed to explore the molecular mechanisms underlying inflammation-driven senescence. The findings demonstrated a notable increase in IL-1β and IL-17 levels in periodontitis patients, supporting their role in promoting cellular aging. In vitro studies further confirmed that exposure to these cytokines led to an upregulation of senescence markers, including SA-β-Gal, p21, p53, plasminogen activator inhibitor-1 (PAI-1), and p16. The combination of clinical and laboratory data provided a comprehensive understanding of the link between periodontal inflammation, aging, and neurodegenerative conditions, highlighting the potential systemic impact of chronic periodontitis. The methodological approach used in this study is illustrated in Figure 1.

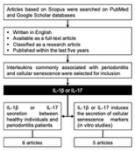


Figure 1. Methodological Approach for Literature Review on Periodontitis and Senescence-Associated Secretory Phenotype (SASP)

The results of cytokine secretion studies comparing periodontitis patients to healthy individuals are summarized in Table 1. Aleksandrowicz et al. (2021) reported IL-1β levels of 16.90 ± 18.65 pg/mL in healthy individuals and 61.04 ± 41.41 pg/mL in periodontitis patients (n = 189).[12] Al-Taweel et al. (2021) found higher concentrations, with healthy controls at 585.11 ± 53.19 pg/mL and periodontitis patients at 1356.38 ± 132.98 pg/mL (n = 80).[13] Kim et al. (2021) observed IL-1β levels of 94.55 ± 96.93 pg/mL in healthy subjects compared to 216.98 ± 180.81 pg/mL in 33 periodontitis patients.[14] For IL-17, Kaczynski et al. (2019) reported levels of 12.64 ± 28.28 pg/mL in healthy individuals and 49.43 ± 75.40 pg/mL in 106 periodontitis patients.[15] Wankhede et al. (2022) found lower levels, with healthy controls at 0.64 ± 0.23 pg/mL and periodontitis patients at 1.96 ± 1.71 pg/mL (n = 45).[16] Kalate et al. (2018) reported IL-17 concentrations of 38.18 ± 11.23 pg/mL in healthy controls and 53.46 ± 45 pg/mL in 69 periodontitis patients.[17] These results highlight a significant increase in IL-1β levels in periodontitis and variable changes in IL-17, reflecting the disease's inflammatory nature.

Table 1. Comparative Analysis of Cytokine Secretion Levels in Healthy and Periodontitis Patients. **(A)** IL-1β Secretion Levels. **(B)** IL-17 Secretion Levels

A

Article	Number of Subjects	IL-1β Secretion (pg/mL)	
		Healthy Individuals	Periodontitis Patients
Aleksandrowicz et al., 2021	189	16.90 ± 18.65	61.04 ± 41.41
Al-Taweel et al., 2021	80	585.11 ± 53.19	1356.38 ± 132.98
Kim et al., 2021	33	94.55 ± 96.93	216.98 ± 180.81

B

Article	Number of Subjects	IL-17 Secretion (pg/mL)	
		Healthy Individuals	Periodontitis Patients
Kaczynski et al., 2019	106	12.64 ± 28.28	49.43 ± 75.40
Wankhede et al., 2022	45	0.64 ± 0.23	1.96 ± 1.71
Kalate et al., 2018	69	38.18 ± 11.23	53.46 ± 45

The findings from multiple in vitro studies, as detailed in Table 2, demonstrate the effects of IL-1β and IL-17 administration on cellular senescence markers in various cell lines. Huang et al. (2021) demonstrated that treating C28/I2 cells with IL-1β (10 ng/mL) significantly increased the expression of senescence markers, with SA-β-Gal-positive cells rising from 0.99 ± 0.12 to 3.19 ± 0.33, PAI-1 levels from 0.99 ± 0.09 to 2.79 ± 0.20, and p21 from 1.01 ± 0.09 to 2.49 ± 0.27.[18] In a separate study, Huang et al. (2022) found that IL-1β administration in HNPC cells elevated SA-β-Gal positivity from 7.18 ± 0.21% to 27.46 ± 1.06%, p16 levels from 0.97 ± 0.05 to 2.51 ± 0.39, and p53 from 0.97 ± 0.06 to 3.54 ± 0.39.[19] Zhao et al. (2021) reported similar findings in hVSMCs, with SA-β-Gal increasing from 0.99 ± 0.11 to 3.10 ± 0.33, p16 from 1.01 ± 0.10 to 2.59 ± 0.30, and p21 from 1.00 ± 0.10 to 2.87 ± 0.35.[20]

Regarding IL-17, Wang et al. (2021) observed a substantial rise in SA-β-Gal-positive ATDC5 cells from 1.01 ± 0.10 to 3.69 ± 0.39, and p21 levels from 24.81 ± 7.52 to 77.44 ± 8.27 after treatment with 10 ng/mL IL-17.[21] Similarly, Zhang et al. (2021) demonstrated that IL-17A (5 ng/mL) markedly increased SA-β-Gal positivity in MAECs from 5.23 ± 4.58% to 71.90 ± 13.73%, along with a rise in p53 from 17.01 ± 1.84 to 30.80 ± 3.22 and p21 from 17.77 ± 1.65 to 36.78 ± 2.48.[22] These results collectively highlight the strong pro-senescence effects of IL-1β and IL-17 across various cell types, underscoring their potential role in driving cellular senescence.

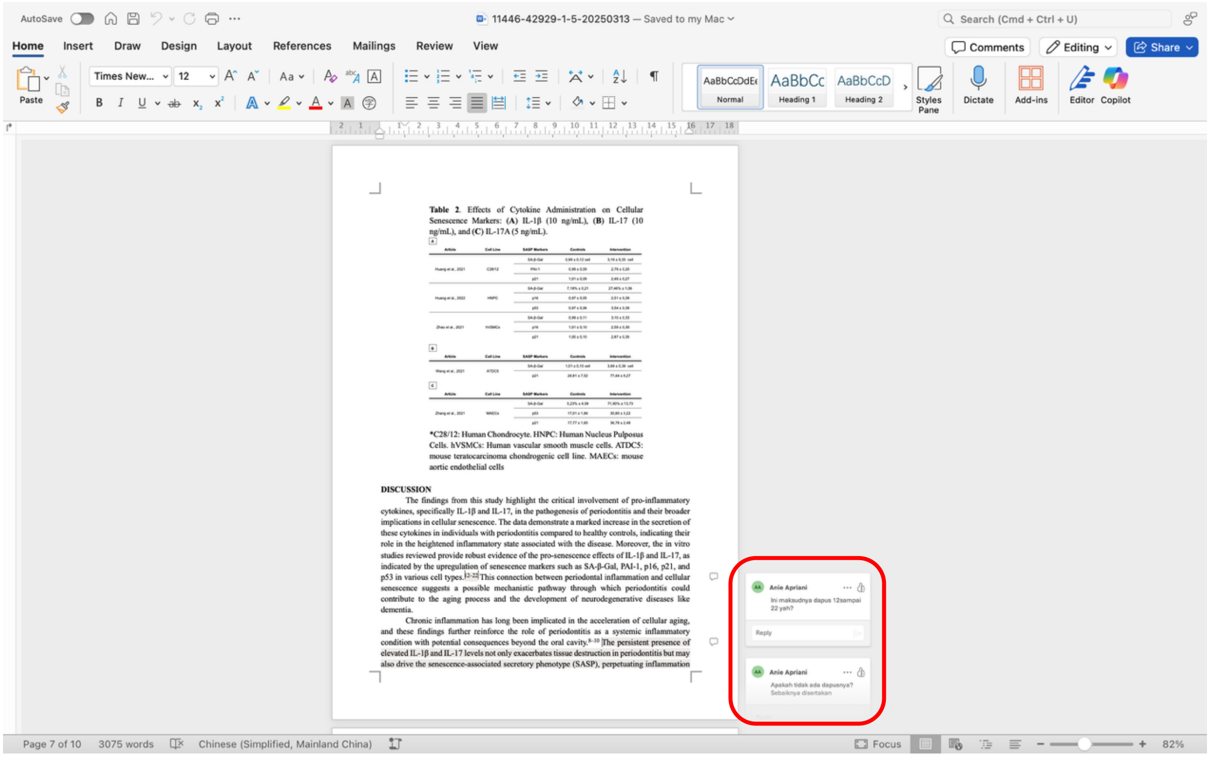


Table 2. Effects of Cytokine Administration on Cellular Senescence Markers: (**A**) IL-1β (10 ng/mL), (**B**) IL-17 (10 ng/mL), and (**C**) IL-17A (5 ng/mL).

A

Article	Cell Line	SASP Markers	Controls	Intervention
Huang et al., 2021	C28/12	SA-β-Gal	0,99 ± 0,12 cell	3,19 ± 0,33 cell
		PAI-1	0,99 ± 0,09	2,79 ± 0,20
		p21	1,01 ± 0,09	2,49 ± 0,27
Huang et al., 2022	HNPC	SA-β-Gal	7,18% ± 0,21	27,46% ± 1,06
		p16	0,97 ± 0,05	2,51 ± 0,39
		p53	0,97 ± 0,06	3,54 ± 0,39
Zhao et al., 2021	hVSMCs	SA-β-Gal	0,99 ± 0,11	3,10 ± 0,33
		p16	1,01 ± 0,10	2,59 ± 0,30
		p21	1,00 ± 0,10	2,87 ± 0,35

B

Article	Cell Line	SASP Markers	Controls	Intervention
Wang et al., 2021	ATDC5	SA-β-Gal	1,01 ± 0,10 cell	3,69 ± 0,39 cell
		p21	24,81 ± 7,52	77,44 ± 6,27

C

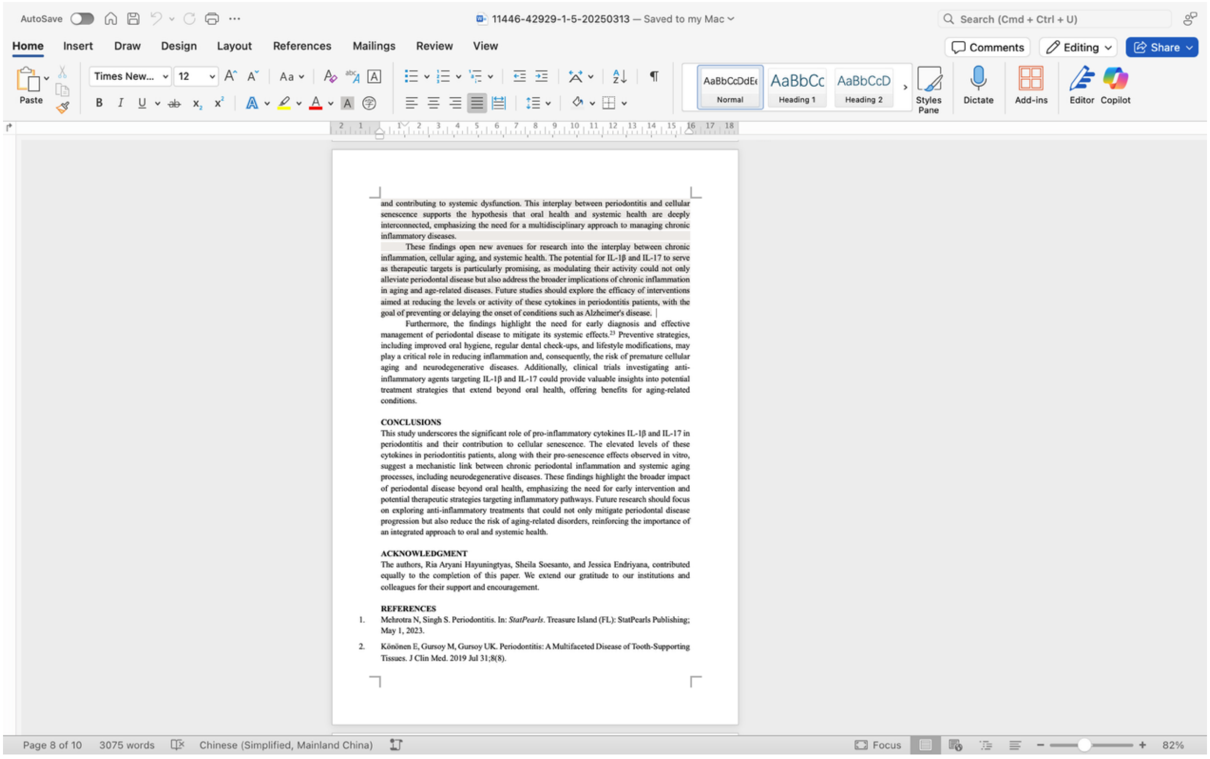
Article	Cell Line	SASP Markers	Controls	Intervention
Zhang et al., 2021	MAECs	SA-β-Gal	5,23% ± 4,58	71,90% ± 13,73
		p53	17,01 ± 1,86	30,80 ± 3,22
		p21	17,77 ± 1,65	36,78 ± 2,48

*C28/12: Human Chondrocyte. HNPC: Human Nucleus Pulposus Cells. hVSMCs: Human vascular smooth muscle cells. ATDC5: mouse teratocarcinoma chondrogenic cell line. MAECs: mouse aortic endothelial cells

DISCUSSION

The findings from this study highlight the critical involvement of pro-inflammatory cytokines, specifically IL-1β and IL-17, in the pathogenesis of periodontitis and their broader implications in cellular senescence. The data demonstrate a marked increase in the secretion of these cytokines in individuals with periodontitis compared to healthy controls, indicating their role in the heightened inflammatory state associated with the disease. Moreover, the in vitro studies reviewed provide robust evidence of the pro-senescence effects of IL-1β and IL-17, as indicated by the upregulation of senescence markers such as SA-β-Gal, PAI-1, p16, p21, and p53 in various cell types.[12-22] This connection between periodontal inflammation and cellular senescence suggests a possible mechanistic pathway through which periodontitis could contribute to the aging process and the development of neurodegenerative diseases like dementia.

Chronic inflammation has long been implicated in the acceleration of cellular aging, and these findings further reinforce the role of periodontitis as a systemic inflammatory condition with potential consequences beyond the oral cavity.[8-10] The persistent presence of elevated IL-1β and IL-17 levels not only exacerbates tissue destruction in periodontitis but may also drive the senescence-associated secretory phenotype (SASP), perpetuating inflammation



and contributing to systemic dysfunction. This interplay between periodontitis and cellular senescence supports the hypothesis that oral health and systemic health are deeply interconnected, emphasizing the need for a multidisciplinary approach to managing chronic inflammatory diseases.

These findings open new avenues for research into the interplay between chronic inflammation, cellular aging, and systemic health. The potential for IL-1β and IL-17 to serve as therapeutic targets is particularly promising, as modulating their activity could not only alleviate periodontal disease but also address the broader implications of chronic inflammation in aging and age-related diseases. Future studies should explore the efficacy of interventions aimed at reducing the levels or activity of these cytokines in periodontitis patients, with the goal of preventing or delaying the onset of conditions such as Alzheimer's disease.

Furthermore, the findings highlight the need for early diagnosis and effective management of periodontal disease to mitigate its systemic effects.[23] Preventive strategies, including improved oral hygiene, regular dental check-ups, and lifestyle modifications, may play a critical role in reducing inflammation and, consequently, the risk of premature cellular aging and neurodegenerative diseases. Additionally, clinical trials investigating anti-inflammatory agents targeting IL-1β and IL-17 could provide valuable insights into potential treatment strategies that extend beyond oral health, offering benefits for aging-related conditions.

CONCLUSIONS

This study underscores the significant role of pro-inflammatory cytokines IL-1β and IL-17 in periodontitis and their contribution to cellular senescence. The elevated levels of these cytokines in periodontitis patients, along with their pro-senescence effects observed in vitro, suggest a mechanistic link between chronic periodontal inflammation and systemic aging processes, including neurodegenerative diseases. These findings highlight the broader impact of periodontal disease beyond oral health, emphasizing the need for early intervention and potential therapeutic strategies targeting inflammatory pathways. Future research should focus on exploring anti-inflammatory treatments that could not only mitigate periodontal disease progression but also reduce the risk of aging-related disorders, reinforcing the importance of an integrated approach to oral and systemic health.

ACKNOWLEDGMENT

The authors, Ria Aryani Hayuningtyas, Sheila Soesanto, and Jessica Endriyana, contributed equally to the completion of this paper. We extend our gratitude to our institutions and colleagues for their support and encouragement.

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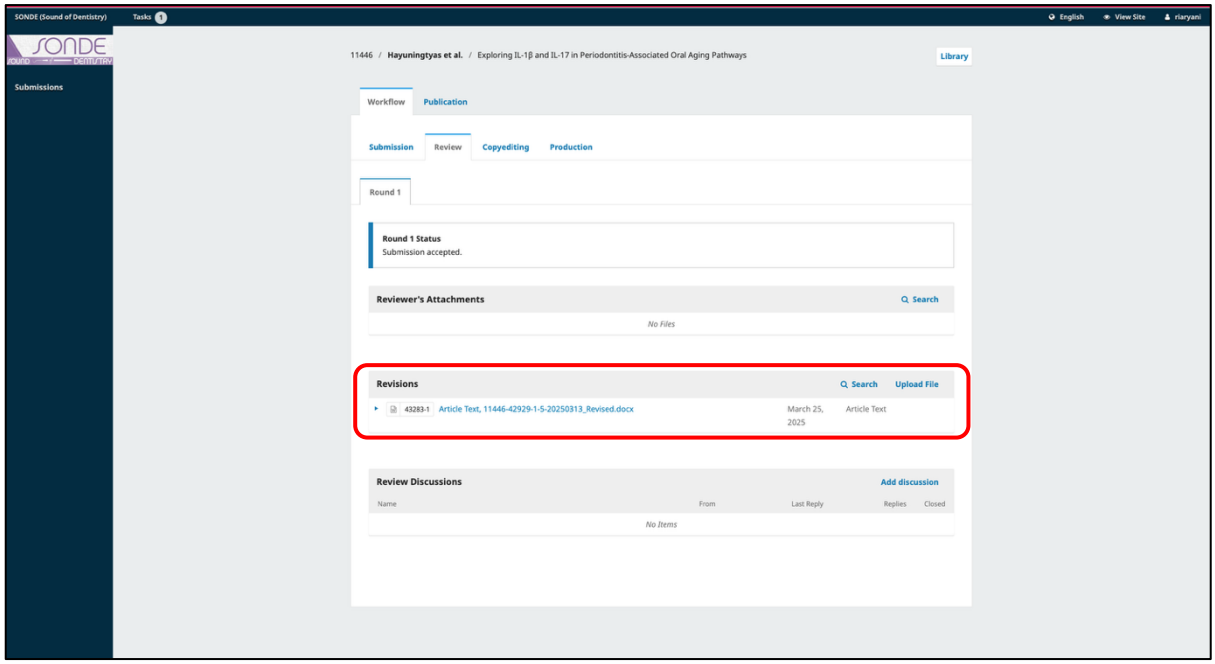
3. Bukti pengiriman hasil revisi artikel – 24 Maret 2025



4. Bukti artikel terpublikasi online – 25 Maret 2025