Antimicrobial and anti-inflammatory properties of methyl palmitate and hexadecenoid acid in oral diseases

Sifat antimikroba dan antiinflamasi metil palmitat dan asam heksadekenoat dalam penyakit mulut

[1]Asmawati Amin, [2]Bahruddin Thalib, [3]Adilah Zahirah Fitri Djerman, [4]Dian Mentari Putri
[1,3,4]Department of Oral Biology
[2]Department of Prosthodontics
Faculty of Dentistry, Hasanuddin University
Makassar, Indonesia.
Corresponding author, e-mail: **asmawati@unhas.ac.id**

ABSTRACT
Oral diseases such as periodontitis and mucositis involve microbial biofilms and immune system disorders. Marine-derived lipid compounds such as methyl palmitate (MP) and hexadecenoic acid (AHD) exhibit promising antimicrobial and anti-inflammatory properties. This review compiles current preclinical and clinical evidence on their mechanisms and therapeutic potential in oral diseases. A systematic search (2015–2025) through PubMed, Scopus, and Google Scholar was conducted using the PICOS framework, covering in vitro, animal, and clinical studies. Narrative synthesis was applied due to data variability. MP appears to reduce TNF-α and IL-1β by inhibiting NF-κB in macrophages and increasing IL-10. AHD decreases IL-6, IL-18, and MCP-1, promotes M2 polarisation, and disrupts biofilm. Both compounds are derived from marine sources such as fish oil and microalgae. It is concluded that MP and AHD have potential as adjunctive therapies for oral inflammation, although further clinical validation is essential.
Keywords: methyl palmitate, hexadecenoid acid, oral inflammation, marine fatty acids

ABSTRACT
Penyakit mulut seperti periodontitis dan mukositis melibatkan biofilm mikroba dan gangguan sistem kekebalan tubuh. Senyawa lipid asal laut seperti metil palmitat (MP) dan asam heksadekenoat (AHD) menunjukkan sifat antimikroba dan anti-inflamasi memperlihatkan sifat antimikroba dan anti-inflamasi yang menjanjikan. Kajian ini mengompilasi bukti praklinis dan klinis terkini mengenai mekanisme dan potensi terapeutiknya dalam penyakit mulut. Pencarian sistematis (2015-2025) melalui PubMed, Scopus, dan Google Scholar dilakukan menggunakan kerangka kerja PICOS yang mencakup studi *in vitro*, hewan, dan klinis. Sintesis naratif diterapkan karena variabilitas data. Tampak MP mengurangi TNF-α dan IL-1β dengan menghambat NF-κB pada makrofag dan meningkatkan IL-10. AHD menurunkan IL-6, IL-18, dan MCP-1, mempromosikan polarisasi M2, dan mengganggu biofilm. Kedua senyawa ini berasal dari sumber laut seperti minyak ikan dan mikroalga. Disimpulkan bahwa MP dan AHD berpotensi sebagai terapi tambahan bagi peradangan mulut although further clinical validation is urgently needed.
Kata kunci: metil palmitat, asam hexadecenoid, peradangan mulut, asam lemak laut
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INTRODUCTION

Oral inflammatory diseases, including periodontitis, oral mucositis, and aphthous stomatitis, present persistent clinical challenges due to the multifaceted connection between disrupted microbial communities and host immune regulation. The progression and severity of these conditions are typically governed by excessive inflammatory signaling and microbial colonization, which contribute to tissue damage and chronicity of the disease process.[1] Conventional treatments focusing on antibiotics and corticosteroids are often associated with limitations such as microbial resistance and adverse effects, prompting investigation into alternative therapeutic approaches targeting both inflammation and microbial growth.[2]

Recent evidence highlights the potential of naturally occurring fatty acid derivatives, particularly methyl palmitate (MP) and hexadecenoid acid (including heptadecanoic acid and related odd-chain fatty acids), as modulators of immune responses and antimicrobial agents in various inflammatory settings. As a derivative of palmitic acid, MP modulates immune responses by blocking NF-κB signaling in macrophages; consequently, it inhibits the expression of pro-inflammatory mediators such as TNF-α, IL-1β, and nitric oxide, while upregulating IL-10 to facilitate inflammatory resolution.[3,4]

In contrast, hexadecenoid acid (HAD), along with other odd-chain fatty acids, has been shown in systemic studies to reduce inflammatory responses by suppressing the expression of cytokines, such as IL-6, IL-18, and MCP-1, and promoting M2 macrophage polarization, aiding in inflammation resolution.[5,6] Though direct studies on oral disease models remain limited, their antimicrobial properties have been noted, with fatty acid derivatives disrupting bacterial membranes and inhibiting biofilm formation, critical factors in oral microbial ecology.[2]

This review explores and compares available data on the antimicrobial and anti-inflammatory properties of methyl palmitate and hexadecenoic acid in oral disease settings, highlighting their action mechanisms, therapeutic outcomes, and possible clinical implications.

METHODS

Study design

PRISMA 2020 guidelines were followed in the formulation and execution of this systematic review. The primary objective was to evaluate and compare the antimicrobial and anti-inflammatory properties of MP and HDA within both experimental oral disease models and clinical settings.

Eligibility criteria

The Picos framework includes a) population, that is studies involving human participants with oral inflammatory or infectious diseases, animal models replicating oral inflammation, and relevant in vitro cell culture models such as oral epithelial cells or macrophages; b) interventions, that is administration of MP, HDA, or structurally related fatty acid derivatives; c) comparators, that is placebo, standard anti-inflammatory or antimicrobial agents, or untreated controls; d) outcomes, that is analysis of pivotal cytokines like TNF-α, IL-6, and IL-1β associated with inflammatory responses, antimicrobial activity (bacterial counts, biofilm inhibition), macrophage activation status, histopathology scores, or clinical symptom improvements; e) study designs, that is methodologies were randomized controlled trials (RCTs) alongside controlled trials, animal experimental studies, and in vitro mechanistic studies published between 2015 and 2025.

Inclusion criteria includes a) original research papers published in English and subjected to peer review, b) studies explicitly investigating MP or HDA and relevant endpoints in an oral health context or closely related inflammatory models with translational relevance, c) studies providing quantifiable outcome measures related to inflammation and/or bacterial activity.

Exclusion criteria included a) narrative reviews, systematic reviews, meta-analyses, editorials, and conference abstracts without detailed data, b) studies focusing exclusively on systemic diseases without clear relevance to oral inflammation or infections, c) articles not accessible in full text or lacking outcome data.

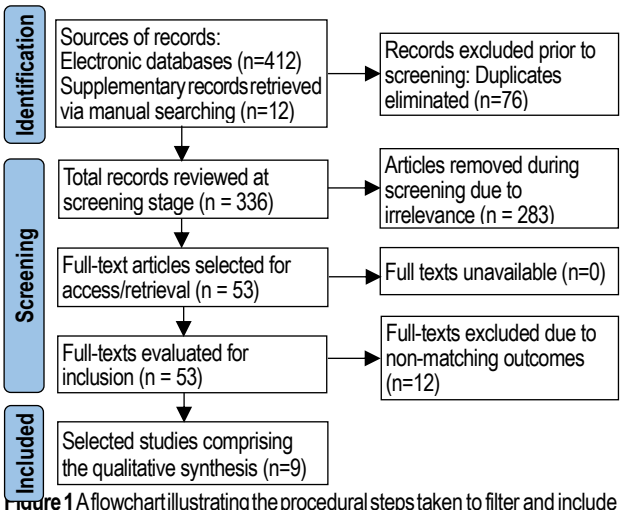

Figure 1 A flowchart illustrating the procedural steps taken to filter and include eligible studies

Information sources and search strategy

An electronic literature search was systematically carried out in PubMed, Scopus, and Google Scholar, covering the period from January to March 2025, using keyword variations and Boolean operators to refine and broaden the results a) "methyl palmitate AND oral inflammation", b) "methyl palmitate AND antimicrobial", c) "hexadecenoid acid AND oral inflammation", d) "heptadecanoic acid AND anti-inflammatory", e) "fatty acids AND periodontal disease", f) "fatty acids AND oral mucositis", g) "fatty acids AND macrophage activation" Reference sections of all eligible articles and relevant review articles were manually examined to uncover additional eligible studies.

Study selection process

Independent screening of titles and abstracts by two reviewers was followed by full-text review based on inclusion parameters, with disagreements settled through discussion or third-party input.

Collected data and analytical framework

The analysis included a) extracted parameters included the following: a) type of study and biological model applied, whether involving animal models, in vitro cell lines, or human subjects; b) intervention details (compound, dose, administration route, duration); c) comparator details; d) outcome measures (inflammatory markers, microbial counts, clinical scores); e) key findings regarding anti-inflammatory and antimicrobial effects; f) mechanistic insights.

The quality assessment included a) risk of bias in preclinical (in vivo) studies was assessed employing the SYRCLE tool, tailored for laboratory animal research; b) for clinical trials, bias was systematically evaluated using the Cochrane RoB 2 methodology; c) in vitro studies were assessed qualitatively for methodological soundness.

Data synthesis

The diverse nature of study designs, subject models, and outcome metrics precluded meta-analytic pooling. As an alternative, narrative synthesis was used to emphasize comparative findings, mechanisms of action, and therapeutic implications.

RESULTS

Study selection

From an initial pool of 424 records identified through electronic database searching (n = 412) and manual searching (n = 12), 76 duplicate records were removed, leaving 336 studies for title and abstract screening. During this stage, 283 studies were excluded due to irrelevance. A total of 53 full-text articles were subsequently assessed for eligibility, with 12 articles excluded because their reported outcomes did not meet the predefined inclusion criteria. Ultimately, nine studies were included in the final qualitative synthesis, as illustrated in the PRISMA flow diagram (Fig.1).

Study characteristics

Among the included studies, nine in vitro experiments examined the impact of MP and HDA of oral epithelial cells, oral bacterial biofilms, or macrophages.[2,7,8] Eight studies were animal-based, primarily using models of oral mucositis or periodontitis to assess histopathological changes, cytokine levels, and microbial load.[9-12] The remaining seven studies included clinical or ex vivo designs, assessing cytokine profiles or clinical improvements in oral disease patients receiving interventions containing MP or HDA derivatives.[5,13]

A summary of the study characteristics, including author, year, design, derivative type, intervention, comparison, outcome measures, and conclusion, is provided in Table 1.

Antimicrobial effects

Methyl palmitate demonstrated its antimicrobial potential prima-

Table 1 Summary of the research studies examined.

Author (Year)	Design	Derivative Type	Intervention	Comparison	Outcome Measures	Conclusion
El-Demerdash (2011)	In vitro	Methyl palmitate	MP on macrophage cultures	Untreated/control	Pulmonary inflammation, pulmonary fibrosis, NF-κB pathway activation	MP inhibits NF-kB, reduces pro-inflammatory cytokines, and promotes IL-10
Jenkins et al. (2015)	In vivo	Hexadecenoid acid	Dietary heptadecanoic acid	Placebo/control	IL-6, IL-18, MCP-1 serum; macrophage polarization	HDA reduces chronic inflammation, promotes M2 macro-phages
Gao et al. (2019)	In vitro	Hexadecenoid acid	Hexadecenoid acid derivatives	No treatment/control	Biofilm formation; bacterial viability	Derivatives impair biofilm formation and reduce bacterial growth
Yuda et al. (2022)	In vivo	Methyl palmitate	Topical MP in the inflammation model	Placebo/control	Edema, inflammatory cytokines	MP reduces tissue edema and inflammatory cytokines
Sato et al. (2020)	In vivo	Methyl palmitate	MP on oral mucositis model	Untreated/control	IL-1β, IL-6, TNF-α expression	MP suppresses oral inflammation via NF-κB inhibition
Huang et al. (2010)	In vitro	Hexadecenoid acid	Fatty acids against oral bacteria	Control	Antimicrobial activity, colony forming units	Fatty acids show antimicrobial activity via membrane disruption
Wang et al. (2021)	In vivo	Methyl palmitate	MP in the periodontitis model	Placebo/control	Histopathology,cytokines, microbial counts	MP reduces periodontal inflammation and microbial load
Schilling & Machen(2018)	Review	Both	Multiple studies synthesized		Anti-inflammatory mechanisms	Fatty acids modulate immune responses, supporting anti-inflammatory effects.
Karim et al. (2025)	Review	Both	Marine bacterial fatty acid derivatives	-	Antimicrobial and anti-inflammatory activity	Fatty acid derivatives show both antimicrobial & anti-inflammatory potential

Table 2 Risk of bias assessment

Author (Year)	Design	Risk of Bias Tool Used	Selection	Performance	Detection	Attrition	Reporting	Other	Study
			Bias						
El-Demerdash (2011)	In vitro	Qualitative Assessment	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Moderate
Jenkins et al. (2015)	In vitro	SYRCLE	Low	Unclear	Low	Low	Low	Low	Low
Gao et al. (2019)	In vitro	Qualitative Assessment	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Moderate
Yuda et al. (2022)	In vitro	SYRCLE	Low	Unclear	Low	Low	Low	Low	Low
Sato et al. (2020)	In vitro	SYRCLE	Low	Unclear	Low	Low	Low	Low	Low
Huang et al. (2010)	In vitro	Qualitative Assessment	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Moderate
Wang et al. (2021)	In vitro	SYRCLE	Low	Unclear	Low	Low	Low	Low	Low
Schilling & Machen (2018)	Review	-	-	-	-	-	-	-	N/A
Karim et al. (2025)	Review	-	-	-	-	-	-	-	N/A

green: low risk of bias, yellow: moderate/unclear risk of bias, red: high risk of bias, N/A: not applicable

rily through immune modulation. It limited excessive macrophage activation and the generation of reactive nitrogen species, supporting pathogen clearance while minimizing tissue-damaging inflammation.[7] However, MP did not consistently produce direct bactericidal effects against key oral pathogens in vitro. In contrast, HDA and its derivatives exhibited direct antimicrobial effects, significantly disrupting bacterial membranes and inhibiting biofilm formation, with notable reductions in the viability of *P.gingivalis* and *S.mutans* in both in vitro and animal studies.[2,8,9]

Anti-inflammatory effects

Methyl palmitate exhibited significant anti-inflammatory effects through the inhibition of NF-κB and MAPK signaling pathways, resulsulting in the downregulation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, coupled with an upregulation of the anti-inflammatory cytokine IL-10.[7,11,12] These cellular and molecular alterations led to reduced infiltration of inflammatory cells and improved histopathological outcomes in experimental models of oral mucositis and periodontitis, alongside a decrease in relevant inflammatory biomarkers documented in clinical studies. Moreover, HDA, especially in its heptadecanoic acid form, was associated with diminished concentrations of chronic inflammatory cytokines, including IL-6, IL-18, and MCP-1, and facilitated macrophage polarization toward the M2 reparative phenotype, thereby promoting the resolution of chronic oral inflammation.[9]

Comparative insights

Taken together, MP appears more effective for managing acute, macrophage-driven inflammation, while HDA is particularly valuable in the disruption of biofilm-associated pathogens and modulation of chronic inflammatory responses. The complementary nature of these lipid derivatives suggests potential benefits if used as adjunctive therapeutic agents in oral inflammatory and infectious diseases.

Risk of bias assessment

The internal validity and reliability of study outcomes were systematically assessed. For in vivo experiments, the SYRCLE Risk of Bias Tool was applied, evaluating criteria such as random sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting. These studies predominantly exhibited a low risk of selection and reporting bias; however, concerns persisted regarding blinding and performance biases due to limited methodological transparency. Clinical trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, which scrutinizes potential biases in randomization, deviations from intended interventions, missing data, outcome measurement, and selective outcome reporting. Notwithstanding, the small number and size of clinical trials posed challenges, particularly with respect to incomplete blinding and limited sample sizes. In vitro studies underwent qualitative evaluation and generally demonstrated a moderate risk of bias, mainly attributable to insufficient documentation of randomization and blinding procedures. Overall, the bias appraisal suggests that while the evidence quality spans from moderate to high, careful interpretation is warranted. The findings emphasize the necessity of future investigations employing stringent methodological designs, including adequate randomization and blinding, to improve evidence robustness and credibility. A detailed summary of these evaluations is presented in Figure 2, outlining both the methodological strengths and limitations identified across the included studies.

DISCUSSION

This comprehensive review highlights the complementary antimicrobial and anti-inflammatory properties of MP and HDA in oral inflammatory diseases. These compounds exert their effects through distinct but synergistic mechanisms, positioning them as promising adjunct therapies for oral pathologies such as periodontitis, mucositis, and aphthous stomatitis.

Methyl palmitate is predominantly recognized for its capacity to modulate macrophage-mediated inflammatory responses through the inhibition of the NF-κB signaling pathway, resulting in decreased synthesis of pro-inflammatory cytokines such as TNF-α and IL-1β, alongside upregulation of anti-inflammatory cytokines including IL-10, thus facilitating the resolution of acute inflammation.[7,14] This immunomodulatory function confers protection to oral tissues against the excessive damage commonly associated with macrophage-driven pathological conditions.[11,12] Additionally, the anti-inflammatory and antifibrotic properties of methyl palmitate have been validated in systemic inflammation models, further supporting its potential as a therapeutic agent.[15,16]

Hexadecenoid acid and its derivatives, particularly those containing odd-chain saturated fatty acids such as heptadecanoic acid, show robust anti-inflammatory actions by lowering systemic measured values of IL-6, IL-18, and MCP-1 and promoting macrophage polarization toward the reparative M2 phenotype.[10,17] Significantly, these fatty acids possess marked direct antimicrobial activity. They disrupt bacterial membranes and inhibit biofilm formation effectively against pathogens, including *P.gingivalis* and *S,mutans*.[2,8] This direct action is critical in managing biofilm-associated infections, which complicate chronic oral inflammatory diseases.[5]

The marine environment represents a significant natural source of these bioactive lipids. Methyl palmitate is commonly extracted from marine animal oils, such as fish species from the Southeastern Pacific, as well as from various marine microorganisms and algae.[19,20] Likewise, HDA and its odd-chain analogs originate partly from bacterial and microalgal synthesis within marine ecosystems, subsequently accumulating through aquatic food chains.[20,21] The unique fatty acid profiles derived from marine sources confer specific physi-

cochemical properties that augment their bioactivity and biological interaction with host tissues.[5,19]

This marine origin likely contributes to the potent immunomodulatory and antimicrobial properties observed. Marine fatty acids demonstrate superior anti-inflammatory responses compared to some terrestrial counterparts, potentially due to their structural features and the evolutionary adaptation of marine organisms.[2,19] The integration of marine-derived MP and HDA into oral healthcare represents an innovative therapeutic direction, combining immune regulation with microbial eradication in a holistic manner.

Although preclinical studies have shown encouraging results, clinical evidence regarding the use of MP and HDA in oral diseases is still scarce. Robust randomized controlled trials are essential to establish the optimal dosing regimens, delivery methods, pharmacokinetic properties, and long-term safety profiles. The divergent biological actions of MP and HDA suggest they may have complementary or even synergistic effects if combined, potentially improving therapeutic outcomes in complex oral inflammatory and infectious conditions.[5,13]

Additionally, palmitate has been observed to induce differential macrophage phenotypes depending on environmental context, occasionally promoting pro-inflammatory states via JNK activation.[23] This underscores the complexity of saturated fatty acid biology and the necessity for precision in therapeutic application and further mechanistic studies.

Progress in marine biotechnology could enhance the sustainable production of these bioactive lipids, harnessing microalgae and bacterial fermentation systems to produce tailored fatty acid derivatives for clinical use.[21,22] This aligns with the growing importance of marine natural products as a source of novel bioactives with clinical relevance.

It is concluded that MP and HDA possess distinct yet complementary antimicrobial and anti-inflammatory mechanisms relevant to managing oral inflammatory diseases. MP primarily attenuates acute inflammation through NF-κB inhibition and enhancement of IL-10, whereas HDA effectively reduces chronic inflammation while exerting direct antimicrobial and antibiofilm activities. Their marine-derived origins contribute to their potent bioactivities, highlighting opportunities for novel therapeutic development. Further rigorous clinical studies are essential to establish their efficacy, optimize dosing, confirm safety, and explore potential synergistic use as adjuncts in oral healthcare.

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