Marine-derived 9-octadecenoic acid and α-tocopherol acetate as antioxidant and anti-inflammatory agents in oral health

Asam 9-oktadekenoat yang berasal dari laut dan asetat α-tokoferol sebagai agen antioksidan dan antiinflamasi dalam kesehatan mulut

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ABSTRACT
Natural bioactive compounds such as α-tocopherol and 9-octadecenoic acid (OOA), both found in *Stichopus hermanii*, have demonstrated potential antioxidant and anti-inflammatory properties. This article reviews systematically and compare the biological activities of α-tocopherol and OOA in managing oxidative and inflammatory processes relevant to the oral cavity. A descriptive-comparative literature review was conducted using PubMed, ScienceDirect, MDPI, and Google Scholar (2015-2025). Inclusion criteria covered in vitro, in vivo, clinical, and in silico studies evaluating the antioxidant and anti-inflammatory effects of α-tocopherol or OOA. α-tocopherol primarily acted by enhancing antioxidant defenses and suppressing inflammatory signaling, while OOA modulated pro-inflammatory pathways and epigenetic mechanisms. It is concluded that α-tocopherol and OOA exhibit complementary mechanisms in reducing oxidative stress and inflammation. Their combined use and marine-derived origin from *S.hermanii* offer promising directions for future research and therapeutic application in oral health.
Keywords: α-tocopherol, 9-octadecenoic acid, anti-inflammatory, antioxidant, oral cavity

ABSTRAK
Senyawa bioaktif alami seperti α-tokoferol dan asam 9-oktadekenoat (OOA), yang keduanya terdapat dalam *Stichopus hermanii*, telah menunjukkan potensi sifat antioksidan dan anti-inflamasi. Artikel ini melakukan tinjauan sistematis dan membandingkan aktivitas biologis α-tokoferol dan OOA dalam mengelola proses oksidatif dan inflamasi yang berkaitan dengan rongga mulut. Kajian pustaka deskriptif-komparatif dilakukan dengan menggunakan PubMed, ScienceDirect, MDPI, dan Google Scholar (2015–2025). Kriteria inklusi mencakup studi in vitro, in vivo, klinis, dan in silico yang mengevaluasi efek antioksidan dan anti-inflamasi dari α-tokoferol atau OOA. α-tokoferol terutama bekerja dengan meningkatkan pertahanan antioksidan dan menekan sinyal inflamasi, sedangkan OOA memodulasi jalur proinflamasi dan mekanisme epigenetik. Disimpulkan bahwa α-tokoferol dan OOA menunjukkan mekanisme yang saling melengkapi dalam mengurangi stres oksidatif dan peradangan. Penggunaan gabungan keduanya serta asal-usulnya yang berasal dari laut, *S.hermanii* menawarkan arah yang menjanjikan untuk penelitian dan aplikasi terapeutik di masa depan dalam bidang kesehatan mulut.
Kata kunci: α-tokoferol, asam 9-oktadekenoat, anti-inflamasi, antioksidan, rongga mulut
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INTRODUCTION

Maintaining redox balance is essential for preserving the health and function of oral mucosal tissues. Under normal conditions, the body's antioxidant systems can neutralize reactive oxygen species (ROS), keeping oxidative stress in check.[1] However, when ROS production surpasses the body's defense capacity, oxidative stress (OS) occurs and contributes to a variety of oral pathologies.[2]

Given its constant exposure to external and internal stressors, the oral cavity serves as the body's first line of defense and is particularly susceptible to oxidative and inflammatory challenges. This exposure may originate from various sources, including bacteria, inhaled pollutants (e.g., cigarette smoke), by products of metabolism, and long-term physical or chemical irritation. Over time, these factors can lead to excessive ROS buildup in the oral tissues, disrupting cellular homeostasis and triggering tissue damage.[3]

Such redox imbalances are closely associated with the development of chronic oral conditions, including periodontitis, stomatitis, and mucositis. ROS are known to directly harm cells and also activate enzymes and signaling pathways that worsen inflammation, such as the NF-κB pathway. In many cases, reactive nitrogen species (RNS) are also involved, further exacerbating damage and increasing the likelihood of long-term complications, including precancerous lesions. This highlights the importance of managing oxidative stress and inflammation in maintaining oral health.[1]

In response to this, one bioactive molecule that has garnered significant attention is 9-octadecenoic acid (also known as oleic acid or OOA), a long-chain monounsaturated fatty acid. Both its native and oxidized derivatives, such as 8-oxo-ODA and 9-hydroxyoctadecadienoic acid (9-HODE), exhibit notable anti-inflammatory and immunomodulatory effects. Unlike classic antioxidants, OOA does not directly scavenge free radicals but modulates intracellular signaling pathways. Several studies have demonstrated that OOA and its derivatives activate peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor that suppresses chronic inflammatory pathways. This activation leads to reduced expression of pro-inflammatory cytokines such as TNF-α and IL-6, and inhibition of MAPK (JNK and ERK) and NF-κB signaling cascades.[4]

Alongside OOA, α-tocopherol, the most biologically active form of vitamin E, has long been recognized for its pharmacological antioxidant properties. This fat-soluble compound helps maintain cellular membrane integrity by preventing lipid peroxidation under OS conditions. Vitamin E is a fat-soluble essential nutrient with pharmacological properties as an antioxidant. It comprises two main groups of compounds: tocopherols (α, β, γ, δ) and tocotrienols (α, β, γ, δ), with α-tocopherol being the most biologically active form.[5] This compound helps maintain cellular membrane integrity by preventing lipid peroxidation under OS conditions. Furthermore, α-tocopherol also exhibits anti-inflammatory and vascular effects, including inhibition of platelet aggregation and improvement of microcirculation and local blood flow.[6] These combined properties suggest its potential as a promising candidate for supporting tissue repair, especially in the oral mucosa.[7]

In Indonesia, the golden sea cucumber (*Stichopus hermanii*) has attracted attention due to its therapeutic potential. Traditionally used in Southeast Asia for its healing properties, this marine organism contains various bioactive compounds, including OOA and α-tocopherol. Recent findings by Fatwati et al have confirmed the presence of these compounds in *S.hermanii* extracts using GC–MS. Their docking studies also showed that both compounds had strong affinities for PKC-β, suggesting they may be helpful in reducing inflammation at the molecular level.[8]

Despite the promising data, studies that directly compare OOA and α-tocopherol, particularly those derived from *S.hermanii*, remain limited, especially in the context of oral health. Therefore, this review aims to explore and compare their antioxidant and anti-inflammatory potential systematically, with the goal of better understanding their role in protecting and restoring oral mucosal tissue.

METHODS

This study employed a descriptive comparative literature review to evaluate and compare the potential of OOA and α-tocopherol as antioxidant and anti-inflammatory agents relevant to oral mucosal health. The review included original experimental research, encompassing *in vitro*, *in vivo*, *in silico*, and clinical trials that investigated these compounds in the context of oxidative stress and inflammation.

A systematic literature search was conducted using four major elec-tronic databases: PubMed, ScienceDirect, MDPI, and Google Scholar. The search strategy combined the following keywords: *"9-octadecenoic acid", oleic acid", "*α-tocopherol a*cetate", "vitamin E", "anti-inflammation", "antioxidant", "oral cavity"*, *"Stichopus hermanii"*. The search covered studies published between January 2015 and May 2025.

The inclusion criteria are original experimental studies (excluding review articles), research involving 9-octadecenoic acid (OOA) or α-tocopherol, whether in pure form or derived from *S.hermanii*, studies conducted on biological models relevant to inflammation and oxidative stress, particularly those involving the oral mucosa or cell lines associated with the immune system, as well as articles reporting biomolecular results including, but not limited to, NO, iNOS, COX-2, IL-6, TNF-α, GPx, NRF2, or NF-κB.

Exclusion criteria included studies that did not focus on 9-octadecenoic acid or α-tocopherol as the primary intervention; articles that did not report antioxidant or anti-inflammatory activity or did not include relevant biomarkers; studies using models not relevant to oral administration (e.g. liver, skin, kidney, nervous tissue); articles for which the full text was not available or which were published before 2015; and duplicates identified during the screening process.

The selection process followed the PRISMA 2020 guidelines, including the identification, screening, eligibility, and inclusion stages. A PRISMA flow diagram was used to visualize the study selection steps and criteria.

To ensure methodological rigor, included studies were independently assessed by two reviewers. Appraisal was based on the clarity of objectives, the appropriateness of models, and the validity of measured outcomes. Discrepancies were resolved through discussion and consensus. Formal scoring tools were not applied.

Data extraction and synthesis

Data from each eligible study was extracted into a structured table that included the type of study model, source, concentration of the compound, and key findings related to antioxidant or anti-inflammatory activity. A qualitative synthesis was then conducted to assess similarities and differences across the studies, highlight limitations, and explore potential synergistic mechanisms between 9-octadecenoic acid and α-tocopherol.

RESULTS

Study selection

A systematic searching of four electronic databases (PubMed, ScienceDirect, MDPI, and Google Scholar) yielded a total of 85 records, with an additional five articles identified through manual searching. After removing 18 duplicate records, 72 articles remained for title and abstract screening.

Of these, 20 full-text articles were retrieved and assessed for eligibility. Following a detailed review, 11 studies were excluded for reasons including the use of biological models unrelated to oral applications (e.g., hepatic or dermal tissues), the absence of 9-octadecenoic acid or α-Tocopherol as primary interventions, or the lack of relevant outcome measures related to antioxidant or anti-inflammatory activity. In total, nine studies fulfilled the inclusion criteria and were incorporated into the qualitative synthesis. The study selection process is summarized in the PRISMA 2020 flow diagram (Fig.1).

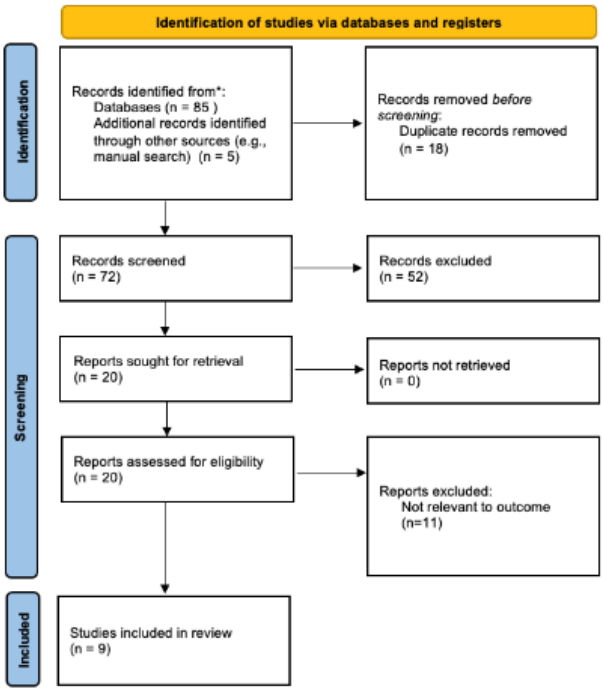

Figure 1 Flowchart showing the process of including and excluding studies in different phases.

Study characteristics

Each study was examined based on several key characteristics: the experimental model used, the form and source of the compound tested, and the primary outcomes measured. Specifically, outcomes were categorized into reductions in pro-inflammatory biomarkers (e.g., NO, iNOS, COX-2, TNF-α, IL-6) or enhancements in antioxidant-related markers (e.g., NRF2, GPx, IL-10). To facilitate interpretation, the findings were synthesized into a comparative summary table, which forms the basis for the subsequent narrative analysis.

A total of nine studies published between 2015 and 2025 met the eligibility criteria and were included in the qualitative synthesis. The included studies comprised a range of experimental designs, including in vitro models (n = 6), an in vivo animal study (n = 1), a randomized clinical trial (n = 1), and in silico molecular docking analysis (n = 1). The selected articles evaluated either OOA or α-tocopherol and their effects on antioxidant and inflammatory pathways. A summary of the study characteristics and outcomes is presented in Table 1.

9-octadecenoic acid (OOA) or oleic acid

Four studies investigated OOA or oleic acid, primarily in in vitro models. These compounds demonstrated consistent anti-inflammatory effects through the suppression of pro-inflammatory mediators.

Kang et al, showed that 8-oxo-OOA significantly reduced NO, TNF-α, and IL-6 production in LPS-stimulated RAW264.7 macrophages,[4] while Müller et al found similar outcomes using lipid-extracted OA, with decreased iNOS and COX-2 expression. Both studies support OOA's efficacy in suppressing key inflammatory markers involved in oral tissue inflammation.[9]

Schuldt et al explored a more epigenetic angle, demonstrating that OA exposure enhanced H3K acetylation and IL-10 expression in

Table 1. Summary of experimental studies evaluating the antioxidant and anti-inflammatory effects of 9-Octadecenoic Acid and α-Tocopherol

Author (Year)	Design	Derivative Type	Intervention	Comparison	Outcome Measures	Conclusion
Kang et al. (2018)[4]	In vitro (RAW264.7 macrophages)	8-oxo-9-octadecenoic acid (OOA)	Treat with OOA for inflammation inhibition	LPS-treated macrophages (control)	↓ NO, TNF-α, IL-6 production →anti-inflammatory effect	An Effective anti-inflammatory agent through inhibition of LPS-induced mediators
Müller et al. (2021)[9]	In vitro (RAW264.7 macrophages)	oleic acid (OA)	Treat with OA (lipid extract) for inflammation reduction	LPS-stimulated RAW264.7 cells (control)	↓ iNOS, COX-2 expression → anti-inflammatory effect	Reduces inflammation and cytokine production in RAW264.7 cells
Schuldt et al. (2022)[10]	In vitro (HPdLFs under mechanical stress)	Oleic acid (OA)	Exposure to OA for modulation of H3K acetylation in fibroblasts	BSA control	↑ H3K acetylation → ↑ IL-10 expression → Anti-inflammatory	OA regulates the inflammatory response through epigenetic modification in fibroblasts
Ma et al. (2025)[11]	In vitro (tongue squamous cell carcinoma (TSCC) cells under high glucose)	Oleic acid (OA)	Treat with OA to inhibit TSCC cell proliferation, invasion, and migration	High glucose TSCC cells (control)	↓ Proliferation, invasion, migration → Anti-cancer effect	OA inhibits the progression of TSCC under high glucose conditions by regulating S100A9
Hatipoğlu et al. (2016)[12]	In vivo (rats with periodontitis and diabetes)	α-Tocopherol	Topical application of α-Tocopherol	Control group (untreated)	↓ iNOS expression → Anti-inflammatory effect	Effective in reducing gingival inflammation and oxidative stress
Zulkapli et al. (2017)[13]	In vitro (ORL-48 cell line)	α-Tocopherol acetate	Induction of apoptosis and inhibition of proliferation	Control group (untreated)	Induced apoptosis → Reduced oral cancer cell proliferation	Induces apoptosis in oral cancer cells, promising antitumor agent
Fernandes et al. (2020)[14]	In vitro (parotid gland cell culture)	α-Tocopherol	Increased NRF2 & GPx expression, reduced NF-κB	Control group (untreated)	↑ NRF2 & GPx expression → ↓ NF-κB expression → antioxidant & anti-inflammatory effects	Supports antioxidant and anti-inflammatory effects in diabetic conditions
Baldin et al. (2025)[15]	Randomized clinical trial (oral biopsy patients)	Tocopherol acetate	Topical application of tocopherol acetate vs. chlorhexidine	Chlorhexidine digluconate 0.2%	↓ Pain (VAS) → Wound healing (height & width reduction)	Comparable efficacy to chlorhexidine with no side effects
Fatwati et al. (2025)[8]	In silico and GC–MS analysis	α-Tocopherol acetate & Oleic acid	Docking of *Stichopus hermanii* compounds to PKC-β	No control group (computational docking)	↑ Binding affinity to PKC-β → Inhibition of inflammatory signaling	α-tocopherol acetate & OA from *S.hermanii* show strong potential as PKC-β inhibitors, suggesting their use as marine-derived anti-inflammatory agents.

periodontal fibroblasts under mechanical stress, indicating potential for anti-inflammatory modulation via epigenetic pathways.[10]

Ma et al, evaluated OA in an oral squamous carcinoma model under hyperglycemic conditions. Their findings highlighted OA's capacity to inhibit proliferation, invasion, and migration of cancer cells via S100A9 regulation, suggesting additional protective roles in metabolic-compromised oral environments.[11]

Lastly, Fatwati et al reported high binding affinity of oleic acid from *S.hermanii* to PKC-β, indicating potential synergy with α-tocopherol acetate at the molecular level for inflammatory pathway inhibition.[8]

α-tocopherol and its derivatives

Five studies focused on α-Tocopherol or its acetate derivative. These studies used both oral tissue–relevant models and systemic inflammatory models to evaluate anti-inflammatory and antioxidant effects.

Hatipoğlu et al, conducted an in vivo study using rats with induced periodontitis and diabetes, reporting a reduction in iNOS expression following topical α-tocopherol application, suggesting its protective effect on gingival inflammation.[12] Similarly, Fernandes et al, through an in vitro study on diabetic parotid gland cells, showed increased expression of NRF2 and GPx, coupled with decreased NF-κB activity, indicating a robust antioxidant response.[14]

In a clinical context, Baldin et al, compared topical α-tocopherol acetate with chlorhexidine in patients undergoing oral biopsies. The study found that tocopherol acetate promoted wound healing with comparable efficacy to chlorhexidine and no reported adverse effects.[15]

Zulkapli et al utilized an oral cancer cell line (ORL-48) to demonstrate that α-tocopherol acetate induced apoptosis and inhibited proliferation, suggesting additional potential as an antitumor agent within oral epithelial contexts.[13]

Finally, Fatwati et al employed in silico docking to evaluate the interaction of α-tocopherol acetate with PKC-β. The compound exhibited strong binding affinity, reinforcing its molecular capability to modudulate inflammation pathways.[8]

Risk of bias and limitations

To ensure the reliability and validity of the included studies, a structured risk of bias appraisal was conducted using the SYRCLE tool for animal and in vitro studies, and the Cochrane RoB-2 framework for the randomized clinical trial. A total of nine studies were assessed, encompassing diverse experimental models including in vivo, in vitro, clinical, and in silico designs. Each study was evaluated across key domains such as sequence generation, blinding, outcome assessment, reporting transparency, and model relevance. Overall, the majority of studies demonstrated a low to moderate risk of bias, with consistent methodological clarity and appropriate outcome measures. However, several in vivo and mechanistic studies presented unclear risk in domains related to allocation concealment and blinding of personnel, which is common in laboratory-based settings. The detailed evaluation is summarized in Fig.2, providing a comprehensive overview of methodological strengths and potential limitations within each included study.

DISCUSSION

This review brings together evidence supporting the antioxidant and anti-inflammatory roles of 9-Octadecenoic Acid (OOA) and α-tocopherol, particularly in the context of oral health. While these two compounds differ in their molecular pathways, their effects ultimately converge on a common goal: protecting oral tissues from oxidative damage and chronic inflammation.

Author (Year)	Randomization (Selection Bias)	Blinding of Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Model Relevance	Overall Risk of Bias
Kang et al. (2018)	Low	Low	Low	Low	Low	✓	Low
Müller et al. (2021)	Low	Low	Low	Low	Low	✓	Low
Schuldt et al. (2022)	Low	?	Low	Low	Low	✓	Moderate
Ma et al. (2025)	Low	Low	Low	Low	Low	✓	Low
Hatipoğlu et al. (2016)	Low	?	?	Low	Low	✓	Moderate
Zulkapli et al. (2017)	Low	Low	Low	Low	Low	✓	Low
Fernandes et al. (2020)	Low	Low	Low	Low	Low	✓	Low
Baldin et al. (2025)	Low	?	Low	Low	Low	✓	Moderate
Fatwati et al. (2025)	N/A	N/A	N/A	N/A	Low	✓	Low (in silico)

Judgement

Green = Low risk of bias
Yellow = Moderate/unclear risk of bias
Red = High risk of bias
N/A = Not applicable

Figure 2 Risk of bias assessment

The role of 9-octadecenoic acid (OOA)

Among the compounds reviewed, OOA, commonly referred to as oleic acid, has shown notable anti-inflammatory properties through a set of mechanisms distinct from classical antioxidants. Rather than directly neutralizing reactive oxygen species, OOA acts by modulating key intracellular signaling pathways associated with inflammation. It inhibits phosphorylation of MAPK (JNK and ERK) and the activation of NF-κB, which in turn reduces the pro-inflammatory mediators such as TNF-α, IL-6, and COX-2.[4,9,16]

Beyond signaling inhibition, OOA exhibits additional advantages in the context of oral delivery. Notably, it has been shown to enhance mucosal absorption through caveolin-mediated endocytosis, which may improve its bioavailability in topical formulations.[19] Moreover, one of the most distinctive features of OOA is its ability to contribute to immune resolution via epigenetic modulation. Specifically, OOA increases H3K acetylation at the IL-10 promoter, thereby upregulating anti-inflammatory cytokine expression and promoting tissue healing, particularly in mechanically stressed fibroblasts.[10,17,18] These findings highlight OOA's multifaceted role as both a modulator of inflammation and a facilitator of tissue regeneration.

The case for a-tocopherol

While OOA demonstrates its benefits through signaling modulation and epigenetics, α-tocopherol contributes to oral health through its well-established antioxidant and anti-inflammatory actions. Multiple studies have confirmed that α-tocopherol, especially in its acetate form, is effective in reducing inflammatory markers such as iNOS and NF-κB, while also enhancing antioxidant defenses through the upregulation of NRF2 and GPx.[12,14]

Importantly, α-tocopherol has also shown encouraging results in clinical applications. For example, a randomized trial found that topical α-tocopherol acetate promoted oral wound healing with comparable efficacy to chlorhexidine yet without adverse effects making it a safer option for long-term use.[15] This clinical relevance is echoed by Sener et al, who observed that vitamin E was the most effective agent for managing oral mucositis in pediatric ICU patients, outperforming both honey and chlorhexidine.[19] These outcomes reinforce α-tocopherol's reputation as a reliable agent for mucosal protection and recovery. Beyond inflammation, α-Tocopherol has also exhibited antitumor activity in oral epithelial models by inducing apoptosis, further extending its potential applications in oral oncology.[13]

Complementary mechanisms and synergistic potential

Although they operate through different mechanisms, OOA and α-tocopherol appear to offer complementary roles in managing oxidative stress and inflammation in oral tissues. OOA primarily functions as a regulator of intracellular signaling, influencing the transcriptional activity of pro-inflammatory cytokines through pathways such as NF-κB and MAPK. In addition, its ability to enhance epigenetic modulation, notably through increased H3K acetylation at the IL-10 promoter positions, OOA as a unique agent that not only suppresses inflammation but also promotes immune resolution and tissue repair.

Meanwhile, α-tocopherol acts as a chain-breaking antioxidant, stabilizing cell membranes by neutralizing lipid peroxyl radicals.[19] This fundamental action helps maintain membrane integrity and protects cells from oxidative damage. Moreover, α-tocopherol is an integral part of the cellular redox cycle, as its oxidized form (α-tocopheroxyl radical) can be regenerated by other antioxidants such as vitamin C or coenzyme Q10, allowing for sustained antioxidant activity.[20,21] It also modulates inflammation indirectly by inhibiting transcription factors like NF-κB, further supporting its dual role in tissue protection and repair.

Interestingly, both OOA and α-tocopherol, particularly when extracted from *S.hermanii*, have been shown to bind strongly to protein kinase C-beta (PKC-beta), a critical molecule involved in inflammatory signaling.[8] This shared molecular target provides a rationale for their combined application and suggests potential synergistic effects in oral therapeutic formulations aimed at modulating inflammation and supporting mucosal healing.

Limitations and future directions

Several limitations of the present review must be acknowledged. First, only a small number of studies were conducted using oral-specific models, while most of the available evidence was derived from general inflammatory or systemic models. Although these provide mechanistic insights, they may not fully replicate the complexity of oral mucosal environments.

Second, only one study explicitly used *S.hermanii* as the source of OOA and α-tocopherol, which limits the strength of conclusions regarding the therapeutic potential of this marine species. While both compounds are known to be present in *S.hermanii*, further verification through direct marine-derived experimentation is needed.

Third, there was notable heterogeneity in experimental design, including differences in compound concentration, delivery method, and biomarker selection. This variability hindered the ability to compare outcomes across studies or conduct a quantitative meta-analysis. To address these gaps, future research should aim to 1) investigate combined formulations of OOA and α-tocopherol to explore potential synergistic effects, 2) utilize standardized oral mucosal models, both in vitro and in vivo, to better simulate clinical relevance, 3) focus on clinical outcomes, such as wound healing time, reduction in pain or inflamflammation, and tissue regeneration under real-world conditions.

It is concluded that both 9-octadecenoic acid (OOA) and α-tocopherol show potent antioxidant and anti-inflammatory potential relevant to oral health. Despite differing in their mechanisms, they offer complementary effects, OOA through inflammatory signaling modulation and epigenetic regulation and α-tocopherol through redox stabilization. Their presence in *S.hermanii* supports its value as a marine-derived therapeutic source. While findings are promising, further studies using oral-specific models and combined formulations are needed to confirm their clinical utility in managing oral inflammation and promoting tissue healing.

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