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Statins in the treatment of oral diseases

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ABSTRACT

Introduction: Statins, as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are crucial in managing blood cholesterol levels and, consequently, in the prevention of cardiovascular diseases. Studies also indicate the role of statins in maintaining the homeostasis of the oral mucosa.

The aim of this study was to evaluate the effectiveness of statins in treating oral diseases and their multifaceted pharmacological effects on the oral mucosa.

Materials and methods: Publications from PubMed and ResearchGate (2008–2024) were analyzed, focusing on original research and review articles on the role of statins in oral health. Keywords included: statins, oral mucosa, oral health. From a total of 824 papers, 22 were selected after thorough abstract analysis. Criteria centered on the effects of statins on the oral mucosa, oral microbiome, and jawbone physiology. Limitations included reliance on *in vitro* and animal models, which may not fully represent the complexity of the human organism, limiting the extrapolation of results to humans.

Results: Based on the analysis, it was found that statins, as HMG-CoA reductase inhibitors, effectively control hyperlipidemia and play an important role in maintaining oral health. Statins exhibit anti-inflammatory and immunomodulatory effects, which are crucial in treating periodontal diseases and reducing bacterial and fungal infections. Moreover, they have shown potential in treating advanced oral diseases, such as squamous cell carcinoma, primarily by modulating biochemical pathways related to the proliferation and survival of cancer cells. Research also highlights the ability of statins to improve salivary gland function and their potential protection against bone loss around implants.

Conclusion: Statins effectively treat periodontal diseases, infections, and oral cancers, promoting wound healing and bone regeneration. Local application with carriers like gelatin hydrogel enhances benefits while minimizing side effects, but further research is needed to balance their benefits against potential risks in dental applications.

Keywords: simvastatin; oral mucosa diseases; oral health; periodontal treatment; anti-inflammatory effects.

INTRODUCTION

Statins, as specific 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, play a crucial role in regulating cholesterol levels in the body [1, 2]. There are 2 main categories of statins based on their origin. Type-1 statins, including simvastatin, lovastatin, and pravastatin, are derived from fungal fermentation. These statins closely resemble their founding member, demastatin, and have proven efficacy in lowering cholesterol levels. On the other hand, type-2 statins, such as atorvastatin and fluvastatin, are fully synthetic molecules developed through advanced chemical synthesis techniques (Tab. 1).

Both types of statins, regardless of their origin, function as potent HMG-CoA reductase inhibitors, contributing significantly to the management of hypercholesterolemia and improving overall cardiovascular health [3]. Statins, widely recognized for their effectiveness in treating hyperlipidemia and reducing cardiovascular risk, also contribute significantly to maintaining oral mucosa homeostasis. Their pleiotropic effects – such as immune regulation, anti-inflammatory action, enhanced endothelial function, antioxidant properties, and antithrombotic qualities – play a pivotal role in oral health maintenance [2, 4]. Additionally, their antimicrobial, antiviral, and fungicidal properties make them highly appealing in the field of periodontal diseases (PD). Remarkably, statins show promising effects on salivary gland function and even anticancer properties [5]. These multifaceted attributes underscore the profound impact of statins, not only in cardiovascular health but also in the comprehensive maintenance of oral health and well-being.

The aim of this study was to analyze the use of statins in the treatment of oral diseases.

MATERIALS AND METHODS

Publications available in the PubMed and ResearchGate databases from 2008–2024 were used for the analysis. Both original research and review articles regarding the role of various statins in the context of oral health were included. The selected articles provided a comprehensive overview of the current state of knowledge and highlighted existing gaps. Keywords used in the search included: statins, mucosa, oral health. A total of 824 papers were identified, of which 22 were selected after thorough abstract analysis. The inclusion criteria focused on the effects of statins on the oral mucosa, the oral microbiome, and jawbone physiology.

TABLE 1. Examples of type-1 and type-2 statins and their effects on oral health

Examples of statins		The effects
Type-1 statins	simvastatin	antibacterial antifungal anti-inflammatory antioxidant immunomodulatory salivary gland function anticancer wound healing bone formation
	lovastatin	
	pravastatin	
	demastatin	
Type-2 statins	atorvastatin	
	fluvastatin	
	pitavastatin	
	rosuvastatin	

To assess the quality of the selected publications, the Scale for the Assessment of Narrative Review Articles (SANRA) was applied. This validated tool evaluates narrative reviews based on 6 criteria: (1) justification of the article's importance for the journal's readership; (2) statement of specific aims or formulation of questions; (3) transparency about the sources of information and accurate description of the search history; (4) adequate referencing to support key statements; (5) appropriate scientific reasoning; and (6) proper presentation of data. Each criterion was scored from 0 (lowest) to 2 (highest), with a maximum total score of 12 points per article. Two independent reviewers assessed the articles, and discrepancies were resolved through discussion [6].

Despite offering valuable insights, these studies had certain limitations. Primarily, most of the research was conducted under *in vitro* conditions or on animal models. Additionally, the experimental models used may not fully reflect the complexity of the human organism, limiting the extrapolation of results to the human population.

RESULTS

The anti-inflammatory and immunomodulatory effects of statins are well documented. In the context of oral health, these effects have shown promising results in managing PD, as well as bacterial and fungal infections. A detailed analysis revealed anti-cancer properties, influence on salivary gland function, and potential protective effects of systemic statins on peri-implant bone health. In addition to their systemic effects, statins also exhibit local effects at the site of direct application (Tab. 1). Based on the information collected, the statins most important for oral health were identified as simvastatin, pitavastatin, and atorvastatin.

Systemic effects of statins in the oral cavity

Simvastatin (Fig. 1), notable for its antibacterial properties, selectively targets Gram-positive bacteria due to the protective barrier of Gram-negative bacterial membranes. It also exhibits anti-inflammatory effects, aiding in wound healing by disrupting bacterial protein synthesis. This mechanism shows promise in combatting methicillin-resistant *Staphylococcus aureus* (MRSA), reducing toxin production, and preventing biofilm formation. Moreover, simvastatin may help manage radiation-induced hyposalivation in head and neck cancer (HNC) patients. Radiation exposure creates reactive oxygen species, triggering inflammation through transforming growth factor-1 (TGF-1) activation Simvastatin administration curtails TGF-1 levels, preserving the submandibular gland and potentially restoring salivary function [4].

In cancer therapy, simvastatin's exact mechanisms are still under investigation. It inhibits the mevalonate pathway, reducing cholesterol synthesis and destabilizing cancer cell membranes. It also affects cancer cells via other pathways, such as transient receptor potential cation channel subfamily C member 6 (TRPC6) inhibition and suppression of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase subunits. In oral squamous cell carcinoma (OSCC), simvastatin reduces cell proliferation through transmembrane member 16A (TMEM16A) channel inhibition and induces apoptosis, suggesting its potential as an OSCC treatment [7]. Research suggests the *KLF2* gene, often downregulated in cancer, may be involved in statin-induced OSCC inhibition, although direct evidence is lacking [8].

In a study by Parolina de Carvalho et al., simvastatin, atorvastatin, pravastatin, and rosuvastatin were tested against oral bacteria, and their interactions with amoxicillin and metronidazole were analyzed. Except for pravastatin, all exhibited antibacterial activity. *Fusobacterium nucleatum* was resistant to all statins, while rosuvastatin affected only *Porphyromonas gingivalis*. Simvastatin showed the highest efficacy with the lowest MIC values. Combined with amoxicillin or metronidazole, it displayed synergistic effects, particularly with amoxicillin against *Streptococcus oralis* and *Streptococcus sanguinis*, and with metronidazole against *P. gingivalis* and *Prevotella intermedia*. These combinations reduced the minimum inhibitory concentration (MIC) values, amplifying antibacterial effects [9].

Research by Kamińska et al. examined statins' effects on bacterial growth, identifying MIC values for atorvastatin, fluvastatin, lovastatin, and simvastatin against key anaerobic periodontal pathogens and commensal bacteria. All tested statins, particularly simvastatin, were most effective against *P. gingivalis*, while *Streptococcus gordonii*, *Actinomyces naeslundii*, and *F. nucleatum* showed resistance [3].

Alkakhan et al. used a gingival fibroblast–macrophage co-culture model to assess simvastatin's potential in reducing inflammation in PD. The study revealed simvastatin's ability to inhibit pro-inflammatory M1 macrophages while promoting anti-inflammatory M2 macrophages. This shift was supported by changes in chemokine expression, macrophage morphology, and gene expression, with downregulation of pro-inflammatory markers and upregulation of anti-inflammatory ones. Simvastatin's potential to modulate macrophage responses and promote tissue homeostasis suggests its utility in managing inflammatory disorders such as PD [10].

Cai et al. explored simvastatin's effects on the human SACC-83 cell line of salivary adenoid cystic carcinoma (SACC). They

observed that simvastatin reduced cell proliferation in a time- and dose-dependent manner, with higher concentrations causing significant inhibition. Flow cytometry showed simvastatin-induced cell cycle arrest in the G1 phase, with a decrease in survivin expression. Additionally, simvastatin increased apoptosis and reduced cell invasiveness. These findings suggest simvastatin as a potential therapeutic agent for treating salivary gland adenoid cystic carcinoma, warranting further clinical research [11].

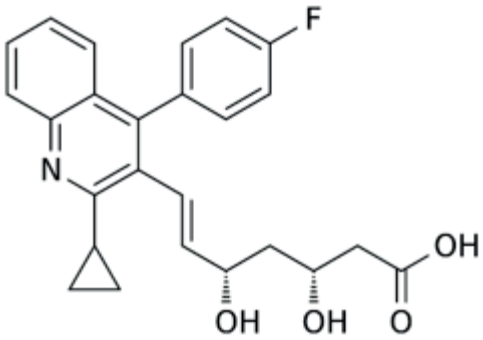

FIGURE 1. Chemical structure of simvastatin

Pitavastatin (Fig. 2) is distinguished by a heptenoate backbone, a quinoline ring, and fluorophenyl and cyclopropyl groups. This unique chemical structure minimizes its interaction with cytochrome P450 3A4 and enhances enterohepatic recirculation, leading to effective low-density lipoprotein-cholesterol (LDL-C) reduction and prolonged action [12].

In a study by Lee et al., pitavastatin's impact was assessed alongside simvastatin on 2 OSCC cell lines (OSCC15 and OSCC4). Pitavastatin effectively induced apoptosis in OSCC15 cells, increasing apoptosis by 31% at 0.1 μmol and by 53% at 0.25 μmol. It also reduced the colony-forming ability of OSCC15 cells, demonstrating its potential to inhibit tumor growth. Overall, pitavastatin was more effective than simvastatin in limiting metastasis in these cell lines [13].

Ishikawa et al. compared the anticancer effects of various statins on canine oral melanoma, finding that lipophilic statins, including pitavastatin, were significantly more effective than the hydrophilic rosuvastatin. Pitavastatin proved to be the most potent, requiring only 1/20th of the concentration of rosuvastatin to achieve comparable effects, making it the best candidate for treating this aggressive cancer in dogs [14].

Gupta et al. studied the effects of statins on overall survival (OAS) and cancer-specific survival in patients with HNC, using data from the SEER-Medicare linked dataset. They divided participants into 3 groups: those without hyperlipidemia, those with hyperlipidemia but not on statins, and those with hyperlipidemia on statin therapy. Patients on statins exhibited significantly better OAS and cancer-specific survival compared to the other groups. These findings suggest the potential of statins as an adjunct therapy in HNC, linking their use with improved survival outcomes [15].

Spoerl et al. investigated the impact of long-term statin use on OSCC. Their retrospective study involved 602 patients who underwent primary curative tumor resection and neck dissection. They found a strong correlation between statin use and improved OAS and recurrence-free survival, especially in patients under 70. This research underscores the potential role of statins in improving oncological outcomes and advocates for further clinical trials to confirm these benefits [16].

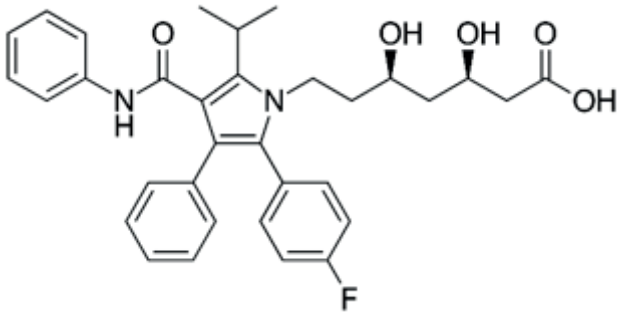

FIGURE 2. Chemical structure of pitavastatin

Atorvastatin (Fig. 3) is a lipid-regulating medication with a molecular weight of 558.65 g/mol. In its calcium trihydrate form, it becomes a soluble white crystalline powder with a molecular weight of 1209.41 g/mol. This drug effectively reduces harmful cholesterol levels – LDL-C, very-low-density lipoprotein-cholesterol (VLDL-C) – while increasing beneficial high-density lipoprotein-cholesterol (HDL-C) in the bloodstream. It is typically prescribed in 10–80 mg daily doses to prevent cardiovascular events [17].

Ajdidi et al. tested atorvastatin's antifungal properties against *Candida albicans*, which relies on sterol biosynthesis. They added varying amounts of atorvastatin to cultured colonies and observed colony growth inhibition after 24 h. A dose of 96 μg/mL significantly inhibited growth, and cells exposed to atorvastatin showed lower ergosterol levels than the control group. Infected larvae treated with atorvastatin exhibited higher survival rates than the untreated group, with no observed toxic effects [18].

In 2015, Rahal et al. assessed atorvastatin's antimicrobial and immunomodulatory effects in mice infected with *C. albicans*. They divided the mice into 5 groups, each receiving atorvastatin at different times. The lowest survival rate (11.1%) occurred in the group treated for 5 days before infection. In contrast, the group treated 5 days post-infection had a 22.2% survival rate, while a single injection provided a 44.4% survival rate. This study suggests that atorvastatin's immunosuppressive effects outweighed its antifungal action, with decreased serum levels of interferon-gamma (IFN-γ) and interleukin-4 (IL-4) [19].

Biselli-Chicote et al. explored atorvastatin's effects on OSCC cell lines, particularly HN13 [20]. Cells were exposed to atorvastatin at concentrations of 1 μM, 5 μM, and 10 μM to measure reactive oxygen species. Higher atorvastatin doses increased vascular endothelial growth factor-A (VEGF-A) protein levels, indicating elevated oxidative stress and potentially leading to tumor growth inhibition. Overall, statins, particularly

lipophilic ones like atorvastatin, effectively suppress various cancer cell lines by inhibiting tumor proliferation and survival [21]. Compared to hydrophilic statins like rosuvastatin and pravastatin, atorvastatin proved most effective.

Bahrami-Hessari and Jansson analyzed statins' impact on peri-implant bone health in a retrospective cohort study of 256 patients, dividing them into 60 statin users and 196 non-users. Results indicated a significant correlation between statin use and reduced peri-implant bone loss, even after adjusting for age and sex. However, no significant association was found between statin use and peri-implantitis severity, suggesting a nuanced relationship requiring further investigation [22].

These findings emphasize atorvastatin's potential benefits in antifungal treatment, cancer therapy, and dental health.

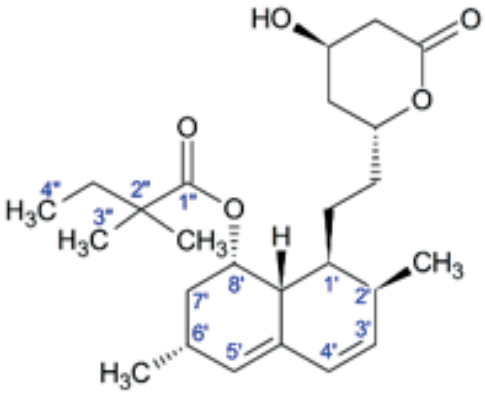

FIGURE 3. Chemical structure of atorvastatin

Local effects of statins in the oral cavity

The localized application of statins can serve as a significant therapeutic approach in periodontology and oral health due to their multifaceted pharmacological effects. Beyond cholesterol management, statins exhibit anti-inflammatory, immunomodulatory, and antimicrobial properties that are valuable in treating oral diseases. As mentioned above, statins such as simvastatin and atorvastatin effectively address PD, oral cancers, and infections within the oral cavity. Simvastatin, for example, demonstrates efficacy against Gram-positive bacteria like MRSA by inhibiting protein synthesis and biofilm formation. It also mitigates TGF-1 elevation, reducing radiation-induced hyposalivation – a common issue among HNC patients – thus protecting salivary gland function. Atorvastatin exhibits antifungal properties against *C. albicans* by inhibiting fungal sterol biosynthesis. Both statins also possess significant anticancer activity, with simvastatin shown to inhibit OSCC cell proliferation and induce apoptosis, although the underlying mechanisms are still being investigated [4, 8, 18, 20].

In vitro and *in vivo* studies in animals and humans suggest positive effects of both systemic and local application of statins on oral health. Topical application offers an alternative treatment route, as systemic oral administration decreases bioavailability, requires higher doses, and increases the risk of adverse effects. Suitable carriers, such as gelatin hydrogel, can support statin-induced bone regeneration and enhance local delivery [5, 23]. When applied locally via gels or other carriers, statins can promote wound healing, enhance bone metabolism, and reduce pain. For example, local application of simvastatin in low doses (10 mg/mL) is safe and promotes wound healing. Furthermore, local injection of simvastatin has been shown to induce bone formation. In a study by Madi and Kassem, a topical simvastatin/chitosan gel (10 mg/mL), applied 3 times daily for 7 days, improved healing and reduced pain at the palatal donor site after free gingival grafts [24].

Studies have also shown that simvastatin gel (1.2 mg/0.1 mL) used as an adjunct to scaling and root planing (SRP) for the treatment of class II furcation defects improves clinical parameters and bone formation after 6 months [4]. Topically applied statins have also been found to support osseointegration of implants and help control orthodontic relapse, highlighting their potential as adjuncts in oral health management [5, 22]. Türer et al. demonstrated that an absorbable collagen sponge soaked with 1 mg of rosuvastatin in saline solution stimulated regeneration following mandibular fracture in rats [25].

Several studies have confirmed the antifungal properties of statins. A study conducted by de Oliveira Neto on the use of 3% atorvastatin emulgel for the treatment of oral candidiasis showed a complete reduction in fungal burden after 9 days of treatment [26]. These diverse pharmacological actions reveal the potential of local statin application in oral health management, providing an innovative treatment modality for oral mucosal diseases. However, this area remains in the developmental stage, and further research is essential to fully understand and harness the therapeutic potential of statins in dental and oral health applications [1, 2, 3, 4, 7, 18].

Adverse effects of statins in the oral cavity

A study conducted by Glick et al. from the University of Texas School of Dentistry at Houston analyzed the frequency of statin prescriptions in the US population, noting 96,942,508 prescriptions for atorvastatin and 65,144,488 for simvastatin in 2019. The study also examined adverse oral reactions associated with various medications, including statins. Reported side effects potentially linked to statin use included disturbances in taste and mucosal dryness. Additionally, allergic reactions (e.g., anaphylaxis, angioedema) and severe skin conditions (e.g., erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis) were observed, although not exclusively linked to statins [27].

A study by Pascual Cruz et al. supported these findings, identifying dry mouth, itchiness or paresthesia (in the tongue, lips, and throat), bitterness, cough, and insomnia as among the most frequently reported adverse effects of statins. Distribution by statin type included: simvastatin (n = 15), pravastatin (n = 7), atorvastatin (n = 3), and lovastatin (n = 1). Improvement rates varied by symptom: dry mouth (74%), bitterness (93%), cough (92%), tongue itchiness (47%), throat itchiness (40%), and insomnia (94%) [28]. These findings highlight the importance

of monitoring statin-induced oral symptoms to ensure timely intervention and patient well-being.

Patients receiving statin therapy should remain vigilant for potential side effects and consult healthcare professionals if adverse symptoms occur. Regular dental check-ups are also recommended to monitor and manage any oral health complications during statin treatment, ensuring a proactive approach to care and patient safety.

Although this review provides valuable insights into the adverse oral effects of statins, it is important to note that only a limited number of studies have explored this topic. This scarcity underscores the need for further investigation to better understand the mechanisms and clinical implications of these adverse effects.

CONCLUSION

Statins exhibit significant anti-inflammatory, immunomodulatory, and antimicrobial properties that are beneficial in managing PD, infections, and oral cancers. Simvastatin, pitavastatin, and atorvastatin have demonstrated efficacy in promoting wound healing, bone regeneration, and reducing inflammation. The local application of statins, especially when delivered via carriers such as gelatin hydrogel, enhances their therapeutic potential while minimizing systemic side effects. Regular dental check-ups and careful monitoring are essential to manage adverse effects and ensure optimal treatment outcomes. Although current findings are promising, the mechanisms underlying the effects of statins in the oral cavity remain incompletely understood, highlighting the need for further research to evaluate the balance between their benefits and potential risks in dental applications.

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