



Expanding horizons of Simvastatin in dentistry: A literature review

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Abstract

Simvastatin, traditionally used for managing hypercholesterolemia, has recently emerged as a promising bioactive agent in dentistry due to its diverse biological actions. Growing scientific evidence indicates its potential role in enhancing hard tissue regeneration, modulating inflammatory responses, and exerting antimicrobial effects within the oral environment. By influencing molecular pathways involved in bone metabolism and cellular differentiation, simvastatin contributes to improved tissue repair and mineralized tissue formation.

Experimental and clinical studies suggest beneficial outcomes in periodontal therapy, endodontic management, implant healing, and osseous defect regeneration when simvastatin is applied locally or systemically. Its adjunctive use has been associated with improved healing responses and enhanced clinical parameters in various dental conditions.

Despite encouraging findings, differences in study protocols, concentrations, and delivery systems necessitate further well-designed, long-term clinical trials to establish standardized guidelines. Simvastatin holds significant potential as an adjunctive therapeutic agent in modern regenerative dentistry.

Keywords: Simvastatin, regenerative dentistry, bone regeneration, periodontal therapy, endodontics, implant healing, anti-inflammatory effects

Introduction

Simvastatin, a synthetic lipid-lowering drug that acts by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is primarily indicated for the management of hypercholesterolemia. In recent years, its biological actions beyond cholesterol regulation have gained considerable attention in dental research. Recent dental literature highlighted the expanding role of simvastatin in dentistry, emphasizing its regenerative capacity, anti-inflammatory effects, and antimicrobial properties^[1].

Comprehensive evaluations of statins in oral health have further reinforced this perspective. Experimental and clinical data reports that statins contribute to improved periodontal health, enhanced bone metabolism, and modulation of inflammatory mediators^[2]. These findings indicate that simvastatin may exert beneficial effects on oral tissues through multiple biological pathways.

The regenerative potential of simvastatin has been particularly associated with stimulation of osteoblastic activity and upregulation of bone morphogenetic protein-2 (BMP-2), thereby promoting mineralized tissue formation. It has synergistic role in oral health applications, suggesting its usefulness in periodontal regeneration, treatment of intrabony defects, and dentin repair procedures^[3].

In endodontics, achieving effective canal disinfection and smear layer removal remains essential for successful outcomes. Research exploring novel irrigants and biologically active adjuncts continues to evolve. Its effectiveness as a new endodontic irrigant in smear layer removal, underscoring the importance of agents that combine antimicrobial efficacy with biocompatibility—an area where simvastatin-based formulations may offer promising potential^[4].

Moreover, the antimicrobial influence of simvastatin has been investigated against endodontic biofilms. Studies demonstrated its inhibitory action on biofilm models in vitro, indicating its possible role in disrupting microbial colonization and persistence within root canal systems^[5].

The osteogenic benefits of statins have also been supported by clinical evidence. Through meta-analytic evaluation, reported an association between statin use and increased bone mineral density, reinforcing their bone-forming capabilities^[6]. Translating these findings to dental practice suggests that simvastatin may enhance alveolar bone regeneration and periapical tissue healing.

Taken together, the multifaceted properties of simvastatin—including bone stimulation, inflammation control, and antimicrobial activity—position it as a promising adjunct in contemporary dental therapy. However, standardized protocols regarding concentration, delivery systems, and long-term clinical outcomes remain to be established. This literature review therefore aims to critically appraise existing evidence on the therapeutic applications and future potential of simvastatin in dentistry.

Pharmacological Background

Simvastatin is widely used in the management of hypercholesterolemia. It is a semi-synthetic derivative obtained from a fermentation product of *Aspergillus terreus*. Structurally, simvastatin, along with lovastatin, contains a lactone ring and is administered as an inactive prodrug. Once in the body, it is metabolized into its active β -hydroxy acid form.

Pharmacologically, simvastatin acts by competitively and reversibly inhibiting HMG-CoA reductase, the key rate-limiting enzyme involved in cholesterol biosynthesis. It is administered orally in doses ranging from 5 to 80 mg per day, depending on the severity of the condition. The therapeutic effects typically begin within 1–2 weeks, with maximum efficacy observed after 4–6 weeks of treatment.

Like other statins, simvastatin is generally well tolerated; however, it may be associated with adverse effects such as muscle pain (myalgia) and, in rare cases, more severe muscle damage like rhabdomyolysis^[7]. Beyond its primary indication, simvastatin has demonstrated multiple pleiotropic effects that extend its therapeutic relevance into

fields such as dentistry. A narrative review by Alsaeed et al. ^[1] emphasized that simvastatin exhibits regenerative, anti-inflammatory, and antimicrobial properties, making it a potential adjunct in oral healthcare.

One of the significant pharmacological actions of simvastatin is its ability to modulate inflammatory pathways. It can regulate cytokine expression when used as an intracanal medicament, reducing pro-inflammatory mediators such as interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9), while increasing anti-inflammatory interleukin-10 (IL-10) ^[8]. This host-modulatory effect contributes to improved healing responses in inflamed periapical tissues.

In addition to its anti-inflammatory action, simvastatin plays a crucial role in bone metabolism. The emerging role of statins in osteoporosis management, highlighting their capacity to enhance bone formation and reduce bone resorption ^[9]. These effects are attributed to stimulation of osteoblastic activity and promotion of bone matrix formation, which are particularly relevant in periodontal regeneration and alveolar bone healing.

Furthermore, simvastatin has demonstrated notable antimicrobial properties. Thangamani et al. ^[10] explored its potential as a topical antibacterial agent and reported its effectiveness against a variety of microbial strains. This antimicrobial action is believed to result from interference with bacterial cell membrane integrity and metabolic pathways, supporting its use in controlling oral infections.

The pharmacological profile of simvastatin encompasses lipid-lowering, anti-inflammatory, osteogenic, and antimicrobial actions. These multifaceted properties provide a strong biological basis for its emerging applications in dentistry, particularly in regenerative and endodontic therapies.

Mechanism of Action

Simvastatin reduces cholesterol synthesis and increases LDL clearance from the blood. It also has additional effects such as reducing inflammation and promoting bone formation, which are beneficial in dental applications.

Molecular Mechanisms Underlying Regenerative Effects

The osteogenic potential of simvastatin has been extensively studied. Ruan et al. ^[11] described the molecular mechanisms by which statins stimulate bone formation, primarily through upregulation of bone morphogenetic protein-2 (BMP-2) and enhanced osteoblastic differentiation. Immunohistochemical investigations have confirmed statin-induced BMP-2 expression during bone regeneration ^[12]. Clinical evidence also supports this anabolic action; studies demonstrated increased bone mineral density among statin users ^[6]. Reviews exploring statins in osteoporosis management further reinforce their capacity to improve bone metabolism ^[9].

Experimental studies provide additional evidence of enhanced bone remodeling following local simvastatin application. Wu et al. ^[13] reported improved alveolar bone healing after tooth extraction. Studies confirmed stimulation of both endochondral and intramembranous ossification in animal models ^[14]. Animal research has also demonstrated increased bone formation around titanium implants and jaw defects following simvastatin use ^[15, 16].

The regeneration of dentin and pulp is impacted by statins. It has also been demonstrated to encourage the mineralizing phenotype in dental pulp stem cells (DPSCs) ^[3].

Anti-Inflammatory effects

Simvastatin exhibits notable anti-inflammatory properties that enhance its potential use in dental therapy. An in vitro study by Sharma et al. ^[17] assessed root canal sealers containing simvastatin and reported a decrease in the release of the pro-inflammatory cytokine interleukin-6 (IL-6), suggesting its ability to regulate inflammatory activity at the cellular level.

Clinical evidence further substantiates these effects. In a triple-blind randomized controlled trial, demonstrated that intracanal application of simvastatin in teeth with symptomatic apical periodontitis led to a significant reduction in pro-inflammatory markers such as IL-6 and matrix metalloproteinase-9 (MMP-9), along with an increase in the anti-inflammatory cytokine interleukin-10 (IL-10) ^[8]. This modulation of cytokine expression indicates a favorable shift toward resolution of inflammation and improved tissue healing.

At the molecular level simvastatin suppresses lipopolysaccharide-induced production of inflammatory cytokines and cell adhesion molecules in human dental pulp cells. This effect limits inflammatory signaling and cellular interactions that contribute to tissue damage ^[18].

Hence simvastatin reduces inflammation by downregulating pro-inflammatory mediators, enhancing anti-inflammatory responses, and influencing cellular pathways, thereby supporting its role as an adjunct in the management of inflammatory dental conditions.

Host-modulatory effects

Simvastatin has been increasingly recognized for its host modulatory actions in addition to its lipid-lowering effects. In the context of dentistry, host modulation involves altering the inflammatory and immune responses of the body to minimize tissue destruction and enhance healing. Reviews by Alsaeed et al. ^[1] and Tahamtan et al. ^[2] emphasized that simvastatin possesses anti-inflammatory and immunoregulatory properties, supporting its use as an adjunct in periodontal and endodontic therapy.

At the cellular level, simvastatin plays a role in regulating inflammatory mediators. It suppresses lipopolysaccharide-induced production of pro-inflammatory cytokines and adhesion molecules in human dental pulp cells ^[18]. In a similar context, Sharma et al. ^[17] observed decreased levels of interleukin-6 (IL-6) when simvastatin was incorporated into root canal sealers, indicating its ability to attenuate inflammatory responses.

Clinical studies further validate these findings. Intracanal application of simvastatin in cases of symptomatic apical periodontitis led to a significant reduction in pro-inflammatory markers, including IL-6 and matrix metalloproteinase-9 (MMP-9), along with an increase in the anti-inflammatory cytokine interleukin-10 (IL-10) ^[8].

In addition to controlling inflammation, simvastatin contributes to tissue regeneration. It has role in enhancing bone morphogenetic protein-2 (BMP-2) expression and promoting osteoblastic activity and has ability to stimulate bone formation and reduce bone resorption ^[9, 11]. Moreover, statins can facilitate wound healing, which is beneficial in the repair of oral tissues ^[19].

Clinical periodontal studies also demonstrate the host-modulating potential of simvastatin. Improved clinical and biochemical parameters when simvastatin was used alongside conventional therapy ^[21]. Agarwal et al. ^[22] reported significant gains in clinical attachment and

reductions in probing depth with local simvastatin delivery. Additionally, a systematic review by Greethurst et al. [23] concluded that statins enhance periodontal treatment outcomes, likely through their effects on host inflammatory pathways.

In summary, simvastatin modulates the host response by reducing pro-inflammatory mediators, increasing anti-inflammatory cytokines, promoting bone regeneration, and supporting tissue healing, thereby establishing its role as a valuable adjunct in the management of dental diseases.

Antimicrobial Properties and Biofilm Control

Simvastatin has demonstrated notable antimicrobial activity, making it a potential adjunct in controlling oral infections and endodontic biofilms. Studies have shown that, apart from its systemic effects, simvastatin can inhibit the growth of various microorganisms. It exhibits antibacterial activity comparable to other statins against multiple microbial strains [24]. Similarly, its potential as a topical antimicrobial agent, suggest its ability to interfere with bacterial cell function and viability [10].

In endodontics, biofilm eradication is critical for successful treatment outcomes. Simvastatin effectively inhibits endodontic biofilm formation *in vitro*, indicating its usefulness in disrupting microbial colonization within root canal systems [5]. Supporting this, Shroff et al. [25] found that simvastatin showed significant antimicrobial efficacy as an intracanal medicament, comparable to conventional double antibiotic paste.

The effectiveness of simvastatin in combination therapies has also been explored. Almarji et al. [26] evaluated a modified 3Mix-Simvastatin formulation in non-instrumental endodontic treatment and reported favourable clinical outcomes, suggesting enhanced antimicrobial action when used in combination. Additionally, improved clinical and microbiological parameters when simvastatin gel was used adjunctively with scaling and root planing, indicating its role in reducing periodontal microbial load [21].

While traditional irrigants focus primarily on smear layer removal, studies emphasize the importance of agents that combine antimicrobial activity with tissue compatibility. Selvakumar et al. [4] and related investigations [27] highlighted the need for such advanced irrigants capable of targeting resistant microorganisms like *Enterococcus faecalis*. In this context, simvastatin may serve as a promising adjunct due to its dual antimicrobial and biological properties.

Overall, simvastatin contributes to biofilm control by inhibiting microbial growth, disrupting established biofilms, and enhancing the effectiveness of existing antimicrobial strategies, thereby supporting its potential application in both periodontal and endodontic therapies.

Applications in Dentistry

Simvastatin has gained considerable importance in dentistry due to its diverse biological properties, including osteogenic, anti-inflammatory, and antimicrobial effects. In periodontology, it has been extensively used as a local drug delivery agent. Clinical studies have shown that adjunctive use of simvastatin gel with scaling and root planing results in significant improvements in probing depth reduction, clinical attachment levels, and bone regeneration [21, 22]. Moreover, its application in intrabony and furcation defects has demonstrated enhanced periodontal regeneration outcomes [33, 34].

In endodontic practice, simvastatin has been explored as an intracanal medicament owing to its antimicrobial and host-modulating capabilities. It has been shown to reduce microbial load, disrupt biofilms, and regulate inflammatory responses within the root canal system [5, 8, 25]. Additionally, its incorporation into root canal sealers has exhibited good biocompatibility along with anti-inflammatory effects, indicating its potential to improve treatment success [17].

Simvastatin has also been investigated in vital pulp therapy, where it has shown promising results in enhancing pulp healing and promoting dentin formation in pulpotomy procedures [28]. Furthermore, combination approaches such as the modified 3Mix-Simvastatin formulation have demonstrated favorable outcomes in non-instrumental endodontic treatment, particularly in primary teeth [26].

In oral surgery and implantology, simvastatin has been reported to enhance bone regeneration and accelerate healing processes. Studies indicate improved alveolar bone formation following tooth extraction and increased bone deposition around dental implants when simvastatin is applied locally [13, 15].

Simvastatin shows wide-ranging applications in dentistry, spanning periodontal therapy, endodontics, pulp treatment, and bone regeneration. Its multifunctional properties make it a promising adjunct in clinical practice, although further research is needed to establish standardized protocols for its routine use.

Applications in Endodontics

Simvastatin has been increasingly explored in endodontics due to its antimicrobial, anti-inflammatory, and regenerative properties. Effective disinfection and smear layer removal are essential for successful root canal therapy. The importance of irrigants that not only remove the smear layer but also possess antimicrobial efficacy and biocompatibility, highlighting the need for advanced adjunctive agents such as simvastatin [4].

The antimicrobial potential of simvastatin has been demonstrated in endodontic infections. Ferrer-Luque et al. [5] reported its ability to inhibit endodontic biofilms *in vitro*, indicating its role in disrupting microbial colonization within root canal systems. Similarly, simvastatin, when used as an intracanal medicament, exhibits significant antimicrobial efficacy comparable to that of conventional double antibiotic paste [25].

In addition to its antimicrobial effects, simvastatin has shown promising results in vital pulp therapy. Improved clinical outcomes in pulpotomy procedures of permanent molars with symptomatic irreversible pulpitis, suggesting its potential to promote pulp healing and regeneration [28]. Furthermore, combination therapies have been explored to enhance its effectiveness. Modified 3Mix-Simvastatin formulation in non-instrumental endodontic treatment of necrotic primary molars shows favorable clinical success [26].

Simvastatin also contributes to periapical healing. It can reduce periapical lesion progression, likely due to its anti-inflammatory and osteogenic effects. These findings indicate that simvastatin not only aids in infection control but also enhances tissue repair and regeneration in periapical regions [29].

Simvastatin shows significant potential in endodontics as an intracanal medicament, regenerative agent, and adjunct to conventional therapies. Its combined antimicrobial, anti-

inflammatory, and healing properties make it a promising candidate for improving endodontic treatment outcomes.

Periodontal Therapeutic Applications

Simvastatin has been extensively investigated as an adjunct in periodontal therapy due to its anti-inflammatory, antimicrobial, and regenerative properties. Its local delivery in periodontal pockets has shown promising clinical outcomes when combined with conventional treatment modalities such as scaling and root planing (SRP). Rahman et al. [21] demonstrated that the adjunctive use of 1.2% simvastatin gel, along with antimicrobial photodynamic therapy, resulted in significant improvements in clinical, microbiological, and biochemical parameters compared to SRP alone. Similarly, subgingival delivery of simvastatin gel in patients with chronic periodontitis has been associated with notable reductions in probing depth and significant gains in clinical attachment levels [22].

The beneficial effects of simvastatin in periodontal therapy are further supported by systematic evidence. Greethurst et al. [23], in a systematic review and meta-analysis, concluded that statins used as adjuncts to nonsurgical periodontal therapy significantly enhance clinical outcomes, likely through modulation of host inflammatory responses and promotion of tissue regeneration. Simvastatin in the form of oral gel and mouthwash improved periodontal parameters when used alongside SRP [30].

In addition to nonsurgical therapy, simvastatin has shown effectiveness in managing advanced periodontal defects. Improved outcomes in Class II furcation defects have been observed with subgingival delivery of simvastatin, including enhanced bone fill and greater clinical attachment gain [33]. Similarly, its efficacy has also been demonstrated in patients with type 2 diabetes and chronic periodontitis, indicating its potential benefits even in medically compromised individuals [34]. Improved healing and enhanced bone regeneration have been observed when simvastatin gel is applied during the surgical management of osseous defects [35].

The regenerative potential of simvastatin is also highlighted in studies evaluating bone formation. Killeen et al. [32] reported that simvastatin promotes new bone formation in periodontal defects, although interactions with other agents such as alendronate may influence outcomes. Additionally, systemic statin use is associated with reduced tooth loss in patients with chronic periodontitis, supporting its long-term benefits [31].

Although primarily focused on endodontics, the host-modulatory effects demonstrated by Harikrishnan et al. [8] further reinforce the anti-inflammatory potential of simvastatin, which is relevant to periodontal disease management.

Simvastatin shows considerable promise in periodontal therapy by improving clinical parameters, enhancing bone regeneration, and modulating the host inflammatory response. Its adjunctive use with conventional treatments may offer improved therapeutic outcomes, although further standardized clinical protocols are needed for routine application.

Implantology and Bone Augmentation

Simvastatin has been widely investigated for its osteogenic potential, making it a promising adjunct in implantology and bone augmentation procedures. Its ability to enhance bone

formation and improve bone quality is supported by both clinical and experimental evidence. A meta-analysis by Uzzan et al. [6] demonstrated a positive association between statin therapy and increased bone mineral density, suggesting a systemic benefit in bone metabolism. Similarly, Jadhav and Jain [9] highlighted the emerging role of statins in osteoporosis management, emphasizing their capacity to stimulate bone formation and reduce bone resorption.

At the molecular level, simvastatin promotes bone regeneration by upregulating osteogenic pathways. Statins enhance osteoblastic differentiation and increase the expression of bone morphogenetic proteins, particularly BMP-2 [11]. This was further supported by Alam et al. [12], who demonstrated increased BMP-2 expression during bone regeneration following statin application, indicating a direct stimulatory effect on bone formation.

Experimental studies have provided strong evidence for the role of simvastatin in bone regeneration. Enhanced alveolar bone remodeling following tooth extraction with simvastatin application, suggest its potential in post-extraction socket preservation [13]. Also topical simvastatin promotes both endochondral and intramembranous ossification, further confirming its osteoinductive capabilities [14].

In implantology, simvastatin has shown promising results in improving osseointegration. Ayukawa et al. [15] observed increased bone formation around titanium implants in animal models, indicating enhanced implant stability. Similarly, augmented bone formation in the jaw when simvastatin was locally applied, support its use in bone augmentation procedures [16].

Hence simvastatin enhances bone regeneration through stimulation of osteoblastic activity, increased bone matrix formation, and upregulation of growth factors such as BMP-2. These properties make it a valuable adjunct in implant dentistry and bone augmentation, with potential applications in improving implant success rates and managing bone defects.

Biocompatibility and Safety Considerations

Biocompatibility remains essential for clinical adoption. Incorporation of simvastatin into root canal sealers did not produce significant cytotoxic effects and may modulate inflammatory cytokine production favorably.¹⁷ Research on novel irrigants also emphasizes the importance of maintaining tissue compatibility while achieving antimicrobial effectiveness [4, 7].

Broader Therapeutic Perspective and Future Directions

The diverse biological actions of statins have led to their description as potentially transformative therapeutic agents in medicine. In dentistry, accumulated evidence from *in vitro* studies, animal experiments, randomized controlled trials, and systematic reviews consistently supports the osteogenic, anti-inflammatory, antimicrobial, and wound-healing properties of simvastatin. Simvastatin demonstrates multifaceted therapeutic potential across periodontology, endodontics, implantology, and regenerative dentistry. While current findings are promising, variability in study designs, drug concentrations, and delivery systems highlights the need for standardized clinical protocols and long-term randomized controlled trials. Further research will determine its optimal integration into routine dental practice.

Conclusion

Simvastatin, beyond its conventional lipid-lowering role, has shown considerable potential in dentistry due to its anti-inflammatory, antimicrobial, osteogenic, and host modulatory properties. Evidence suggests its beneficial applications in periodontology, endodontics, regenerative procedures, and implantology, where it enhances healing and promotes bone formation.

However, variability in study designs and delivery methods highlights the need for further standardized clinical research. Overall, simvastatin emerges as a promising adjunct in dental therapy with the potential to improve clinical outcomes.

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