Mustansiria Dental Journal
DOI: [10.32828/mdj.v21i2.1209]

E- ISSN: 2618-0944
P- ISSN: 1813-8500

Research Article | **Open Access** | **Volume: 21, Issue: 2, 2025**

Simvastatin's Application in Dentistry. A Narrative Review

Muna Alaa Alsaaed [1], Nada M H Al-Ghaban [2], Enas Fadhil Kadhim [2], Zaid A. Abdulhussein [3], and Mohammed A. Abdalqader [4]

[1] *Department of Oral pathology, College of Dentistry, Mustansiriyah University, Baghdad, Iraq*
[2] *Department of Oral Diagnostic Sciences, College of Dentistry, University of Baghdad, Baghdad, Iraq*
[3] *Department of Orthodontics, College of Dentistry, AL Mashreq University., Baghdad, Iraq*
[4] *Faculty of Medicine, University of Cyberjaya, Persiaran Bestari, Cyber 11, 63000 Cyberjaya, Selangor Darul Ehsan, Malaysia*

Correspondence: *Nada M H Al-Ghaban*
Email: *nada.mohammed@codental.uobaghdad.edu.iq*
Received: 13 July 2025; Accepted: 3 October 2025; Published: 30 December 2025

Abstract

Simvastatin, a pharmaceutical drug, belongs to the statin family, which shares the same properties of its mechanism of action, which is summarized by the lowering of hypercholesterolemia, by averting the production of mevalonate from HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA), which is a compulsory product in the cholesterol synthesis pathway. The proven effect of oral administration of Simvastatin on increasing bone formation and reducing bone resorption by overexpression of BMP-2 (Bone morphogenic protein 2) and lowering the bone resorption markers, abetted by its safe use and feasibility, made it an interesting point of many researchers. In terms of periodontal health, a number of dental studies have demonstrated a favorable response to both oral and local statin administration, including a significant reduction in tooth movement, improved clinical attachment levels, and increased bone fill in type II diabetic patients with chronic periodontitis. Researchers propose that simvastatin may partially mitigate the frequency and severity of relapse, while others indicate that exosome-based drug delivery holds considerable promise for therapeutic applications in orthodontics. Furthermore, simvastatin exhibits diverse effects and applications across various fields of dental practice. This review aims to entail the benefits and applications of statins in many domains of dentistry, including original manuscripts for the last five years.

.

Keywords: Simvastatin, Dentistry, Orthodontics, Endodontics, Periodontics

Introduction

Simvastatin is a member of the statins family, which constitutes a class of pharmaceuticals employed in the management of hypercholesterolemia. They are selective inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-COA) reductase, which plays a keystone role in the conversion of HMG-CoA to mevalonate, a preliminary rate-limiting product in hepatic cholesterol production (Calixto et al., 2011). They are generally well tolerated and possess an exemplary safety profile. However, their widespread use has resulted in an increase in many additional advantageous benefits, referred to as pleiotropic effects (Wong and Rabie, 2005). The first discovery of the effect of simvastatin on bone was made by Mundy et al.(Mundy et al., 1999). Later studies have shown its ability to reduce farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) expression (Ruan et

© The Author(s). Published by Mustansiriyah University. This article is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY) license.

al., 2012), inhibiting osteoblast death (Borton et al., 2001), and decreasing the rate of the osteoclast formation process (Kaji et al., 2005). Oral administration of Statin with a dose (20-40mg/day) daily dose accelerates osteogenesis by elevating the expression of the bone morphogenic protein-2 gene and diminishing bone resorption indicators (Okamoto et al., 2009, Hassan and Al Kayat, 2015, Jia et al., 2016, Sharaf Eldeen et al., 2022, Granat et al., 2024), while oral and local administration of statins has been shown to reduce tooth mobility, improve clinical attachment levels, and increase bone thickness in dental patients diagnosed with chronic periodontitis and type II diabetes (Estrela et al., 2008, Saifi et al., 2017). Simvastatin can be applied locally in multiform, either as a powder with the aid of carriers, including organic and non-organic types (Harsha et al., 2023, Alsaeed and Al-Ghaban, 2023, Granat et al., 2024), infused with gelatin hydrogel scaffold and other types of scaffolds (Ishihara et al., 2017). Their antibacterial properties, a critical factor, along with the requirements and the demand of the oral healthcare system on the currently available antibiotics, have rendered them the focus of numerous investigations (Thangamani et al., 2015). This review concentrated on recent dental studies for the last five years that incorporated simvastatin in their research.

Material and Methods

The data for this review were original articles collected from the PubMed database for the period from 2020 to 2025 using medical words indexed in MESH (Simvastatin, dentistry, orthodontic, endodontic, periodontic). All review articles and non-English written manuscripts were excluded from the search results.

Simvastatin application in orthodontic treatment

Relapse following orthodontic therapy constitutes a significant clinical concern in dentistry (AlSwafeeri et al., 2018). While researchers suggest that simvastatin may partially reduce the frequency and severity of relapse status (Guthrie, 2006, Han et al., 2010), others indicate that exosome-based medication delivery possesses significant potential for therapeutic application (Peng et al., 2024). A study evaluated the impact of simvastatin encapsulated in exosomes on osteogenesis and preventing recurrence following orthodontic tooth movement (OTM) on a rat model during the relapse phase. The periodontal ligament stem cells and their exosomes were isolated, followed by the extraction of the exosomal simvastatin, this group have shown elevated levels of osteogenic-related genes and proteins on the molecular level which were identified by Western blot, and quantitative RT-PCR analysis, and decrease in the number of bones resorptive lacunae histologically, which proves its effect to suppress relapse following orthodontic tooth movement (Liu et al., 2022).

Rapid palatal expansion (RPE) is routinely employed in paediatric orthodontics to widen the maxilla in young patients exhibiting transverse maxillary constriction, deep palatal vault, and associated cross-bite and crowding. Before the complete ossification of the palatal suture, this therapy involves the application of an expansion screw affixed to the bands on the first premolars and first molars or through analogous methods (Agarwal and Mathur, 2010, Cerritelli et al., 2022). It has been demonstrated to have faster bone development when low-level laser therapy (LLLT) and certain drugs are used. The duration of the retention phase may be shortened by combining these two therapeutic approaches. Farzan et al. experimented with the effects of LLLT and simvastatin, both separately and in combination, on the development of sutural bone in rats. The effect of 10 mg simvastatin with low-level laser therapy was compared with 5 mg simvastatin, 10 mg simvastatin, LLLT, and control. In each group, the expansion appliance was positioned in the parietal bone. Biomechanical and computed tomography [CT] evaluations after 30 days, and biomechanical, CT, and immunohistochemistry [IHC] evaluations after 60 days revealed that sutural bone growth was considerably enhanced by LLLT, simvastatin, and their combination as compared to the control group; however, the combined treatment produced noticeably better clinical outcomes than other therapies (Farzan et al., 2022).

Rosyida et al., who considered the effect of a gelatin-simvastatin hydrogel on bone remodeling during orthodontic relapse, found that during the retention phase, using gelatin-simvastatin hydrogel can promote bone development, prevent orthodontic relapse, and improve tooth stability. An orthodontic model was created by applying an open coil spring to shift the lower incisors distally while applying orthodontic force. During stabilization, a local gelatin-simvastatin hydrogel was injected, and compared to the control, which only received gelatin hydrogel. In order to promote a relapse, the springs from both groups were deboned following the stabilization phase. Digital calipers were used to measure the proportion of relapse. ELISA (Enzyme-linked immunosorbent assay) was used to analyze the levels of OPG (Osteoprotegrin) and RANKL (receptor activator of nuclear factor kappa-B ligand). The RANKL is mandatory for the differentiation of the bone resorptive cell (osteoclast); on the other hand, OPG is known for its role in blocking osteoclastogenesis by binding to RANKL, preventing it from binding to RANK, which is an osteoclast surface receptor (Kohli and Kohli, 2011). The RANKL level and relapse rate are considerably reduced in the therapy group when gelatin-simvastatin hydrogel is applied locally. Furthermore, the OPG level and OPG/RANKL ratio were raised. The RANK–RANKL–OPG signaling pathway elucidates the regulation of osteoclast formation activity by the osteoblast lineage during orthodontic movement (Rosyida et al., 2025)

Simvastatin application in oral medicine

The simvastatin anti- fibrotic potential has been discussed and investigated by many researches, which made it the focus of a study considering oral mucosa fibroses (OSMF) which is a chronic inflammatory illness, causing trismus and limited mouth opening, it has been linked to TGF-β signaling pathways, and areca nut extract

(ANE) has been involved in the disease's progression, as its stimulates fibrosis due to the major alkaloids in its composition, and reduces collagen degradation. It is considered a precursor to squamous cell carcinoma. Simvastatin's therapeutic value in the treatment of OSMF is still unknown. A study conducted on Male mice was randomly assigned to three groups according to various time points for this investigation. Injecting areca nut extracts into the mouse's back subcutaneous layer produced submucous fibrosis, which, within four weeks, resulted in skin fibrosis. Four distinct medication formulations were then administered to each mouse. Following treatment, samples were gathered for staining and histopathological analysis in order to evaluate collagen deposition, fibrosis, and skin thickness using histological and histochemical analysis. After four weeks, ANE treatment by itself markedly increased skin thickness and collagen deposition in comparison to the control group. Skin thickness and collagen deposition were significantly reduced when ANE and simvastatin were administered together. Simvastatin successfully inhibited the production of fibrosis-related proteins, such as CTGF and α-SMA, in ANE-induced subdermal fibrosis, according to Western blot analysis. These findings lay the groundwork for further research and potential clinical uses by indicating that simvastatin may have therapeutic benefits on ANE-induced subdermal fibrosis (Chang et al., 2023).

Application of simvastatin in Pedodontics and Endodontic dentistry

Pulpectomy is known as the traditional method for treating decidous necrotic molars, a new technique known as lesion sterilization and tissue repair (LSTR) or non-instrumentation endodontic treatment (NIET), which utilizes a mix of antibiotics to irradicate microorganisms from carious dental tissues, may be considered as a simpler substitute; LSTR seeks to eradicate or diminish the microbial burden within the diseased pulp, so averting more damage and infection, and restore the tooth health and function by stimulating repair, healing, and regeneration of necrotic pulp tissue. Research reveals that statins could enhance osteoblasts and odontoblasts functionality, while also providing anti-inflammatory benefits that promote bone repair. The use of statins in triple antibiotic paste is a viable approach in improving inter-radicular lesion healing, since they improve osteoblasts and odontoblasts' function, which can preserve necrotic deciduous dentition until their shedding (Chak et al., 2022, Moreira et al., 2022). A study compared the conventional pulpectomy and non-instrumentation endodontic treatment (NIET), which utilizes simvastatin added to a mix of cefixime, ciprofloxacin, and metronidazole on forty necrotic primary molars clinically and radiographically. Forty mandibular primary second molars from 38 healthy patients, ages 4 to 8, that had necrotic pulp tissue were distributed into two groups in a random manner. Group A teeth had received standard root canal therapy. 3Mixtatin was used to treat the teeth in Group B. Two external examiners performed clinical evaluations on all teeth at one, three, six, and twelve months, as well as radiographically at the same intervals. For teeth with shorter roots, non-instrumental endodontic therapy with 3Mixtatin appears to be a viable substitute for traditional pulpectomy, providing a less involved therapeutic strategy that might help prevent the glitches connected to traditional pulpectomy (Almarji et al., 2024).

Pulpotomy is a vital pulp therapy used to preserve the vital root pulps in teeth with carious pulp exposures. It involves removing the inflamed coronal pulp and applying medication. Simvastatin, a medication, has recently been linked to the ability of pulp to regenerate, so a parallel two-arm randomized control trial was performed to assess and contrast the radiographic and clinical effectiveness of simvastatin gel (SG) and diode laser (DL) in pulpotomy of carious primary molars. One hundred primary molars that needed pulpotomy were randomly assigned to either the DL or SG group. All teeth were repaired using resin-modified glass ionomer cement and covered by crowns made of stainless steel after pulpotomy was completed in accordance with the established procedure. Clinical and radiographic criteria were used to conduct follow-up evaluations at three and twelve months. After a year, SG and DL both had shown comparable clinical and radiographic effectiveness for primary tooth pulpotomy, which highly supports the use of simvastatin gel pulpotomy medication for primary molars, taking into consideration its affordability and simplicity of use (Aripirala et al., 2021).

On another hand, regenerating functional pulp tissue is crucial to restoring tooth vitality, as dental pulp necrosis is a dangerous pathologic entity that results in aberrant root development and tooth nutritional deficiencies, loss of the innate biological defense provided by dental pulp, resulting in thinning in the walls of the root canals(Cvek, 1992), Which make them fragile and susceptible to fracture, significantly impacting their survival rate. The tooth becomes weak and devitalized as a result of current endodontic therapies that are unable to restore pulp vitality and functionality. Nowadays, there is a lot of interest in pulp regeneration using dental pulp stem cells (DPSCs) which are established as progenitor cells in stem cell-mediated endodontic regeneration therapy (Piva et al., 2017), so a study worked on human exfoliated deciduous teeth (SHEDs) stem cells were isolated and injected into simvastatin (SIM) functionalized gelatin methacrylate (GelMA) cryogel microspheres (SMS), a novel design that improves the biological behaviors of SHEDs and encourages the regeneration of a pulp like tissue. Additionally, SHEDs loaded with SMS (SHEDs/SMS) also act on boosting vascularization by urging the migration of human umbilical vein endothelial cells. SMS also improved SHEDs' odontogenic differentiation and angiogenic potential. For subcutaneous implantation in mice, where SHEDs/SMS were inoculated into segments of dental tissue roots that had been cleansed, a vessel-rich pulp-like tissue could be promoted to regenerate, which suggests that the combination of simvastatin and human exfoliated deciduous teeth stem cells may have a bright future in the regenerative endodontic field (Yuan et al., 2022).

The multi-appointment of endodontic therapy requires the application of medicaments inside the canal (ICM), like calcium hydroxide, triple antibiotic paste (TAP), and double antibiotic paste (DAP), to disinfect and improve the sterilization of the root canal system, which might also induce the release of biologically active growth factors from the dentin. Calcium hydroxide has been utilized for years owing to its antibacterial properties and ability to disintegrate tissue, diminishing fracture resistance and microhardness due to its ability to modify the root canal surface (Ferreira et al., 2020, Moazami et al., 2014). TAP, on the other hand, is an effective root canal disinfection; however, it has multiple limitations, including discoloration, cytotoxicity to stem cells at high concentrations, diminished growth factor release, and difficulties in removal from root canals (Bilvinaite et al., 2024), while DAP, consisting of metronidazole and ciprofloxacin, does not induce discoloration and is thought to possess antibacterial effects akin to TAP(Hegde and Arora, 2015). Reddy et al. revealed that double antibiotic paste (DAP), combined with simvastatin as an intracanal medication (ICM), affects the release of transforming growth factor beta 1 (TGF-β1) from root canal dentin, which has a positive impact on collagen synthesis by fibroblasts in the tooth pulp and is essential for odontoblast development and mineral deposition. In order to get root segments 12 mm long, forty-five premolar teeth gathered and sectioned in cross sections, following access cavity preparation and irrigation with 17% ethylenediaminetetraacetic acid. The teeth equally distributed into three groups, for each of the ICMs: Group A received DAP, Group B received DAP combined with simvastatin, and Group C received simvastatin. The enzyme-linked immunosorbent assay kit was used to measure the amount of TGF-β1 growth factor secreted. The results of this study confirm that simvastatin and DAP with simvastatin, when utilized as an ICM, induce a greater release of TGFβ1 from the dentin matrix compared to DAP. Consequently, they may serve as a viable option in regenerative endodontic operations owing to their substantial antibacterial activity and capacity to release growth factors (Reddy et al., 2025).

As the success of endodontic therapy is directly correlated with infection management, an in vitro study assessed the effectiveness of a solution made of Simvastatin (SIM) and diclofenac (DC) on the biofilms cultivated on dentin in the root canal area. The dentin samples were submerged for five minutes in the solutions prior to a 3-week microbial infection. The study groups consisted of: (1) eight percent SIM, (2) four percent SIM, (3) four percent dimethyl sulfoxide (DC), (4) two and a half percent sodium hypochlorite (NaOCl), and (5) 0.9% saline solution (SS). Adenosine triphosphate assay and flow cytometry were methods used to assess cell viability. The greatest decrease in the percentage of biofilm among the study groups was achieved with 2.5% NaOCl, succeeded by SIM 8% and 4%. Four percent and eight percent SIM solutions, along with four percent Diclofenac, exhibit antibacterial and residual efficacy against multispecies endodontic biofilms (Ferrer-Luque et al., 2024).

Application of Simvastatin in oral surgery

Bone alterations surrounding an osseointegrated implant are regarded as a critical determinant for predicting implant survival, long-term prognosis, and overall success. Consequently, the primary objective for implantologists is to minimize bone loss surrounding a dental implant (Mumcu and Beklen, 2019).

The effect of simvastatin around dental implants was studied by El Shafei et al, who compared the impact of autologous platelet-rich fibrin (PRF) alone and PRF combined with simvastatin regarding peri-implant bone alterations and stability in patients receiving implants. The study comprised eight patients. For each patient, two implants were placed; one side received PRF only, while the opposite side received PRF infused with SIM. The osseous alterations surrounding the implant sites were assessed using cone-beam computed tomography at three, six, and twelve months, while the stability of the implants was assessed using the Osstel device at baseline and three months post-operatively. Simvastatin, when added to PRF, resulted in less bone alterations compared to PRF alone, which suggests long-term success of implants. SIM has shown encouraging outcomes in mitigating peri-implant bone resorption (El Shafei et al., 2022).

Another research investigation assessed sandblasted, large grit acid-etched titanium dental implants subjected to ultraviolet (UV) treatment and simvastatin (SIM) immersion to quantify osseointegration at two different time points in rabbit tibias, with and without the addition of xenogeneic bone graft materials. The surface modification of titanium discs treated with simvastatin was examined using an infrared spectrometer. Implants are classified into four categories based on the type of surface modification. Two implants were placed in a tibial defect of twelve rabbits, with implants in direct contact with the bone surface, and bovine bone graft filling the gap in between. The rabbits were euthanized after two to four weeks. UV treatment and SIM immersion improved bone-to-implant contact (BIC) on nongrafted surfaces, while both techniques increased BIC and bone area (BA) on grafted surfaces. The application of both treatments did not produce a superior BIC or BA compared to a single treatment. At two separate time points, the BIC on the nongrafted sides showed no significant differences among the UV and/or SIM treated groups; however, the BA exhibited considerable variation. Thus, SIM treatment of SLA titanium implants enhances osseointegration in tibias, regardless of the presence of xenogeneic bone graft materials (Jun et al., 2021).

Deepanjali et al. accomplished prospective randomized split-mouth research intended to assess the efficacy of simvastatin in facilitating bone repair in the extraction sockets of mandibular third molars, employing cone beam computed tomography (CBCT) at six months post-operation. Fifteen individuals underwent

DOI: 10.32828/mdj.v21i2.1209

concurrent surgical extraction of bilaterally impacted mandibular third molars. The effectiveness of the medication was assessed by implanting 10 mg of simvastatin into the socket (study site), with observations carried out over 6 months to compare healing with the control site. The data suggest a significant change in bone regeneration at the simvastatin site compared to the control site(Deepanjali et al., 2023).

Recently, with the improvements in methods and equipment, apical surgery is considered a last effort to preserve a tooth before extraction, with success rates that are close to or higher than 90% (von Arx, 2005). A study was conducted to assess how Simvastatin (SIM) affected the rate at which endodontic peri-apical defects regenerated bone. Three groups of thirteen for each were created from the sample size: the Simvastatin group, the Autologous Platelet Rich Fibrin group, and the Hydroxyapatite Bone Graft group. Peri-radicular curettage was performed once the endodontic treatment was finished and the osseous defect was accessible. Each group received its own materials. Gelatin sponge was combined with 10 mg of simvastatin. The SIM group showed a substantial shift, according to an intragroup study of CBCT-Periapical Index (PAI) scores at the sixth and twelfth months. Compared to other groups, SIM resulted in a more significant change in the CBCT-PAI score, suggesting a quicker rate of bone regeneration (Gupta et al., 2020).

Simvastatin was experimented on maxillary bony defect in rabbits combined with chitosan in nanoparticle form, histological and histomorphometric analysis had recorded a confounding effect on the quality and density of the formed bone compared to the control side (Alsaeed et al., 2023).

Application of Simvastatin in periodontic dentistry

Conventional regimens for periodontal therapy focus on subgingival debridement using scaling and root planning (SRP) to manage subgingival bacteria and contaminated root surfaces that contribute to periodontium deterioration (Cobb, 2002), either by open flap debridement or minimally invasive flap access enhanced calculus removal and improved access to the depths of the pocket may be attained (Serino et al., 2001), yet, open flap is more efficacious (Brayer et al., 1989). Nonetheless, open flap debridement may have certain drawbacks, including recession or heightened sensitivity, in addition to the patient's distress toward such surgical interventions. The papilla reflection (PR) technique is more conservative than open flap debridement and has demonstrated enhanced calculus removal efficacy (Johnson et al., 1989). Periodontal maintenance therapy (PMT) includes the eradication of bacterial plaque and calculus from both supragingival and subgingival areas by mechanical equipment and selective root planning (Armitage, 2003). The localized application of statins has demonstrated efficacy in diminishing periodontal pocket depth, mitigating clinical attachment loss, and alleviating inflammation in human clinical trials during initial treatment (Pradeep and Thorat, 2010), Killeen et al. assessed the efficacy of local simvastatin (SIM) application, in conjunction papilla reflection at minimum invasive level and root planning (PR/RP) for patients having pocket depths ranging from 6-9mm, in the aspects of attachment level (CAL), probing depth (PD), and augmenting interproximal bone height (IBH). Fifty patients with Stage three, Grade B periodontitis, exhibiting interproximal probing depths of 6-9 mm and a history of blood on probing (BOP), were involved. Experimental therapies (PR/RP+SIM/methylcellulose) (MCL) and control therapies (PR/RP+MCL) were assigned randomly. Root surfaces were reached through the reflection of interproximal papillae, followed by root planning aided by endoscopic assessment, acid etching, and the application of SIM/MCL or MCL. Assessment of the Clinical attachment level, periodontal depth, bleeding on probing, plaque presence, and interproximal bone height was carried out at baseline and after 12 months using standardized vertical bitewing radiographs. The use of SIM/MCL in papilla reflection and root planning enhanced CAL, PD, and BOP relative to papilla reflection and root planning alone in patients undergoing periodontal maintenance (Killeen et al., 2022).

Systemic antibiotic therapy is useful as a supplementary treatment to scaling and root planning (SRP) for different periodontal therapies (Tsai et al., 2018). Nevertheless, it possesses several limitations of use; moreover, the recurrent application of antibiotics has resulted in the creation of resistant microbial targeted species (Al-Askar et al., 2017). Alternative medicines, including local drug delivery (LDD), and anti-microbial photodynamic therapy (aPDT), which is characterized as an oxygen-based treatment approach that employs light-activated photosensitizers to produce cytotoxic reactive oxygen species (ROS) or singlet oxygen, which are detrimental to bacteria, have been utilized to address the issues and difficulties linked to systemic antibiotics (Barca et al., 2015). The localized administration of 1.2% simvastatin gel has become significant in periodontal therapy, demonstrating enhancements in clinical parameters, a decrease in proinflammatory mediators, and the regeneration of alveolar bone defects (Suresh et al., 2013), a study conducted by Rahman et al. who compared the between antibiotic Photodynamic therapy (aPDT), Local Drug Delivery (LDD) of 1.2% Simvastatin gel combined with scaling and root planning (SRP), and SRP on its own in the management of eleven patients having Grade A stage two Periodontitis assigned randomly into three groups: SRP, SRP followed by aPDT (aPDT group); SRP followed by a single subgingival application of 1.2% simvastatin gel (SMV group). The evaluation process was performed at baseline and after three months, and included the clinical markers (API, PBI, PPD, and RAL), RT-PCR technique, which is a two-step molecular technique used to quantify Porphyromonas gingivalis, first the extraction of DNA from subgingival plaque, and then followed by the detection and the identification of the microorganism, in addition to measuring RANKL levels using ELISA. Adjunctive aPDT with 1.2% SMV locally, as well as SRP indivisually, effectively enhance clinical parameters, diminish P. gingivalis DNA copy count, and lower gingival crevicular fluid, RANKL levels (Rahman et al., 2020).

Application of Simvastatin in conservative dentistry

An in vitro study investigated chitosan microspheres (MSCH) containing varying concentrations of simvastatin (2%, 5%, and 10%) as a biomaterial for dentin tissue engineering. the microspheres were utilized on three-dimensional (3D) cultures of human dental pulp cells (HDPCs). Cell viability, proliferation, and in situ mineralized matrix deposition were assessed. HDPCs exhibited a marked enhancement in the deposition of mineralization nodules when 3D cultures were in direct contact with chitosan microspheres compared to the control; however, the greatest expression was noted for MSCH encapsulated with 5% and 10% simvastatin, which was significantly superior to plain MSCH, and facilitated the creation of a regulated release mechanism for bioactive doses in dentin tissue engineering (Bronze-Uhle et al., 2025).

Conclusion

Simvastatin, one of the statin family members, has an effect on bone formation, as it has a beneficial role in preventing relapse after orthodontic treatment. It works on the suppression of osteoclast activity ad this is highly expressed by reduction in the number of resorptive lacunae and RANKL level, which is the chief controller for osteoclast differentiation, proliferation, and survival, In addition to its valuable effect in the reduction of oral mucosal fibrosis, and similar inflammatory disease that is highly attributed to anti-inflammatory action of this drug, it works on cessation of the production of fibrosis related proteins, reducing collagen deposition and skin thickness.

In Endodontic therapy, simvastatin may be considered on the agent that mixed with other antibiotic drugs to perform a material employed in non-instrumental non-conventional pulpectomy, furthermore combination of simvastatin with deciduous extracted stem cells may have bright future in regenerative endodontic medicine, moreover it can be mixed with double antibiotic paste as an intracanal medicament between visits to act as a disinfectant and works on the release of TGF-B.

Regarding its antiosteoclastogenesis, simvastatin reduces preimplant bone resorption and can be used as a conjunctive to scaling and root planning to reduce pocket depth and bleeding upon probing.

Supplementary Material

None.

Author Contributions

Muna Alaa Alsaaed: data curation, writing-original draft preparation. Nada M H Al-Ghaban: Conceptualization, methodology, writing-review and editing. Mohammed A. Abdalqader: validation, formal analysis, investigation, supervision.

Funding

This research received no external funding.

Data Availability Statement

Data are available from the authors upon reasonable request.

Conflict of interest

The authors reported that they have no conflicts of interest.

Acknowledgments

The authors would like to thank Mustansiriyah University (www.uomustansiriyah.edu.iq), Baghdad, Iraq, for their support in the present work.

References

1. Agarwal, A. and Mathur, R. (2010) ‘Maxillary Expansion’, *International Journal of Clinical Pediatric Dentistry*, 3(3), pp. 139–146. Available at: https://doi.org/10.5005/jp-journals-10005-1069.
2. Al-Askar, M. et al. (2017) ‘Effectiveness of mechanical debridement with and without adjunct antimicrobial photodynamic therapy in the treatment of periodontal inflammation among patients with prediabetes’, *Photodiagnosis and Photodynamic Therapy*, 20, pp. 91–94. Available at: https://doi.org/10.1016/j.pdpdt.2017.09.005.
3. Almarji, W., Laflouf, M. and Tolibah, Y.A. (2024) ‘Evaluation of the modified 3Mix-Simvastatin combination in non-instrumental endodontic therapy of necrotic primary molars: A two-arm randomized controlled trial’, *Clinical and Experimental Dental Research*, 10(1), p. e860. Available at: https://doi.org/10.1002/cre2.860.
4. Alsaeed, M.A. and Al-Ghaban, N.M.H. (2023) ‘Chitosan Nanoparticle/Simvastatin for Experimental Maxillary Bony Defect Healing: A Histological and Histomorphometrical Study’, *Biomimetics*, 8(4). Available at: https://doi.org/10.3390/biomimetics8040363.
5. Alsaeed, M.A., Al-Ghaban, N.M.H. and Karaibrahimoğlu, A. (2023) ‘The influence of Simvastatin carried by Chitosan nanoparticle on bone regeneration using Masson's Trichrome histochemical stain’, *Journal of Baghdad College of Dentistry*, 35(4), pp. 65–74. Available at: https://doi.org/10.26477/jbcd.v35i4.3516.
6. Alswafeeri, H. et al. (2018) ‘Effect of local administration of simvastatin on postorthodontic relapse in a rabbit model’, *American Journal of Orthodontics and Dentofacial Orthopedics*, 153(6), pp. 861–871. Available at: https://doi.org/10.1016/j.ajodo.2017.10.024.
7. Aripirala, M. et al. (2021) ‘Comparative evaluation of diode laser and simvastatin gel in pulpotomy of primary molars: A randomized clinical trial’, *Journal of Indian Society of Pedodontics and Preventive Dentistry*, 39(3), pp. 303–309. Available at: https://doi.org/10.4103/jisppd.jisppd_60_21.
8. Armitage, G.C. (2003) ‘Diagnosis of periodontal diseases’, *Journal of Periodontology*, 74(8), pp. 1237–1247. Available at: https://doi.org/10.1902/jop.2003.74.8.1237.
9. Barca, E., Cifcibasi, E. and Cintan, S. (2015) ‘Adjunctive use of antibiotics in periodontal therapy’, *Journal of Istanbul University Faculty of Dentistry*, 49(3), pp. 55–62.

Available at: https://doi.org/10.17096/jiufd.90144.

10. Bilvinaite, G. et al. (2024) 'Effect of Calcium Silicate-Based Intracanal Medicament and Calcium Hydroxide on Growth Factor TGF-β1 Release from Root Canal Dentine', *Journal of Functional Biomaterials*, 15(6). Available at: https://doi.org/10.3390/jfb15060139.
11. Borton, A.J. et al. (2001) 'The loss of Smad3 results in a lower rate of bone formation and osteopenia through dysregulation of osteoblast differentiation and apoptosis', *Journal of Bone and Mineral Research*, 16(10), pp. 1754–1764. Available at: https://doi.org/10.1359/jbmr.2001.16.10.1754.
12. Brayer, W.K. et al. (1989) 'Scaling and root planing effectiveness: the effect of root surface access and operator experience', *Journal of Periodontology*, 60(1), pp. 67–72. Available at: https://doi.org/10.1902/jop.1989.60.1.67.
13. Bronze-Uhle, E.S. et al. (2025) 'Simvastatin-Loaded Chitosan Microspheres as a Biomaterial for Dentin Tissue Engineering', *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 113(3), p. e35536. Available at: https://doi.org/10.1002/jbm.b.35536.
14. Calixto, J.C. et al. (2011) 'The influence of local administration of simvastatin in calvarial bone healing in rats', *Journal of Cranio-Maxillofacial Surgery*, 39(3), pp. 215–220. Available at: https://doi.org/10.1016/j.jcms.2010.03.009.
15. Cerritelli, L. et al. (2022) 'Rapid Maxillary Expansion (RME): An Otolaryngologic Perspective', *Journal of Clinical Medicine*, 11(17). Available at: https://doi.org/10.3390/jcm11175243.
16. Chak, R.K. et al. (2022) 'Clinical Radiographic Evaluation of 3Mixtatin and MTA in Primary Teeth Pulpotomies: A Randomized Controlled', *International Journal of Clinical Pediatric Dentistry*, 15(Suppl 1), pp. S80–S86. Available at: https://doi.org/10.5005/jp-journals-10005-2216.
17. Chang, C.H. et al. (2023) 'Simvastatin Attenuates Areca Nut Extract-Induced Subdermal Fibrosis in Mice by Targeting TGF-β Signaling Pathways', *Current Issues in Molecular Biology*, 45(11), pp. 8622–8632. Available at: https://doi.org/10.3390/cimb45110542.
18. Cobb, C.M. (2002) 'Clinical significance of non-surgical periodontal therapy: an evidence-based perspective of scaling and root planing', *Journal of Clinical Periodontology*, 29(Suppl 2), pp. 22–32. Available at: https://doi.org/10.1034/j.1600-051X.29.s2.4.x.
19. Cvek, M. (1992) 'Prognosis of luxated non-vital maxillary incisors treated with calcium hydroxide and filled with gutta-percha. A retrospective clinical study', *Dental Traumatology*, 8(2), pp. 45–55. Available at: https://doi.org/10.1111/j.1600-9657.1992.tb00228.x.
20. Deepanjali, M., Prasad, T.S. and Manodh, P. (2023) 'Efficacy of simvastatin in bone regeneration after surgical removal of mandibular third molars', *Oral and Maxillofacial Surgery*, 27(3), pp. 427–432. Available at: https://doi.org/10.1007/s10006-022-01081-y.
21. El Shafei, S.F. et al. (2022) 'Effect of local application of platelet-rich fibrin scaffold loaded with simvastatin on peri-implant bone changes', *The Journal of Indian Prosthodontic Society*, 22(2), pp. 152–160. Available at: https://doi.org/10.4103/jips.jips_258_21.
22. Estrela, C. et al. (2008) 'A New Periapical Index Based on Cone Beam Computed

Tomography', *Journal of Endodontics*, 34(11), pp. 1325–1331. Available at: https://doi.org/10.1016/j.joen.2008.08.013.
23. Farzan, A. et al. (2022) 'Effect of Simvastatin and Low-Level Laser Therapy on Sutural Bone Formation After Expansion in Rats: Biomechanical, Computed Tomography and Immunohistochemical Assessment', *Journal of Lasers in Medical Sciences*, 13, p. e21. Available at: https://doi.org/10.34172/jlms.2022.21.
24. Ferreira, L.N., Puppin-Rontani, R.M. and Pascon, F.M. (2020) 'Effect of Intracanal Medicaments and Irrigants on the Release of Transforming Growth Factor Beta 1 and Vascular Endothelial Growth Factor from Cervical Root Dentin', *Journal of Endodontics*, 46(11), pp. 1616–1622. Available at: https://doi.org/10.1016/j.joen.2020.07.034.
25. Ferrer-Luque, C.M. et al. (2024) 'Simvastatin Efficacy on Endodontic Biofilms: An In Vitro Study', *Materials*, 17(22). Available at: https://doi.org/10.3390/ma17225441.
26. Granat, M.M., Eifler-Zydel, J. and Kolmas, J. (2024) 'Statins-Their Role in Bone Tissue Metabolism and Local Applications with Different Carriers', *International Journal of Molecular Sciences*, 25(4). Available at: https://doi.org/10.3390/ijms25042378.
27. Gupta, S. et al. (2020) 'Effect of local application of simvastatin in bone regeneration of peri-apical defects-a clinico-radiographic study', *Journal of Oral Biology and Craniofacial Research*, 10(4), pp. 583–591. Available at: https://doi.org/10.1016/j.jobcr.2020.08.014.
28. Guthrie, R.M. (2006) 'How safe is aggressive statin therapy?', *Progress in Cardiovascular Nursing*, 21(3), pp. 140–145. Available at: https://doi.org/10.1111/j.0889-7204.2006.05616.x.
29. Han, G. et al. (2010) 'Effects of simvastatin on relapse and remodeling of periodontal tissues after tooth movement in rats', *American Journal of Orthodontics and Dentofacial Orthopedics*, 138(5), pp. 550.e1-550.e7. Available at: https://doi.org/10.1016/j.ajodo.2010.04.026.
30. Harsha, G. et al. (2023) 'Evaluation of efficacy of simvastatin in bone regeneration following local application in third molar extraction socket: A randomized control trial', *National Journal of Maxillofacial Surgery*, 14(2), pp. 286–293. Available at: https://doi.org/10.4103/njms.njms_317_21.
31. Hassan, A.M. and Al Kayat, A. (2015) 'Effect of systemic administration of Simvastatin on dental implant stability: A random clinical study', *Journal of Baghdad College of Dentistry*, 27(2), pp. 133–137. Available at: https://doi.org/10.12816/0015277.
32. Hegde, V. and Arora, S. (2015) 'Effect of intracanal medicaments on push-out bond strength of Smart-Seal system', *Journal of Conservative Dentistry*, 18(5), pp. 414–418. Available at: https://doi.org/10.4103/0972-0707.164059.
33. Ishihara, T. et al. (2017) 'Locally Applied Simvastatin Promotes Bone Formation in a Rat Model of Spinal Fusion', *Journal of Orthopaedic Research*, 35(9), pp. 1942–1948. Available at: https://doi.org/10.1002/jor.23479.
34. Jia, W. et al. (2016) 'Simvastatin Promotes Dental Pulp Stem Cell-induced Coronal Pulp Regeneration in Pulpotomized Teeth', *Journal of Endodontics*, 42(7), pp. 1049–1054. Available

at: https://doi.org/10.1016/j.joen.2016.03.007.

35. Johnson, G.K. et al. (1989) ‘Fiber optic probe augmented sonic scaling versus conventional sonic scaling’, *Journal of Periodontology*, 60(3), pp. 131–136. Available at: https://doi.org/10.1902/jop.1989.60.3.131.
36. Jun, J.H. et al. (2021) ‘Improvement of Osseointegration by Ultraviolet and/or Simvastatin Treatment on Titanium Implants with or without Bone Graft Materials’, *Materials*, 14(13). Available at: https://doi.org/10.3390/ma14133707.
37. Kaji, H. et al. (2005) ‘Statins modulate the levels of osteoprotegerin/receptor activator of NFkappaB ligand mRNA in mouse bone-cell cultures’, *Hormone and Metabolic Research*, 37(9), pp. 589–592. Available at: https://doi.org/10.1055/s-2005-870538.
38. Killeen, A.C. et al. (2022) ‘Effect of locally applied simvastatin on clinical attachment level and alveolar bone in periodontal maintenance patients: A randomized clinical trial’, *Journal of Periodontology*, 93(11), pp. 1682–1690. Available at: https://doi.org/10.1002/JPER.21-0708.
39. Kohli, S.S. and Kohli, V.S. (2011) ‘Role of RANKL-RANK/osteoprotegerin molecular complex in bone remodeling and its immunopathologic implications’, *Indian Journal of Endocrinology and Metabolism*, 15(3), pp. 175–181. Available at: https://doi.org/10.4103/2230-8210.83401.
40. Liu, X., Muhammed, F.K. and Liu, Y. (2022) ‘Simvastatin encapsulated in exosomes can enhance its inhibition of relapse after orthodontic tooth movement’, *American Journal of Orthodontics and Dentofacial Orthopedics*, 162(6), pp. 881–889. Available at: https://doi.org/10.1016/j.ajodo.2021.07.025.
41. Moazami, F. et al. (2014) ‘The long-term effect of calcium hydroxide, calcium-enriched mixture cement and mineral trioxide aggregate on dentin strength’, *Iranian Endodontic Journal*, 9(3), pp. 185–189.
42. Moreira, C.P. et al. (2022) ‘Lesion sterilization and tissue repair of primary molar to the eruption of its permanent successor: a case report’, *BDS - Brazilian Dental Science*, 25.
43. Mumcu, E. and Beklen, A. (2019) ‘The effect of smoking on the marginal bone loss around implant-supported prostheses’, *Tobacco Induced Diseases*, 17, p. 43. Available at: https://doi.org/10.18332/tid/109279.
44. Mundy, G. et al. (1999) ‘Stimulation of bone formation in vitro and in rodents by statins’, *Science*, 286(5446), pp. 1946–1949. Available at: https://doi.org/10.1126/science.286.5446.1946.
45. Okamoto, Y. et al. (2009) ‘Simvastatin Induces the Odontogenic Differentiation of Human Dental Pulp Stem Cells In Vitro and In Vivo’, *Journal of Endodontics*, 35(3), pp. 367–372. Available at: https://doi.org/10.1016/j.joen.2008.11.024.
46. Peng, B. et al. (2024) ‘Mesenchymal stem cell-derived exosomes: a potential cell-free therapy for orthodontic tooth stability management’, *Stem Cell Research & Therapy*, 15, p. 342. Available at: https://doi.org/10.1186/s13287-024-03962-3.
47. Piva, E. et al. (2017) ‘Dental Pulp Tissue Regeneration Using Dental Pulp Stem Cells Isolated and Expanded in Human Serum’, *Journal of Endodontics*, 43(4), pp. 568–574. Available

at: https://doi.org/10.1016/j.joen.2016.11.018.
48. Pradeep, A.R. and Thorat, M.S. (2010) 'Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial', *Journal of Periodontology*, 81(2), pp. 214–222. Available at: https://doi.org/10.1902/jop.2009.090429.
49. Rahman, S., GV, G. and Mehta, D.S. (2020) 'A clinico-microbiological and biochemical study evaluating the adjunctive use of antimicrobial photodynamic therapy and local drug delivery of 1.2 % simvastatin gel compared to scaling and root planing alone', *Photodiagnosis and Photodynamic Therapy*, 32, p. 102017. Available at: https://doi.org/10.1016/j.pdpdt.2020.102017.
50. Reddy, K.H. et al. (2025) 'Comparative evaluation of transforming growth factor-beta 1 release from dentin matrix with double antibiotic paste, probiotics, and simvastatin as intracanal medicaments: An in vitro study', *Journal of Conservative Dentistry and Endodontics*, 28(5), pp. 456–461. Available at: https://doi.org/10.4103/JCDE.JCDE_131_25.
51. Rosyida, N.F. et al. (2025) 'Inhibition of Orthodontic Relapse by Local Application of Simvastatin-Loaded Gelatin Hydrogel in a Rabbit Model', *Orthodontics & Craniofacial Research*, 28(3), pp. 289–295. Available at: https://doi.org/10.1111/ocr.12877.
52. Ruan, F., Zheng, Q. and Wang, J. (2012) 'Mechanisms of bone anabolism regulated by statins', *Bioscience Reports*, 32(6), pp. 511–519. Available at: https://doi.org/10.1042/BSR20110118.
53. Saifi, A.M., Giraddi, G.B. and Ahmed, N. (2017) 'Healing of extraction socket following local application of simvastatin: A split mouth prospective study', *Journal of Oral Biology and Craniofacial Research*, 7(2), pp. 106–112. Available at: https://doi.org/10.1016/j.jobcr.2017.04.001.
54. Serino, G. et al. (2001) 'Initial outcome and long-term effect of surgical and non-surgical treatment of advanced periodontal disease', *Journal of Clinical Periodontology*, 28(10), pp. 910–916. Available at: https://doi.org/10.1034/j.1600-051x.2001.028010910.x.
55. Sharaf Eldeen, A., El-Shall, O. and Attia, M. (2022) 'Effect of Systemic Administration of Simvastatin on Dental Implant Stability', *Al-Azhar Journal of Dentistry*, 9(4), pp. 391–402. Available at: https://doi.org/10.21608/adjg.2021.47686.1310.
56. Suresh, S. et al. (2013) 'Evaluation of anti-inflammatory effect of statins in chronic periodontitis', *Indian Journal of Pharmacology*, 45(4), pp. 391–394. Available at: https://doi.org/10.4103/0253-7613.115017.
57. Thangamani, S. et al. (2015) 'Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent', *Scientific Reports*, 5, p. 16407. Available at: https://doi.org/10.1038/srep16407.
58. Tsai, C.-Y. et al. (2018) 'Subgingival microbiota in individuals with severe chronic periodontitis', *Journal of Microbiology, Immunology and Infection*, 51(2), pp. 226–234. Available at: https://doi.org/10.1016/j.jmii.2016.04.007.
59. Von Arx, T. (2005) 'Failed root canals: the case for apicoectomy (periradicular surgery)', *Journal of Oral and Maxillofacial Surgery*, 63(6), pp. 832–837. Available at: https://doi.org/10.1016/j.joms.2005.02.019.

DOI: 10.32828/mdj.v21i2.1209

60. Wong, R.W.K. and Rabie, A.B.M. (2005) ‘Histologic and Ultrastructural Study on Statin Graft in Rabbit Skulls’, *Journal of Oral and Maxillofacial Surgery*, 63(10), pp. 1515–1521. Available at: https://doi.org/10.1016/j.joms.2005.06.009.
61. Yuan, X. et al. (2022) ‘Vascularized pulp regeneration via injecting simvastatin functionalized GelMA cryogel microspheres loaded with stem cells from human exfoliated deciduous teeth’, *Materials Today Bio*, 13, p. 100209. Available at: https://doi.org/10.1016/j.mtbio.2022.100209.