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Review Article

Efficacy of Statins in Tissue Healing Following Tooth Extraction: A Systematic Review of Clinical Studies.

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ABSTRACT

Background: *Statins drugs, known for their remarkable capacity to promote bone formation and soft tissue healing, have the potential to transform dental care. This study seeks to explore the significant impact of statins on bone and soft tissue recovery in dental extraction sites, paving the way for promising advancements for both dental professionals and patients.*

Methods: *This systematic review sought to investigate the role of statins in tissue healing after dental extraction. The study was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) under (CRD42025630720). A thorough search of electronic databases identified 416 manuscripts, of which eleven clinical studies met the eligibility criteria after a meticulous screening process. The final study sample included 268 patients, comprising of 91 males and 97 females.*

Results: *Local application of statin drug holds immense value in dentistry regarding better quality of repaired soft and hard tissues in the proximity of an extracted tooth, as evidenced in majority of the eleven included studies upon investigating parameters like bone formation, bone density and rate of ossification. Furthermore, statin drug was identified to be safe without long-term effects such as dry sockets, infections, and/or draining sinuses. Risk of bias assessment of the randomized and non-randomized controlled trials studies included in the current review were observed to range from moderate to low.*

Conclusion: *This study strongly supports the osteo-inductive properties of statins and their effectiveness in enhancing healing at tooth extraction sites. Based on the findings of the included studies, this review concludes that statins offer significant potential in preserving alveolar bone after tooth extraction. With further large-scale randomized trials, new guidelines can be developed to determine optimal dosage and the most suitable statin for managing alveolar bone healing.* ***Key words:*** *exodontia, tooth extraction, statin drugs, HMG CoA-reductase inhibitors, tissue healing.*

Abbreviations:

BMPs - bone morphogenic proteins

HMG CoA - 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors

PICO - Population, Interventions, Control and Outcome

PROSPERO - International Prospective Register for Systematic Reviews

ROBINS 1 - Risk of Bias in Non-Randomized Studies of Interventions

RoB2 - Risk of Bias 2

PLGA/HA/S - Poly (D, L-lactide-co-glycolide)- Hydroxyapatite

IOPA - Intra-oral periapical radiographs

CBCT - Cone-beam computed tomography

RVG – radiovisuography

VAS – visual analogue scale

NPS – numeric pain scale

BV – bone volume

BV/TV - bone volume/turnover volume fraction

Tb.Th - trabecular thickness

Tb.Sp - trabecular spacing

ACS – absorbable collagen sponge

SMV – simvastatin

SIM- Simvastatin

PPPM-Polypropylene membranes

HA – Hydroxyapatite

S – simvastatin

RCT - randomized controlled trial

Non-RCTs – Nonrandomized controlled trial

Introduction

Tooth extraction, a frequently performed procedure in dentistry, is followed by sequelae of tissue reactions comprising inflammation, epithelization, and remodeling for healing. After primary healing, secondary healing continues at the site of tooth extraction(s) for up to one year [1]. Critical to bone healing at the site of operation includes biological processes like osteo-induction and osteogenesis [2]. Similarly, new bone

formation involves the production of bone matrix by osteoblasts, the bone forming cells, and its subsequent mineralization[3]. Growth factors such as bone morphogenic proteins (BMPs) play a vital role during new bone formation by facilitating the proliferation and differentiation of osteoblasts, which derive their origin from multipotent stem cells (osteoblast like-cells)[4]. Despite these tissue repair attempts by the body, a decrease of alveolar bone in tooth extraction socket and its proximity is an event that is frequently encountered at tooth extraction site(s)[5]. The loss of alveolar bone may eventually complicate rehabilitation attempts by dental professionals[6, 7]. With commendable advancements made in tissue engineering and regenerative medicine, several natural and synthetic materials have been used to facilitate the appropriate healing of bone at the site of injury[3, 8]. Regarding this, several pharmacological agents have also established their mark, with drugs like statins showing robust evidence in promoting new bone formation[3].

Statin drugs, also known as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG CoA), lower cholesterol in patients suffering from hypercholesterolemia[9]. In addition to other benefits, statins demonstrate pleiotropic effects, thereby enhancing the expression of bone mineralization proteins-2 (BMP2) and stimulating the differentiation of osteoblasts, exhibiting an anabolic effect on bone[10]. Recent clinical investigations demonstrated the management of periodontal bone defects by local administration of statin drugs[11-13]. Statins are also adjunct to bone grafting in several oral and maxillofacial procedures[14]. Furthermore, statins have shown coronal pulp and dentin regeneration in beagle dogs[15]. The advantages of the drug in dentistry have been recorded, and statins demonstrated enhanced osseo-integration around dental implants in animal studies[16]. With evidence in place, the current systematic review specifically aims to investigate the effects of local statin administration on bone and soft tissue healing at the tooth extraction site.

Materials and methods

Focused question and protocol registration

The focused question is, “Does local statin administration following dental extraction augment healing?” The study was registered with the International Prospective Register for Systematic Reviews (PROSPERO) (CRD42025630720).

Population, Interventions, Control and Outcome (PICO)

Population (P): patients undergoing dental extraction, Intervention (I): local administration of statin (s), Control (C): no statin drug was administered following extraction of tooth/teeth, Outcome (O): healing of tissues in the extraction socket, and its proximity.

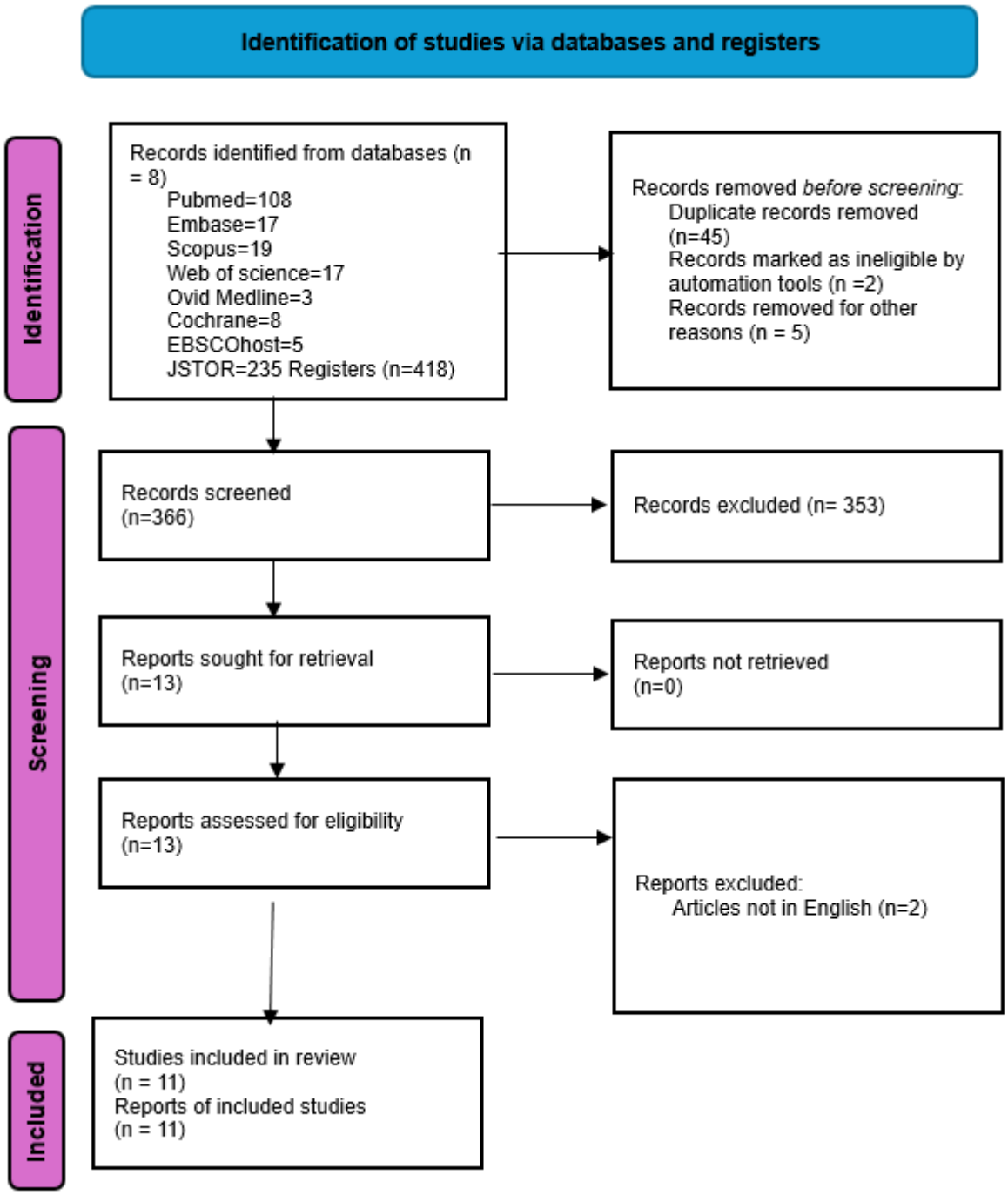
Eligibility criteria

The eligibility for studies to be included in the review were 1) clinical investigations, 2) original studies, 3) presence of intervention (tooth extraction with statin intervention) and comparison with the control group, and 4) studies published in the English language. Studies that were not considered for inclusion included 1) commentaries, 2) case reports, 3) letters to the editor, 4) literature reviews, 5) in vivo studies, 6) abstract proceedings, 7) posters, and 8) animal studies.

Search strategy and data extraction

An electronic search was conducted of indexed databases (PubMed, EMBASE, Scopus, Ovid Medline, ISI Web of Science, Cochrane, and JSTOR) without time and language restrictions up to and including December 2024. The following medical subject headings (MeSH) terms were used to identify relevant studies: 1) tooth extraction, 2) dental extraction, 3) exodontia, 4) statins, 5) HMG CoA reductase inhibitors, 6) tooth socket healing, 7) tissue repair, 8) bone regeneration, 9) alveolar ridge preservation and 10) clinical studies. The following keywords were used in combination: 1) statins AND tooth extraction, 2) statins AND exodontia, 3) HMG CoA reductase inhibitors AND tooth extraction, 4) HMG CoA reductase inhibitors AND dental extraction, and 5) HMG CoA reductase inhibitors AND exodontia. Boolean operators (OR and AND) combined keywords and expanded the search results. Any disagreements in the search strategy were solved through discussion between authors or consulting a third author, MK. The PRISMA checklist has presented the current review [17] (Figure 1).

Figure. 1 Study flowchart based on the PRISMA guidelines



Data extraction

Two authors (NM and KK) independently extracted data from the eligible studies. The following data were extracted: study design, age range of patients included, gender, study groups, group allocations, study duration, primary site of evaluation, primary and/or secondary parameters of investigation, diagnostic tool(s) used for

evaluation of primary and/or secondary parameters of evaluation type of statin drug used in the investigation, dose, delivery method, frequency, site of application.

Risk of bias assessment:

The risk of bias assessment for the included studies was conducted using two different tools: the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) for non-randomized studies and the Risk of Bias 2 (RoB 2) tool for randomized crossover trials. These tools evaluated multiple domains to determine the overall risk of bias for each study. For randomized crossover studies, the RoB 2 tool was used to assess bias across five key domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. All studies were appraised independently by two authors (S.S.K and K.K), with any differences resolved by a third author (J.K).

Figure 2. Traffic plot for RCTS (RoB2)

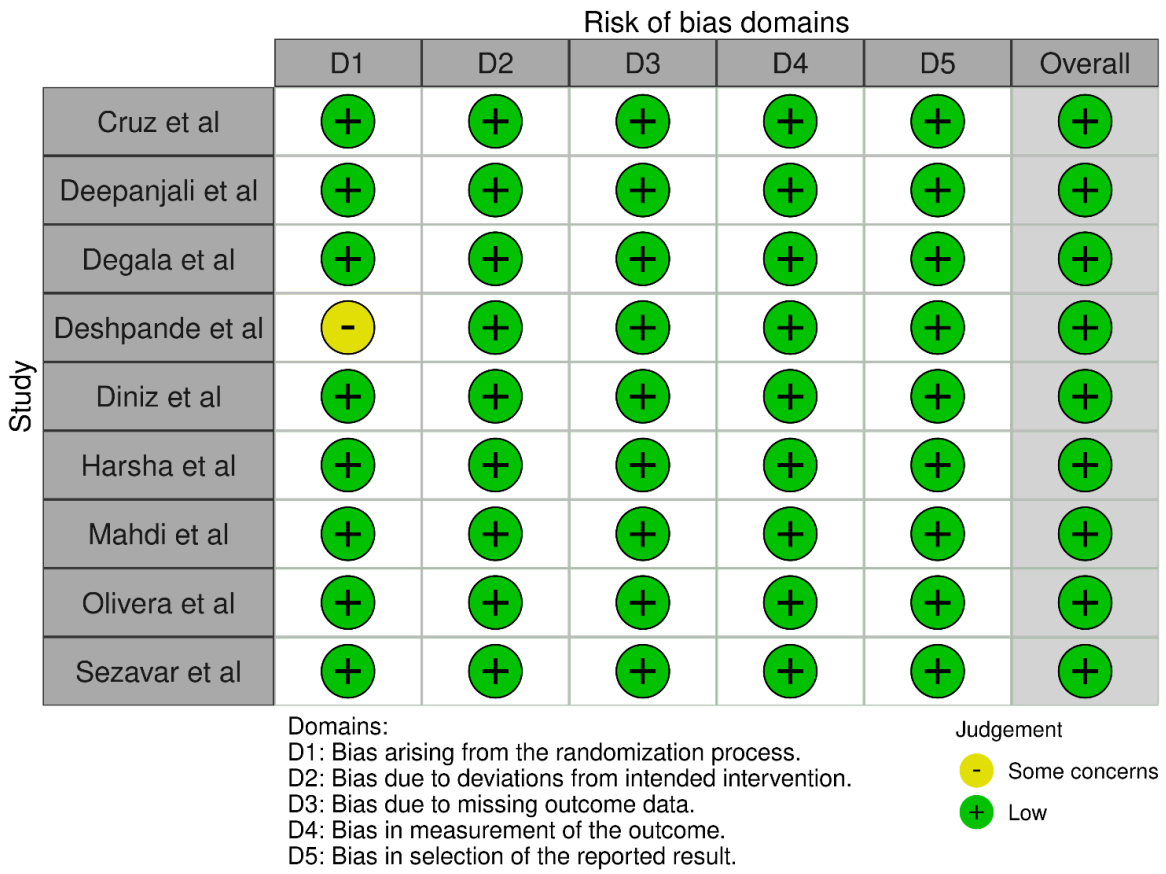


Figure 3. Overall, RoB for RCTS

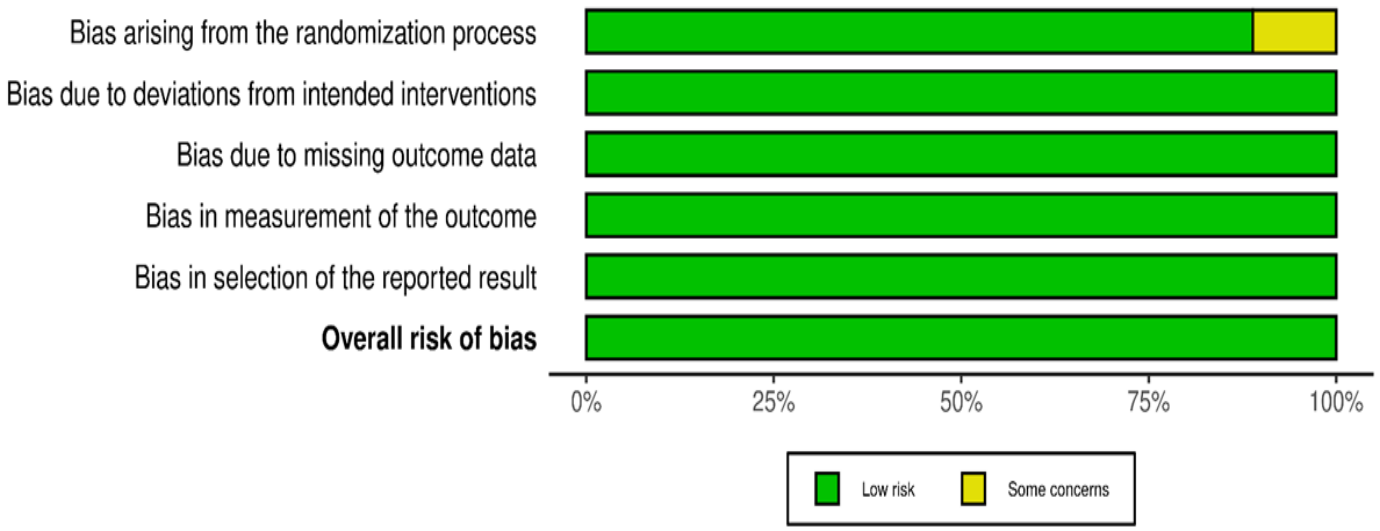


Figure 4. Traffic plot for non-RCTs

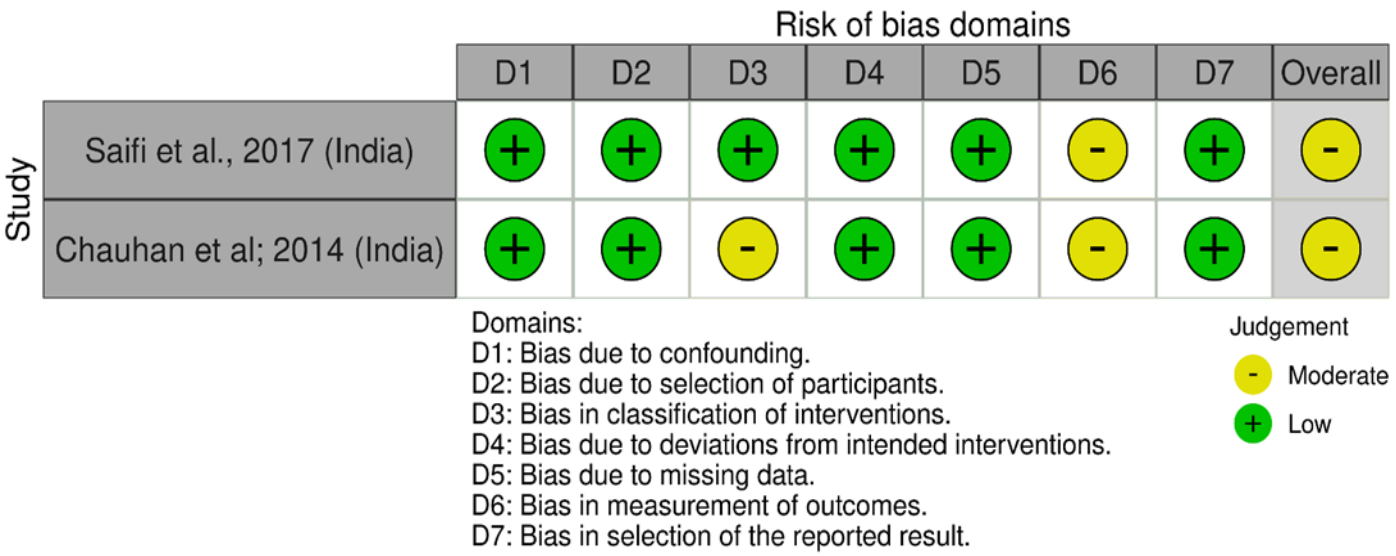
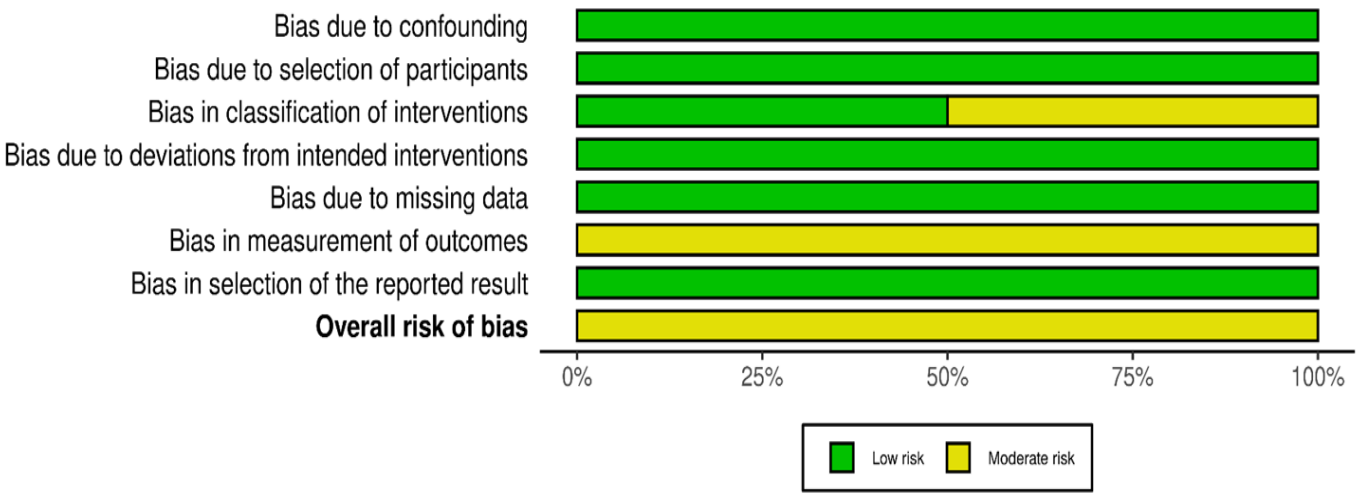


Figure 5. Overall, ROB for Non-RCTS



Results

Study selection

The initial electronic search revealed 416 potential manuscripts. Of these, 395 articles were excluded after screening at the title and abstract level and duplicate removal. The remaining 21 studies were assessed for eligibility. 10 studies were further excluded, and 11 manuscripts were finally included in the systematic review for assessment. Software EndNote was used to cite the 11 included studies and the related reference articles.

General characteristics of the included studies:

In the 11 included studies[18-28], 9 studies adopted a split-mouth investigation approach[18, 20-24, 26-28]. A total of 268 patients participated in the eleven included studies investigated in this review. Of the 268 participants, 91 were male and 97 were female patients. Two studies did not specify the exact number of male and female participants in their study design[18, 24]. The ages of study participants ranged from 18 years to 65 years. Nine of the eleven included studies reported randomized distribution of the experimental sites[19-26, 28]. The study durations ranged from 2 to 6 months between the eleven included studies[18-28]. Six studies investigated the location of mandibular third molars[18, 20, 21, 23-25]. Three studies by Saifi et al., Noronha Oliveira et al., and Cruz et al. performed investigations on first premolars, maxillary third molars, molars, and premolars, respectively[19, 26, 27]. In two studies, Deshpande et al. and Sezavar et al. did not specify the tooth types that were extracted[22, 28].

Seven studies investigated bone density, bone regeneration, pain, and swelling in their study design as their primary parameters for evaluating statin benefits[18, 20-25]. Similarly, Diniz et al. investigated bone volume

(BV) in the extraction sockets[23]. Likewise, studies by Saifi et al., Cruz et al., Sezavar et al., and Noronha Oliveira et al. investigated bone density, dimensional changes in the horizontal and vertical components of the alveolar socket, changes in the alveolar ridge and ridge preservation in their study designs, respectively[19, 26-28].

Table 1. General characteristics of the included studies

Author et al; year (country)	**Study design**	**Total study participants (M/F)**	**Age range (mean age)**	**Study groups**	**Group allocation**	**Total study duration (in months)**	**Primary site of evaluation (alveolar socket)**	**Primary parameter (s) of evaluation**
Saifi et al., 2017 (India)	Prospective split-mouth study	15 participants (6/9)	18-27 years (21.8+/-2.86 yrs.	Control side (right side first premolars: n = 15) Case side (left side first premolars: n = 15)	N/A	4 months	Extraction sockets of all first premolars (bilaterally)	Bone density
Harsha et al, 2023 (India)	Split-mouth RCT	50 participants (N/A)	18-40 yrs.	Study side (simvastatin side: n = 50) Control side (without simvastatin: n = 50)	Random	3 months	Mandibular third molars (bilaterally)	Pain, Swelling, and Bone density
Deshpande et al, 2023 (India)	Split mouth RCT	31participants (17/14)	18–65 yrs.	Study side (simvastatin side: n = 31) and control side (non-simvastatin side: n = 31)	Random	6 months	Extracted tooth sockets (bilaterally)	Pain, swelling, and bone density
Diniz et al; 2022 (Brazil)	Single blind split mouth RCT	22 participants (10/12)	24.6+/-4.7 yrs.	Test side (ACS+ SMV: n = 22); Control side (no intervention after tooth extraction: n = 22)	Random	3 months	Mandibular third molars (bilaterally)	Bone volume (BV), Pain, swelling, and soft tissue healing
Cruz et al; 2021 (Brazil)	Triple blinded RCT	26 participants (13/13)	43.6 ± 4.93 to 44 ± 2.82 yrs.	Test group (1.2% SIM gel and PPPM: (n=13) The control group (placebo gel and PPPM (n =13)	Computer generated random group allocation	3 months	Premolars and molars	Dimensional changes in horizontal and vertical components of alveolar socket

Mahdi et al; 2021 (Iraq)	Prospective comparative randomized study	32 participants (15/17)	18-40 yrs.	Study group (simvastatin group: n = 15) Control group (no simvastatin group: n =17)	Random	3 months	Mandibular third molars	Pain and bone density
Sezavar et al; 2018 (Iran)	Single-blinded split-mouth randomized study	3 participants (2/1)	41 yrs.	Study side (Simvastatin & collagen: n = 10 sockets); Control group side (collagen only: n =10)	Random	2 months	20 tooth sockets	Changes in alveolar ridge bone
Degala et al; 2018 (India)	Single-blinded split mouth randomized trial	30 participants (16/14)	21-25 yrs. (31.5 yrs.)	Study side (gel-foam soaked with Simvastatin: n = 30); Control side (gel-foam soaked with Saline: n = 30)	Random	3 months	Mandibular third molars (bilaterally)	Bone density measurement, pain, and swelling
Noronha Oliveira et al; 2017 (Brazil)	Prospective split-mouth randomized controlled trial	14 participants (6/8)	22.8 ± 3.7 yrs.	Control side (spontaneous healing of tooth extraction: n = 14) Test side (PLGA/HA/S: 2.0% simvastatin scaffold graft: n = 14)	Random	3 months	Maxillary third molars (bilaterally)	Ridge preservation
Chauhan et al; 2014 (India)	Split-mouth investigation	30 patients (including males and females)	18-40 v	Group A (control side: n = 30); Group B (simvastatin side: n=30)	N/A	3 months	Mandibular third molars (bilaterally)	Pain, swelling, and osseous regeneration in the tooth extraction socket.
Deepanjali et al; 2022 (India)	A single-blinded randomized split-mouth prospective study	15 patients (6/9)	18-30 yrs.	Group A (study side: n =15); Group B (control side: n=15)	Random	6 months	Mandibular third molars (bilaterally)	Pain, swelling, and bone density measurement

N/A- Not available, ACS – absorbable collagen sponge, SMV – simvastatin, BV – bone volume, SIM- Simvastatin, PPPM-Polypropylene membranes, PLGA - Poly(D, L-lactide-co-glycolide), HA – Hydroxyapatite, S – simvastatin, RCT-randomized controlled trial

Characteristics of statin administration in the included studies

All eleven included studies used Simvastatin as their preferred choice of drug to investigate the effects of statins during teeth extraction. Throughout the experiments, all eleven studies administered simvastatin drug once in the socket after the preferred tooth was extracted[18-28]. Seven studies used simvastatin at a drug concentration of 10 mg[18, 20-22, 24, 25, 27], whereas two studies used 20 mg of simvastatin drug to perform their experiments[23, 28]. On the other hand, two studies used simvastatin at 12 mg/ml of solution (1.2% SIM gel) [19]and 2% [26] strengths for their investigations. In seven studies, simvastatin was introduced into the extraction socket in a crushed or powdered form [18, 20-22, 25, 27, 28] with a combination of either a gel

foam or collagen carrier. In the study by Cruz et al., simvastatin was administered in a gel form covered in Polypropylene membranes[19]. Noronha Oliveira et al. implanted 2% simvastatin in a scaffold graft combination of Poly (D, L-lactide-co-glycolide)- Hydroxyapatite (PLGA/HA/S)[26]. Diniz et al. introduced simvastatin to the operation site in an absorbable collagen sponge[23].

Table 2. Characteristics of statin administration in the included studies

Author et al; year	Type of statin	Dosage of statin	Statin delivery method	Frequency of administration	Site of application
Saifi et al., 2017 (India)	Simvastatin	10 mg	Placing crushed simvastatin tablets mixed with gelatin sponge and normal saline in tooth extraction sockets	Once after tooth extraction	Extraction sockets of first premolars on left side (bilaterally)
Harsha et al, 2023 (India)	Simvastatin	10 mg	Placing powdered simvastatin in a gel-foam carrier moistened with normal saline	Once after tooth extraction	Mandibular third molar extraction site (bilaterally)
Deshpande et al, 2023 (India)	Simvastatin	10 mg	Impregnation of powdered simvastatin tablet soaked with gel-foam carrier	Once after tooth extraction	Extracted tooth sockets (bilaterally)
Diniz et al; 2022 (Brazil)	Simvastatin	20 mg	SMV deposition (facilitated with ACS) in the extraction socket	Once after tooth extraction	Third molar extraction sockets (bilaterally)
Cruz et al; 2021(Brazil)	Simvastatin	12 mg/ml of solution (1.2% SIM gel)	Simvastatin gel (covered with PPPM) filled into the extraction socket using a syringe	Once after tooth extraction	Premolars and molars extraction sockets
Mahdi et al; 2021 (Iraq)	Simvastatin	10 mg	Placing simvastatin powder and gel-foam combination into the extraction sockets of the study site	Once after tooth extraction	Mandibular third molar extraction sockets
Sezavar et al; 2018 (Iran)	Simvastatin	20 mg	Powdered simvastatin tablets were placed into an extraction socket with collagen	Once after tooth extraction	10 extraction sockets
Degala et al; 2018 (India)	Simvastatin	10 mg	Dispensing Simvastatin crushed tablets with a combination of normal saline at the site of tooth extraction	Once after tooth extraction	Mandibular third molars (bilaterally)
Noronha Oliveira et al; 2017 (Brazil)	Simvastatin scaffold	2%	Implanting Poly (PLGA/HA/S) with 2.0% simvastatin scaffold below the bone crest level in the extraction socket	Once after tooth extraction	Maxillary third molars extraction sockets (bilaterally)

Chauhan et al; 2014 (India)	Simvastatin	10 mg	Inserting Simvastatin powder into the extraction socket in a gel-foam carrier	Once after tooth extraction	Mandibular third molar sockets (bilaterally)
Deepanjali et al; 2022 (India)	Simvastatin	10 mg	Implanting simvastatin powder in tooth extraction socket with gel-foam carrier	Once after tooth extraction	Mandibular third molar sockets (bilaterally)

SMV – simvastatin, ACS – absorbable collagen sponge, SIM- simvastatin, PPPM-Polypropylene membranes, PLGA – Poly (D, L-lactide-co-glycolide), HA – Hydroxyapatite, S – simvastatin

Findings about tissue remodeling upon statin administration in the studies included

Ten studies used radiographic techniques in their experiments to investigate outcome variables. The radiographic techniques included tools like Cone-beam computed tomography (CBCT) in eight studies. [19-26]Intra-oral periapical radiographs (IOPA) in 3 studies [18, 24, 27] and radiovisuography (RVG) by Deshpande et al.[22]. When recording pain, the visual analogue scale (VAS) was used in seven studies[18-24], and the Numeric pain scale (NPS) in the investigation by Mahdi et al.[25]. Six studies measured body landmarks to evaluate the effects of statin drugs in the management of facial swelling caused by extracting teeth [18, 20-24]Deshpande et al. and Sezavar et al. evaluated tissue remodeling by performing histological analyses in two investigations.[22, 28]. The soft tissue healing scale by Cruz et al. [19]and intra-oral examination and photos by Noronha Oliveira et al. [26]Other techniques were used to process their analyses. In their study, Diniz et al. used the Landry index to evaluate the inflammatory response[23].

Table .3. Findings about tissue remodeling upon statin administration in the studies included

Author et al; year	**Measurement technique(s)/tool(s)**	**Primary findings**	**Secondary findings**	**Additional findings**	**Conclusion**
Saifi et al, 2017 (India)	IOPA	Significantly higher radiographic gray value findings on the case side positively demonstrated bone formation	Increased gray value in radiograph was observed in mandibular case sides than the maxilla	Complications like infection, pain, swelling, draining sinus was not observed on the study side	Local administration of simvastatin induces bone formation in extraction sockets.
Harsha et al, 2023 (India)	IOPA, CBCT, VAS score, and measuring body landmarks	Statistically significant accelerated bone regeneration was observed in study sockets	Statistically, no significant difference was observed in the pain scores between the study and control sides	Statistically, no significant differences were observed in the horizontal and vertical dimensions of swellings between study and control sockets	Topical use of statins supports existing evidence of early formation and increase in maturation of bone in tooth extraction socket

Deshpande et al, 2023 (India)	VAS scores, measuring body landmarks, histology, RVG, and CBCT	A statistically significant difference in bone density was observed on the study side. Histology samples revealed increased vital bone and reduced necrotic bone on the study side.	Increased pain score was observed on the study side immediately after tooth extraction	Higher facial swelling was observed on the study side immediately after tooth extraction.	Local application of simvastatin can be considered for bone regeneration in tooth extraction sockets.
Diniz et al; 2022 (Brazil)	CBCT, VAS score, measuring body landmarks, and Landry index	BV, BV/TV, autogenous bone neoformation, and trabeculation were significantly higher on the test side. Similarly, findings positively correlated with Tb. Th and Tb.Sp. on the test side.	Greater facial swelling and pain were observed in the test group immediately after swelling	Test and control groups showed no difference in the late repair of local mucosa	Improved bone healing confirms the osteoinductive potential of simvastatin.
Cruz et al; 2021 (Brazil)	CBCT, VAS, and soft tissue healing scales	Alveolar ridge size did not differ significantly; dimensional changes in alveolar ridge thickness and height were significantly lower in the simvastatin group.	No significant difference in soft tissue healing was observed between the two groups.	No significant difference in post-operative pain was identified between the two groups.	Post-extraction, dimensional changes in the alveolar ridge was effectively reduced by using Simvastatin & PPPM.
Mahdi et al; 2021(Iraq)	NPS scale and CBCT	Mean bone density was statistically higher in the study group	Pain score was significantly lower in the study site immediately after tooth extraction	N/A	Topical administration of simvastatin in tooth extraction socket results in the formation of new bone.
Sezavar et al; 2018 (Iran)	Histology	Although not statistically significant, the percentage of vital, trabecular, and amorphous bone was higher on the test side.	Although not statistically significant, non-vital bone percentage (necrotic bone) was lower on the test side	The non-osteoblastic percentage was lower on the test side but was not statistically significant.	Simvastatin can improve the quality of bone formation in the jaw.
Degala et al; 2018 (India)	VAS score, measuring body landmarks, IOPA and CBCT	Statistically significant accelerated bone formation was reported in the study sockets	Facial swelling was higher on the study side immediately after tooth extraction	Long term complications, such as dry socket, infection, or draining sinus were not observed in the study sockets	Results, statistically and radiographically, favored the topical use of simvastatin to stimulate and expedite osseous regeneration in tooth extraction sockets
Noronha Oliveira et al; 2017 (Brazil)	CBCT, intra oral examination, and intra oral photographs	Radiographic findings suggested loss of graft material on the test site. Connective tissue formation was observed, and no bone regeneration was observed due to graft tissue loss.	Participants experienced discomfort like pain, infection, and graft loss on the test side.	N/A	The study failed to evaluate the benefits of simvastatin due to graft material loss from the investigation site.

Chauhan et al; 2014 (India)	IOPA, measuring body landmarks and VAS scale	The experimental site showed statistically significant accelerated bone formation.	No significant change in facial swelling was seen between groups	No significant change in pain was seen between groups	Faster formation of bone in the simvastatin group as compared to the control group
Deepanjali et al; 2022 (India)	VAS score, measuring body landmarks, and CBCT	Statistically significant accelerated bone formation was observed on the experimental site.	The study site showed a significant increase in facial swelling immediately after tooth extraction.	No significant change in pain was seen between groups	The osteoinductive property of simvastatin was statistically confirmed

IOPA- intraoral periapical radiographs, CBCT-Cone-beam computed tomography, VAS- visual analogue scale for pain measurement; RVG – radiovisuography, SIM-Simvastatin, BV-Bone volume, TV-Total volume, BV/TV – bone volume fraction/total volume, Tb.Th – trabecular thickness, Tb.Sp. – trabecular spacing, NPS – numerical pain score, N/A- Not Available

Bone formation, bone density, and rate of ossification

Of the eleven studies where tooth extraction sockets were treated with simvastatin, eight reported a statistically significant increase in the rate of ossification or a higher bone density[18, 20-25, 27]. In other words, bone formation was more significant on study sites where statin drug was introduced than in the control extraction sockets. Furthermore, in the study by Deshpande et al., histological samples identified an increase in vital bone and a decrease in necrotic bone in the extraction site after administration of simvastatin. Similarly, the study by Diniz et al. reported significantly higher bone volume (BV), bone volume/turnover volume fraction (BV/TV), autogenous bone neoformation, and trabeculation on the experiment side. Also, these findings positively correlated with trabecular thickness (Tb.Th) and trabecular spacing (Tb.Sp.) on the test side when compared to the control side with no statin drug intervention[23].

In the study by Cruz et at., although alveolar ridge size did not show a significant difference, dimensional changes in alveolar ridge thickness and height were observed to be significantly lower in the simvastatin group [19]Similarly, although not statistically significant, Sezavar et al. reported a higher percentage of vital, trabecular, and amorphous bone and lower osteoblastic percentage and necrotic bone in sockets with simvastatin.[28]. The observations by Noronha Oliveira et al. reported connective tissue formation at the site of investigation due to loss of graft material from the experimental sites[26].

Pain and facial swelling

In four studies, Chauhan et al., Cruz et al., Deepanjali et al., and Harsha et al. reported no statistical difference in pain scores when study sites were compared with control sides[18-20, 24]. Two studies by Deshpande et al. and Diniz et al. observed an increase in pain score on the study side immediately after tooth extraction [22, 23]On the other hand, in the study by Mahdi et al., a significantly lower pain score was seen on the experimental site upon administration of simvastatin.[25]. More significant facial swelling on the experimental

sides was recorded in four studies by Deepanjali et al., Degala et al., Deshpande et al., and Diniz et al.[20-23]. On the contrary, in two studies by Chauhan et al. and Harsha et al., no significant change in facial swelling was observed between groups.[18, 24]. Additionally, Saifi et al. reported no complications such as pain, swelling, or infection were identified on study sites[27]. Similarly, Degala et al. reported that long-term effects such as dry sockets, infections, and/or draining sinuses were not observed in the extraction sockets treated with simvastatin drugs, indicating that the drug is well-tolerated in patients. Ten of the eleven included studies favored the potential of simvastatin to stimulate and expedite osseous regeneration in tooth extraction sockets[18-25, 27, 28]. A study by Noronha Oliveira et al. reported loss of graft material from tooth extraction sockets in their study participants, owing to which the understanding of the comprehensive effects of statin drugs on tissue remodeling in tooth extraction sockets remained undetermined[26].

Risk of bias assessment

For non-randomized studies, the ROBINS-I tool was used to assess bias across seven key domains, which included confounding, selection bias, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. The overall risk of bias for these studies varied from low to moderate. Saifi et al. had a low risk of bias across most domains [27]. Still, they showed a moderate risk related to deviations from the intended intervention (D6), leading to an overall classification of moderate risk of bias. Similarly, Chauhan et al. exhibited a moderate risk in two domains (D3 and D6), while other domains had a low risk, resulting in an overall moderate risk of bias classification [18]. For randomized crossover studies, most included trials demonstrated a low risk of bias across all domains. Studies conducted by Cruz et al. [19], Deepanjali et al. [20], Degala et al. [21], Diniz et al. [23], Harsha et al. [24], Mahdi et al. [25], Olivera et al. [26], and Sezavar et al. [28] were classified as having an overall low risk of bias, reflecting strong methodological quality. However, Deshpande et al. had some concerns regarding the randomization process while maintaining a low risk of bias in all other domains [22]. Despite this limitation, it was still classified as having a low risk of bias. In conclusion, the ROBINS-I assessment of non-randomized studies indicated a moderate risk of bias, primarily due to intervention deviations and confounding factors. In contrast, the RoB 2 assessment of randomized crossover studies showed a predominantly low risk of bias, ensuring higher reliability of findings from these trials. This highlights the greater methodological strength of randomized crossover studies compared to non-randomized designs in this review.

Table 5. Risk of Bias for Non-RCTS

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Saifi et al., 2017 (India)	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Chauhan et al; 2014 (India)	Low	Low	Moderate	Low	Low	Moderate	Low	Moderate

Table 6. Risk of Bias for RCTS

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall, Bias
Cruz et al.	Low	Low	Low	Low	Low	Low
Deepanjali et al.	Low	Low	Low	Low	Low	Low
Degala et al.	Low	Low	Low	Low	Low	Low
Deshpande et al.	Some concerns	Low	Low	Low	Low	Low
Diniz et al.	Low	Low	Low	Low	Low	Low
Harsha et al	Low	Low	Low	Low	Low	Low
Mahdi et al.	Low	Low	Low	Low	Low	Low
Olivera et al.	Low	Low	Low	Low	Low	Low
Sezavar et al.	Low	Low	Low	Low	Low	Low

Discussion

This systematic review investigated the healing effects of statin drugs in an extracted tooth socket. Based on clinical studies, the current investigation revealed the potential benefits of statin drugs in augmenting the healing of alveolar bone. In the included studies, several authors reported acceleration of new bone formation and expedition in the maturation of alveolar bone in the tooth extraction socket [18-25, 27, 28]. Findings related to pain and swelling varied between the included studies, ranging from no statistical difference between test and control sides to higher pain and facial swelling scores on experimental sites. Previous animal experiments have demonstrated promising results from statin drug administration in tooth extraction sockets. The observations from these studies revealed bone formation, healing of tissues, reduction in inflammation, improving the continuity of epithelial tissues, and reducing necrotic bone [29-32]. Furthermore, animal studies conducted in rats have revealed prevention of bone-related pathological conditions such as medication related-osteonecrosis of the jaw [33]. These findings align with the observations recorded in the current systematic

review.

Interestingly, the eleven included studies preferred the local route of simvastatin administration in the tooth extraction socket. Previous studies have reported several advantages of administering statin drugs at the site of operation versus using systemic doses. These advantages include but are not limited to lowering widespread muscle and hepatic damage and providing utmost benefit to the area of delivery, maximizing the antimicrobial advantage of stain drug at the application site, and reducing chances of impaired vascularity when used systemically[34, 35]. These findings have further been supported by Gutierrez et al., who reported a higher potency of statins in bone formation in rats when administered locally[36].

To the best of the authors' knowledge, this systematic review is the first to systematically investigate the benefits of statin drugs in the healing of an extracted tooth socket in human trials. The findings of this review resonate with previously reported benefits of statin drugs in dentistry. Additionally, it is essential to note that there were no reports of long-term adverse reactions from statins in the included studies, indicating the drug is clinically safe to use.

The limitations of this systematic review include a low participant count of 268 patients from the eleven included investigations. Secondly, the limited number of studies in the review may not be sufficient to reach meaningful conclusions and establish robust guidelines for the extensive use of statin drugs in managing a tooth extraction socket. Thirdly, a meta-analysis could not be performed due to heterogeneity between the included studies.

Therefore, further trials with larger sample sizes should be undertaken to fully comprehend statin drugs' benefits in healing an extraction socket.

Conclusion

The osteo-inductive potential of statin drugs and their benefits in augmenting the healing of a tooth extraction socket has been strongly supported by the findings of this study. Based on the findings of the included studies and previously reported animal studies, this review concludes that statin holds tremendous value in managing alveolar bone at the tooth extraction site. With more extensive randomized trials and larger sample sizes, new guidelines can be established regarding the dose and the preferred choice of statin drug in managing alveolar bone following a tooth extraction.

Supplementary files: None

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