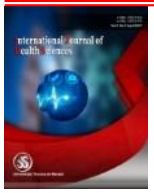

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Effectiveness of Simvastatin with Antibiotics Compared to other material on Clinical and Radiographic Outcomes Following Non-Surgical Endodontic Treatment

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antibiotics;
non-surgical endodontic treatment;
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Abstract

Background and Objective: Postoperative endodontics complications can influence the patient's quality of life. One method of lesion sterilization and tissue repair (LSTR) therapy combines simvastatin with metronidazole, ciprofloxacin, and minocycline, which are used for primary teeth. This review assesses the clinical and radiographic effects of combining simvastatin with antibiotics compared with other materials on pediatric patients. Materials and Methods: This review followed the specifications of the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024552895. The following electronic databases were utilized to search Randomized Clinical Trials (RCTs): MEDLINE(PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, Embase, and OVID up to and including July 2024. The Cochrane Risk of Bias tool was used to evaluate the potential for bias in randomized clinical studies. Results: In the initial search through electronic databases and registers, 1368,764 studies were found. 8 RCTs met the inclusion criteria for qualitative analysis after removing duplicates and enforcing the eligibility criteria. Six out of 8 studies showed that combining simvastatin with antibiotics was effective clinically and radiographically following non-surgical endodontic treatment compared to other treatment modalities. The risk of bias was high in 3, low in 3, and unclear in 3 studies. Conclusion: This review suggests that combining simvastatin with antibiotics may be effective clinically and radiographically following non-surgical endodontic treatment. However, further studies are needed to confirm the potential of that combination in non-surgical endodontic management.

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Contents

1 Introduction

Dental caries is a multifactorial biofilm-mediated disease characterized by cycles of demineralization and remineralization of tooth hard tissues. It is highly prevalent, particularly in children, and can rapidly progress to the pulpal tissue. Treatment approaches may include pulpotomy, pulpectomy, direct pulp capping, or indirect pulp capping. And according to European Society of Endodontology (ESE) guidelines, these approaches are part of non-surgical endodontic treatment and are considered vital pulp therapy (Bindal et al., 2017; Boutsiouki et al., 2021; Endodontology, 2006; Pitts et al., 2017). During and following endodontic treatment, postoperative pain, tenderness to percussion, and swelling can be short or long-lasting, with an overall incidence of 39% - 65% within the first 24 hours (Ozlek et al., 2021; Wang et al., 2010). Several factors impact the endodontic outcomes, such as the preoperative pain level (Karatas et al., 2021; Tanalp et al., 2013), the number of appointments (Hepsenoglu et al., 2018; Karatas et al., 2021), type of tooth (Arias et al., 2013; Karatas et al., 2021), type of the instrument (Karatas et al., 2021; Topçuoğlu & Topçuoğlu, 2017), movement kinematic of the instrument (Arslan et al., 2016; Karatas et al., 2021), extrusion of root canal filling material and sealer (Karatas et al., 2021; Lopes et al., 2019).

Some materials are commonly considered when providing non-surgical endodontic treatment, such as ferric sulfate, formocresol, mineral trioxide aggregate, zinc oxide eugenol, calcium hydroxide, antibiotic paste, and simvastatin (Mohammadi et al., 2018; Smaïl-Faugeron et al., 2018; Takushige et al., 2004; Vijayaraghavan et al., 2012).

One of the materials emerging recently is the Statin component. Evidence supports that statins have 'pleiotropic' actions in experimental and clinical studies. Statins such as simvastatin inhibit biofilm-forming bacteria, improving the effectiveness of antibiotics in eradicating bacteria within the complex anatomy of the root canal system. This reduction in biofilm resilience decreases the risk of persistent infection and enhances the success rate of endodontic treatments (El Kharadly et al., 2022; Shroff et al., 2024). Also, statin improves osteoblastic activity, decreases osteoclastic function, and enhances bone formation. It can be concluded that it might help improve the osteoblastic action that further helps dentin formation. Thus, statins are an ideal ingredient in activating the reparative dentin formation in direct pulp capping (Asl Aminabadi et al., 2016; Okamoto et al., 2009; Chedid et al., 2021).

Antibiotic mixtures are vital in treating persistent or complex endodontic infections (Mohammadi et al., 2018; Vijayaraghavan et al., 2012). Their application should be cautious and targeted to avoid complications like discoloration or resistance (Krastl et al., 2022; Mohan, 2020). Antibiotic mixtures are most commonly employed in regenerative endodontic procedures (REPs) for immature teeth with necrotic pulp and apical periodontitis (Mohammadi et al., 2018; Vijayaraghavan et al., 2012; Ritzel et al., 2002). This mixture often includes ciprofloxacin, metronidazole, and minocycline, mixed into a paste-like consistency for the intracanal

application. It is commonly used to disinfect root canals, particularly in immature teeth with necrotic pulp, enabling continued root development (Ribeiro et al., 2020; Ruparel et al., 2012).

Combining simvastatin with antibiotics is valuable in modern endodontic therapy (El Kharadly et al., 2022; Moreno et al., 2009; Shroff et al., 2024). The localized application of simvastatin with antibiotics in endodontic treatments offers a focused, therapeutic approach. This combination delivers high concentrations of both materials, providing effective inflammation control, tissue healing, and minimizing the systemic side effects (El Kharadly et al., 2022; Moreno et al., 2009; Shroff et al., 2024; Takushige et al., 2004).

In contrast, different materials are used in non-surgical endodontic treatment. For example, Ferric sulfate is a widely used material for pulpotomy in pediatric patients (Yoon & Best, 2011). Formocresol, which contains formaldehyde, is effective due to its bactericidal properties but raises safety concerns due to its potential carcinogenicity and systemic toxicity (Casas et al., 2005; Issrani et al., 2023; Ko et al., 2017; Winters et al., 2013; Zhang et al., 2009). The MTA has become the gold standard for vital pulp therapy due to its bioactivity, sealing ability, and biocompatibility (Altuhafy et al., 2024; Smaïl-Faugeron et al., 2018). Calcium hydroxide is another popular material with its high pH and bactericidal properties. However, the disadvantages of Calcium hydroxide ($Ca(OH)_2$) include its deterioration over some time and tunnel defects under the dentinal bridge, not having a suitable sealing property, and causing pulp and tissue necrosis (Taneja & Singh, 2019). Zinc oxide eugenol (ZOE) has been utilized as a base material in pulpotomy, but its eugenol component may cause inflammation and internal resorption. Reinforced ZOE materials like IRM improve mechanical properties but retain some inflammatory risks (Hui-Derksen et al., 2013).

Therefore, the primary objective of this study was to systematically evaluate the clinical and radiographic effectiveness of combining simvastatin with antibiotics in non-surgical endodontic management compared to other materials.

2 Materials and Methods

Reporting Format

Preferred Reporting Items reviewed for Systematic Reviews and Meta-Analysis (PRISMA) (Page et al., 2021). The study protocol, registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024552895, was not subject to meta-analysis due to its high heterogeneity.

Focused Question

Is the combination of simvastatin with antibiotics effective clinically and radiographically following non-surgical endodontic treatment in pediatric patients?

Patients, Interventions, Control, Outcome (PICO)

The Population, Interventions, Control, and Outcome **(**PICO) format was based on the following: (P) pediatric patients receiving non-surgical endodontic treatment; (I) a combination of simvastatin with antibiotics; (C) other materials or no treatment; and (O) clinical and radiographical effectiveness.

Eligibility Criteria

The inclusion criterion was outlined in the following: (a) children in need of non-surgical endodontic treatments, (b) study group: a combination of simvastatin and antibiotics, (c) control group: use of other materials, (d) studies that compared study and control groups, (e) Randomized Control Trials. To avoid. Excluded studies were in vitro and vivo, case reports and series, commentaries, letters addressed to the editor, and retrospective and non-randomized studies.

Search Strategy and Data Extraction

RCTs were explored and included using the following databases: MEDLINE (PubMed), Web of Science, Scopus Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and OVID, with no publication date or language restrictions or filters up to July 2024. The search string considered all required keywords and MeSH terms: (1) Antibiotics, (2) Simvastatin, (3) Endodontic treatments, (4) 3Mixtatine, (5) Children, (6) Clinical effects, and (7) Radiographic effects. The specified vital language was merged using "OR, AND" Boolean

operators to widen the result outcomes. Two authors (MA and GA) evaluated the abstracts and titles of the included studies using the tools mentioned above. The texts of relevant studies were assessed individually. The reference lists of relevant original studies and review articles were also searched to find studies that may have been overlooked. The presence of any further discrepancies was confirmed by discussion and debate with a third researcher (JK) (Tables 1 and 2).

3 Results and Discussions

3.1 Results

Study Selection and General Characteristics of Study

The computerized search strategy that was done initially through electronic databases and registers found 368,764 studies. Furthermore, the duplicates were searched and removed, and following the eligibility criterion, 8 RCTs were finalized in the inclusion and exclusion criteria for the final qualitative analysis. The ages of the patients ranged from 3 to 9 years. The RCTs included in this systematic review were parallel, double, quadruple-blinded, multi-center group design and included both genders of male and female patients (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). These studies included a study group that combined simvastatin with antibiotics and a control group that used materials such as calcium hydroxide, zinc oxide eugenol, mineral trioxide aggregate, etc. Various diagnoses were included in these studies, such as teeth with pulpal pathology in the presence or absence of radiolucency required endodontic intervention (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). The included studies were taken from Iran; two were from India, two were from Egypt, and one was from Syria (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). The recall intervals spanned from 12 to 24 months, ensuring comprehensive outreach and engagement. Primary posterior molar teeth were used in all the studies (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023) (Table 3, Figure 1).

General characteristics of the combination of simvastatin and antibiotics in the included studies

In the selected studies, the teeth for the included procedures were all primary teeth (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). Different dental treatments were performed. In four studies, pulpotomy was performed (Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023), two studies performed direct pulp capping (Asl Aminabadi et al., 2016; Attia et al., 2023), one study performed non-instrumentation endodontic treatment (Almarji et al., 2024), whereas in one study, conventional pulpectomy and restoration were performed (Aminabadi et al., 2016). Various antibiotics with different dosages were used to prepare the combination of simvastatin and antibiotics (Almarji et al., 2024; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Jamali et al., 2018; Mushtaq et al., 2023). Six studies demonstrate the effectiveness of combining cefixime, metronidazole, ciprofloxacin, and simvastatin to enhance treatment outcomes (Almarji et al., 2024; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Jamali et al., 2018; Mushtaq et al., 2023). Asl Aminabadi et al. (2016), used 100 mg ciprofloxacin, 100 mg metronidazole, and 100 mg cefixime. Because of minocycline contraindication in children, it was replaced by cefixime + 2 mg of simvastatin (Asl Aminabadi et al., 2016). Jamali et al. used 100 mg of ciprofloxacin, 100 mg of metronidazole, and 100 mg of cefixime + 2 mg of simvastatin (Jamali et al., 2018). Chak et al., in their study, included metronidazole, ciprofloxacin, cefixime, and simvastatin powder (Chak et al., 2022). Mushtaq et al. included 100 mg of ciprofloxacin, 100 mg of metronidazole, and 100 mg of cefixime mixed with 2 mg of simvastatin (Mushtaq et al., 2023). Atteya et al. continued with 2 mg of simvastatin to the triple antibiotic paste, composed of ciprofloxacin, Metronidazole, and Cefixime (Attia et al., 2023). Almarji et al. used 100 mg of

three commercially available antibiotics, metronidazole, cefixime, and ciprofloxacin, with 2 mg of simvastatin (Almarji et al., 2024). Aminabadi NA et al. conducted a compelling study that effectively combined ciprofloxacin, metronidazole, minocycline, and simvastatin, showcasing the potential benefits of this innovative treatment approach (Aminabadi et al., 2016). Abdou et al. reported combining dentine and simvastatin in a ratio of 1:1(Elsayed et al., 2023).

No studies mentioned the amount of the combination (simvastatin and antibiotics) applied, but the thickness of that combination (simvastatin and antibiotics) was 1-3 mm in the included studies (Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Jamali et al., 2018; Mushtaq et al., 2023). The studies by Abdou et al., Almarji et al., and Aminabadi NA et al. should have commented on the thickness of the material applied in their RCT (Almarji et al., 2024; Aminabadi et al., 2016; Elsayed et al., 2023). MTA was the primary material in the control group in three studies (Aminabadi et al., 2016; Chak et al., 2022; Mushtaq et al., 2023). Some studies included more than one material as a control group; Atteya et al. used MTA and simvastatin as the control groups (Attia et al., 2023). The study by Jamali et al. used MTA and formocresol as the control group (Jamali et al., 2018). The study by Abdou et al. used biodentine and simvastatin in the control group (Elsayed et al., 2023). A study done by Almarji et al. used zinc oxide eugenol as their control group (Almarji et al., 2024), and studies by Asl Aminabadi et al. and Chak et al. MTA was utilized with a thickness of 3mm (Asl Aminabadi et al., 2016; Chak et al., 2022), whereas Asl Aminabadi et al. used a 1.5-2mm thickness for simvastatin and 1.5-2mm for the combination (simvastatin and antibiotics) (Asl Aminabadi et al., 2016) (Table 4). Different studies used normal saline or propylene glycol as liquid materials to make a paste of the combination (simvastatin and antibiotics). None of the studies mentioned any other materials.

Outcomes of included studies

Due to the effectiveness of combining simvastatin with antibiotics demonstrated in six studies, this combination (simvastatin and antibiotics) may be an effective option for pulpotomy in primary teeth [20, 37, 38, 40, 42, 43]. Chak et al. reported that the 3mixtatine (combining simvastatin with antibiotics) and MTA groups showed no statistically significant difference between clinical success rates in months 3, 6, 9, and 12 ($P < 0.5$). In contrast, radiographically, a higher success rate was seen in months 3, 6, 9, and 12 with the 3Mixtatin group (success rate 78%) compared to the MTA group (success rate 75%) (Chak et al., 2022). Aminabadi NA et al. reported that in the 24-month follow-up, there was a statistically significant difference in the clinical ($P = 0.03$) and radiographical ($P = 0.01$) characteristics between the 3mixtatine and MTA groups (Aminabadi et al., 2016). Radiographic and clinical healing occurred more successfully following 3Mixtatin (combining simvastatin with antibiotics) treatment than with MTA treatment (Aminabadi et al., 2016).

A study done by Atteya et al. compared the effect of simvastatin, 3mixtatine (combining simvastatin with antibiotics), and MTA. By the end of the 12-month follow-up period, the overall success rates were 20.0% in simvastatin, 92.3% in 3Mixtatin, and 92.3% in MTA groups. However, there was no statistically significant difference between the outcomes of MTA and 3Mixtatin groups ($P > 0.05$). At the same time, 3Mixtatin and MTA had statistically superior results compared to the simvastatin group ($P < 0.01$) (Attia et al., 2023). However, a study by Mushtaq et al. compared the effect of 3mixtatine (combining simvastatin with antibiotics) and reported that by the end of 12 months, the overall success rates were 95.5% in MTA and 91.3% in 3Mixtatin. No statistically significant difference was found among the outcomes of the MTA and 3Mixtatin groups ($P > 0.05$) (Mushtaq et al., 2023).

A study by Asl Aminabadi et al. evaluated the efficacy of 3Mixtatin (a combination of simvastatin and 3Mix antibiotic) as a pulp-capping biomaterial in the DPC of human primary molars. It compared it to MTA, 3Mix(antibiotics), and simvastatin. It reported that by the end of 12 months, the overall success rates were 93.8% in MTA, 91.9% in 3Mixtatin, 62.5% in 3Mix(antibiotics), and 57.1% in simvastatin groups. And no statistically significant difference was found between the outcomes of MTA and 3Mixtatin groups ($P > 0.05$). However, 3Mixtatin had statistically superior results compared to 3Mix and simvastatin ($P < 0.01$)(Asl Aminabadi et al., 2016).

The study by Jamali et al. compared the efficacy of 3Mixtatin (a combination of simvastatin and 3Mix antibiotic) with MTA and Formocresol for the pulpotomy of primary molars. The overall success rate was 78.9% for Formocresol, 90.5% for 3Mixtatin, and 88.1% for the MTA group. However, there was no significant

difference in the overall success rate among the groups after 24-month follow-up (P =0.27) (Jamali et al., 2018).

Additionally, a study by Almarji et al. evaluated the clinical and radiographic outcomes of non-instrumentation endodontic treatment (NIET) using a modified antibiotic mix of cefixime, ciprofloxacin, metronidazole, and simvastatin on necrotic primary molars compared to conventional pulpectomy using zinc oxide eugenol paste. All teeth were clinically evaluated after 1, 3, 6, and 12 months and assessed radiographically at 3, 6, and 12 months. The study reported no statistically significant differences between both groups, clinically and radiographically, after 12 months of treatment (Almarji et al., 2024).

The study by Abdou et al. evaluated the clinical and radiological effectiveness of using Simvastatin in combination with Biodentine as a pulpotomy agent for vital primary molars. It reported that Pulpotomized teeth were deemed clinically successful if they fulfilled the following requirements: no tenderness, no pain on percussion, no pathological tooth mobility, and no swelling/sinus (Elsayed et al., 2023) (Table 5). After a year of follow-up, a clinically and radiographically significant difference (P<0.001) was reported between the three groups (Elsayed et al., 2023).

Six studies reported that their clinical and radiological follow-up timing was within one year (Almarji et al., 2024; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Mushtaq et al., 2023). During that time, there were different follow-up intervals. The p-value was significant in all eight studies (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). Measurement criteria were separated into clinical criteria measurement and radiographic criteria management. The power analysis done by all the studies was not consistent. Five included studies had a power analysis of 80% (Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). Almarji et al and Abdou et al had a power of 95% (Almarji et al., 2024; Elsayed et al., 2023). Chak et al. did not mention the power analysis (Chak et al., 2022).

Radiographically, success was reported if they fulfilled the requirements of no lamina dura loss, external/ internal resorption, standard periodontal ligament space, and no periapical/furcation radiolucency. Most studies used similar measurement criteria (Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). However, Almarji et al. had additional criteria (Almarji et al., 2024): No fistula was detected visually, and painful symptoms and abnormal mobility were assessed by putting alternate pressure on the outer and inner areas of the molar crown and using two hand instruments. The unharmed gingival contour was determined by palpation. The lack of pathological resorption of bone was evaluated by checking any further radiolucent areas on the radiographs, and the absence of pathological root resorption was observed on the follow-up imaging to assess the changes in the amount of radiolucency present.

Risk of Bias Assessment

To evaluate the risk of bias used in the individual studies, the Cochrane Risk of Bias Tool was used for Interventions, RevMan 5.4.1 software, Copenhagen, Denmark. We used the Cochrane risk of bias tool and not any other tool, as all our included studies are Randomized clinical trials, and it is a validated tool for evaluating the risk of bias. The domains that were analyzed are as follows: 1) adequate sequence generation, 2) allocation concealment, 3) blinding of participants and an investigator, 4) incomplete outcome data, 5) free of selective outcome reporting, and 6) free of other bias. The overall risk was categorized as high, low, and unclear bias. The Randomization Sequence Generation was low in all seven studies (Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023), except in one study in which it was high (Almarji et al., 2024). Allocation Concealment was considered low in five studies (Aminabadi et al., 2016; Asl Aminabadi et al., 2016) (Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023) and high in two studies (Almarji et al., 2024; Attia et al., 2023). There was a lack of blinding of participants and research personnel in various studies. Thus, performance bias was high in four studies (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Jamali et al., 2018), and there were some concerns related to the process in one study (Mushtaq et al., 2023) and low in three studies (Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023). Blinding of Outcome Assessment was low in four studies (Almarji et al., 2024; Aminabadi et al., 2016; Asl Aminabadi et al., 2016;

Jamali et al., 2018), and some concerns in four studies (Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Mushtaq et al., 2023). Incomplete Outcome Data was low in three included studies(Almarji et al., 2024; Chak et al., 2022; Elsayed et al., 2023) and high in five studies (Aminabadi et al., 2016; Asl Aminabadi et al., 2016; Attia et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023).The selective reporting was high in two studies (Almarji et al., 2024; Aminabadi et al., 2016), low in four studies (Attia et al., 2023; Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018), and some concerns in two studies (Asl Aminabadi et al., 2016; Mushtaq et al., 2023). Other potential reasons leading to bias identified were that not all outcomes were reported in alignment with the aim of the study, and a few participants declined to participate, thereby leading to a lack of accurate representation of the population in the sample. The Other Bias was low in two studies (Chak et al., 2022; Elsayed et al., 2023), high in one (Aminabadi et al., 2016), and some concerns in the other five studies (Almarji et al., 2024; Asl Aminabadi et al., 2016; Attia et al., 2023; Jamali et al., 2018; Mushtaq et al., 2023). In this systematic review, the overall risk of bias includes three studies that were of low-risk bias (Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018), three unclear studies (Asl Aminabadi et al., 2016; Attia et al., 2023; Mushtaq et al., 2023), and two studies that were at high risk of bias (Almarji et al., 2024; Aminabadi et al., 2016) (Table 6, Figures 2 and 3).

3.2 Discussion

The effectiveness of endodontic treatment comes from an acceptable patient experience and successful clinical results. Adverse side effects from endodontic procedures can be managed successfully by considering factors that cause the pain, using available and appropriate treatment methods, and carefully selecting the restorative material used in that procedure. Practitioners usually face challenges in determining the best material for a particular procedure (Chak et al., 2022; Elsayed et al., 2023). Biofilm-forming bacteria are a significant cause of persistent and recurrent endodontic infections. Simvastatin inhibits biofilm formation, improving the effectiveness of antibiotics in eradicating bacteria within the complex anatomy of the root canal system. This reduction in biofilm resilience decreases the risk of persistent infection and enhances the success rate of endodontic treatments (El Kharadly et al.; Shroff et al., 2024). The Triple Antibiotic Paste (TAP) is commonly used to disinfect root canals, particularly in immature teeth with necrotic pulp, enabling continued root development. However, limitations such as tooth discoloration, toxicity, and antibiotic resistance necessitate cautious use (Ribeiro et al., 2020; Ruparel et al., 2012).

This review evaluates the effectiveness of combining simvastatin with antibiotics for the non-surgical endodontic treatment of primary teeth. As a material used for pulp capping, it helps acquire all essential aspects, including pulp exposure site disinfection, antibacterial and anti-inflammatory properties, biocompatibility, and regeneration capacity (Almarji et al., 2024). Combining two or three antibiotics wiped out bacterial contamination, the foremost causative factor in the unsuccessful treatment of primary teeth. Simvastatin was introduced to provide anti-inflammatory, bio-inductive, and angiogenesis-stimulating agents (Chak et al., 2022; Elsayed et al., 2023; Jamali et al., 2018).

The overall direction showed remarkable results in combining simvastatin with antibiotics in non-surgical endodontic treatment of primary teeth at the 12-to-24-month follow-up. The study is consistent with our recent clinical trials' equivalent/higher success rate of combining simvastatin with antibiotics to save primary teeth with a poor prognosis with pathologic root or inter-radicular resorption. This could be attributed to the bio-inductive effects of simvastatin on inhibiting bone resorption and osteocyte apoptosis and promoting osteoblast proliferation and differentiation. As per the Almerji et al. report, it was noted that the non-instrumentation endodontic treatment (NEIT) method using a combination of simvastatin with antibiotics is an effective alternative to the conventional pulpectomy procedure for managing primary molars undergoing necrosis (Almarji et al., 2024). At the same time, Atteya et al. concluded that MTA and a combination of simvastatin with antibiotics yielded favorable clinical and radiographical outcomes compared to simvastatin (Attia et al., 2023). Simvastatin showed a significantly lower success rate than the combination of simvastatin with antibiotics and MTA groups (Attia et al., 2023). They also concluded that combining simvastatin with antibiotics can be an effective and appropriate material in the DPC in addition to MTA for the primary teeth (Attia et al., 2023).

A study by Abdou et al. concluded that Biodentine demonstrated extremely high clinical and radiographic success rates, Simvastatin failed clinically and radiographically, and Combining biodentine and simvastatin

showed good clinical and radiographic results (Elsayed et al., 2023). Aminabadi NA et al., in their study, mentioned that the presence of radiolucent areas in primary molar teeth with poor prognosis with furcation root perforations from dental disease was effectively managed after 24 months with the combination of simvastatin with antibiotics compared to MTA (Aminabadi et al., 2016). The clinical results showed better outcomes for teeth treated with 3Mixtatin (the combination of simvastatin with antibiotics) in the follow-up period than those treated with MTA. Chak et al., in their study, concluded that the expected advantage of the combination of simvastatin with antibiotics can be utilized as a significant option to MTA in pulp therapy in primary teeth with a 12-month follow-up time (Chak et al., 2022). The combination of simvastatin with antibiotics presented superior responses to MTA, which may need further evaluation for the long-term efficacy of both materials. However, Jamali et al. reported that a combination of simvastatin with antibiotics could be used as a pulp capping material in pulpotomy of primary teeth because of its successful clinical and radiographic outcomes after 24 months of the follow-up period (Jamali et al., 2018). The study by Mushtaq et al. suggested that combining simvastatin with antibiotics might be a more economically effective and bio-inductive alternative for specific procedures (Mushtaq et al., 2023). More work must be done to validate this material's effects further, including more clinical trials and significant follow-up periods. Asl Aminabadi et al. reported that combining simvastatin with antibiotics could be an appropriate alternative to treating DPC in deciduous teeth (Asl Aminabadi et al., 2016). The study by Asl Aminabadi et al. (2016), reported that 34 teeth were asymptomatic when using simvastatin with the antibiotics group. Three teeth failed due to pain and tenderness to percussion. While in the MTA group, 30 teeth had no symptoms. One tooth failed because of pain, and one showed a sinus tract (Asl Aminabadi et al., 2016). A study by Jamali et al. (2018), showed a combination of simvastatin with antibiotics—Two (4.1%) teeth had pain at 12 months and one (2.3%) at the 24-month follow-up. No teeth in this group showed radiographic failure in the follow-ups. MTA- Two teeth (4.4%) at 12-month follow-up and two (4.7%) teeth at 24-month follow-up had pain. One tooth (2.3%) had a fistula at the 24-month follow-up examination. However, in a study by Abdou et al. (Elsayed et al., 2023), at the end of the 12 months, no patient in group I had pain, tenderness on percussion, a swollen sinus, or pathological mobility. However, one patient in groups II and III had spontaneous pain and tenderness on percussion without a swollen sinus or pathological mobility.

Biofilm-forming bacteria are a significant cause of persistent and recurrent endodontic infections. Simvastatin inhibits biofilm formation, improving the effectiveness of antibiotics in eradicating bacteria within the complex anatomy of the root canal system. This reduction in biofilm resilience decreases the risk of persistent infection and enhances the success rate of endodontic treatments (El Kharadly et al.; Shroff et al., 2024).

The promising clinical properties of simvastatin with antibiotics could bring about a crucial change in the future of non-surgical endodontic management for primary teeth. This systematic review's strength lies in its comprehensive inclusion of all 8 RCTs from recent studies, considering the lack of previous research in this area of interest. The limitations included only primary teeth utilized in pediatric patients, and the endodontic treatment differed amongst studies from pulpotomy, pulpectomy, and non-instrumentation endodontic treatment. Another limitation was the small sample size and lack of power analysis mentioned in the studies. Also, the heterogeneous methodology and outcome remain one of the critical drawbacks of the current review. Studies were unclear with the gender and age of the participants, the materials considered in the control group for comparison with the combination of simvastatin with antibiotics, and the period and evaluations of the follow-up period.

4 Conclusion

The current review indicates that combining simvastatin with antibiotics may be clinically and radiographically effective following non-surgical endodontic treatment. However, future standardized studies must validate these findings and determine their potential as an alternative to other materials in endodontic procedures.

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The authors do not have any personal or financial conflict of interest.

Data availability
All data, as well as related tables and figures, are incorporated into the article.

Authorship contribution statement
All authors contributed to the conception, design, acquisition, data collection, analysis and interpretation of results. All authors participated in drafting the article and approved the final version of the manuscript.

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Figure 1. PRISMA Flow chart of search in databases

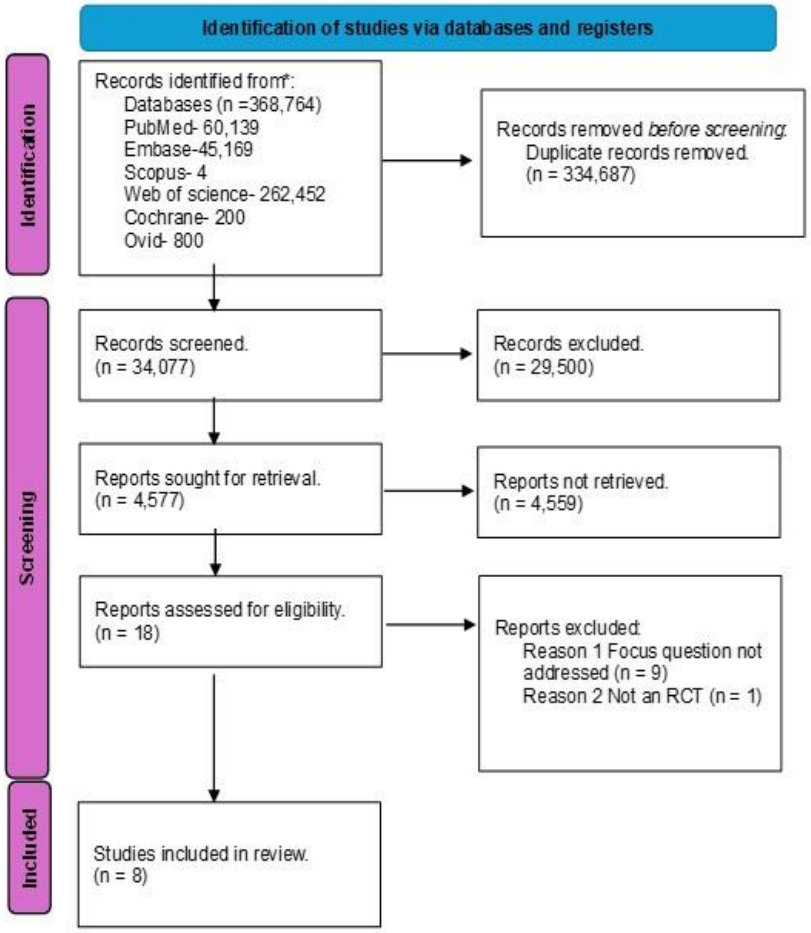


Figure 2. Traffic plot

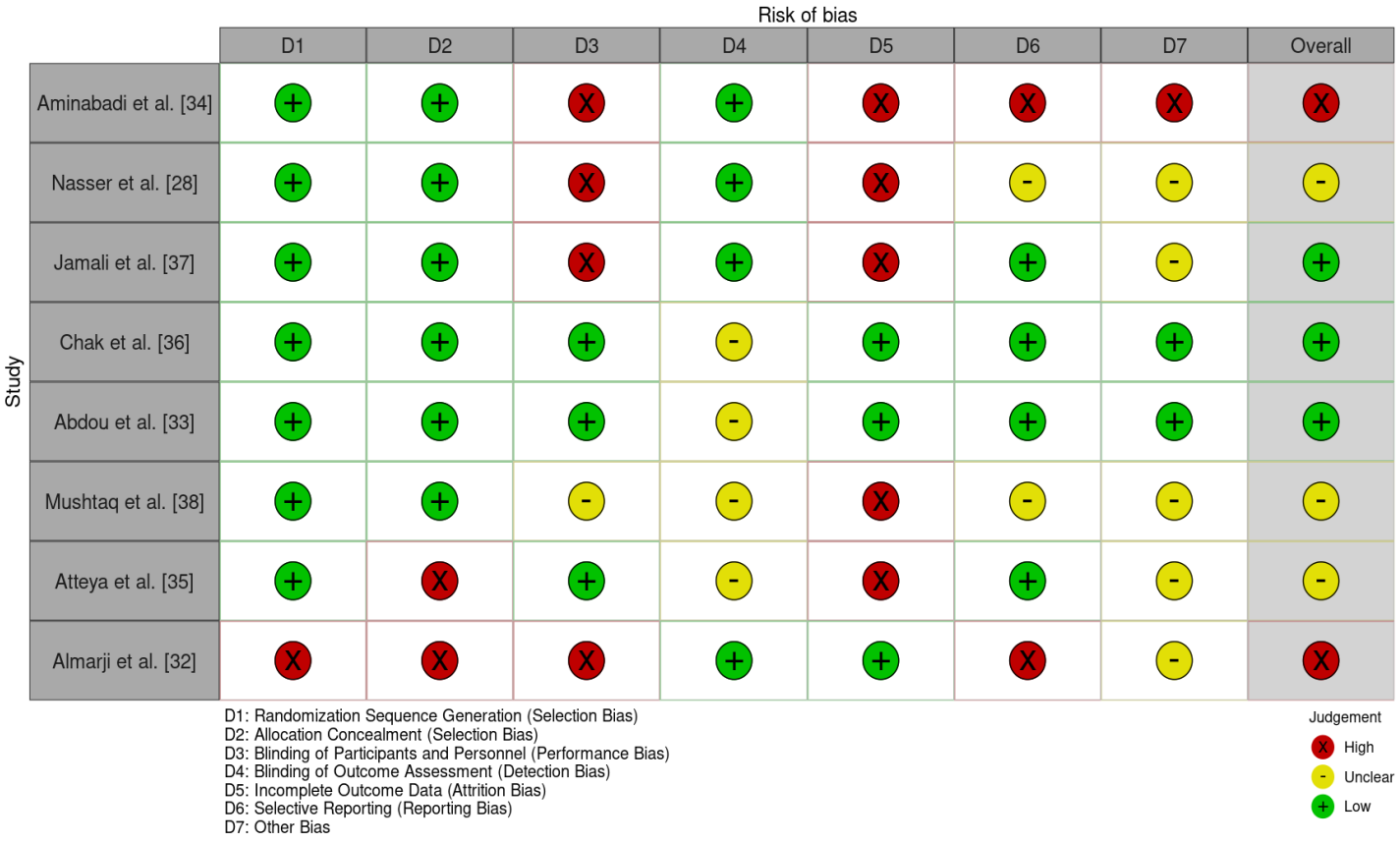


Figure 3. Overall Risk of Bias of Included Studies

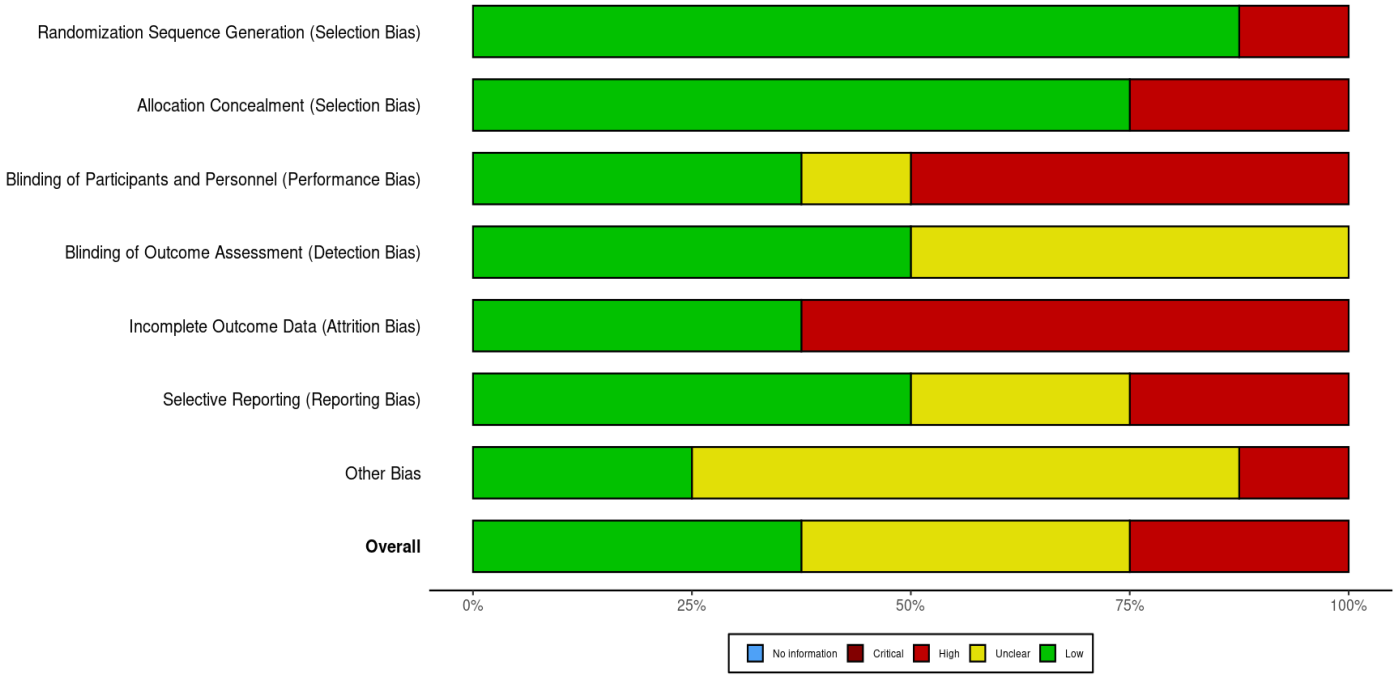


Table 1. Search strategy for electronic databases

Database	Keywords	Results
PubMed	((((((((Simvastatin MeSH Terms]) OR Simvastatin material [Title/Abstract]) AND 3Mixtatin [Title/Abstract]) OR 3Mix [Title/Abstract]) OR modified 3Mixtatin and Biodentine [Title/Abstract]) OR Simvastatin with antibiotic [Title/Abstract]) AND MTA Title/Abstract]) OR 3Mixtatin AND pain [Title/Abstract]) OR discomfort [Title/Abstract])))))))).	60,139
Embase	(((((((("Simvastatin MeSH Terms]") OR "Simvastatin material".tw.) AND 3Mixtatin.tw.) OR 3Mix.tw.) OR "modified 3Mixtatin" AND Biodentine.tw.) OR "Simvastatin with antibiotic".tw.) AND "MTA Title"/) OR 3Mixtatin AND pain.tw.) OR discomfort. tw..	45,169
Scopus	(((((((("Simvastatin MeSH Terms]") OR TITLE-ABS("Simvastatin material")) AND TITLE-ABS(3Mixtatin)) OR TITLE-ABS(3Mix)) OR "modified 3Mixtatin" AND TITLE-ABS(Biodentine)) OR TITLE-ABS("Simvastatin with antibiotic")) AND INDEXTERMS("MTA Title")) OR 3Mixtatin AND TITLE-ABS(pain)) OR TITLE-ABS(discomfort).	**4**
Web of Science	(((((((("Simvastatin MeSH Terms]") OR "Simvastatin material") AND 3Mixtatin) OR 3Mix) OR "modified 3Mixtatin" AND Biodentine) OR "Simvastatin with antibiotic") AND "MTA Title") OR 3Mixtatin AND pain) OR discomfort.	**262,452**
Cochrane	(((((((("Simvastatin MeSH Terms]") OR "Simvastatin material":ti,ab) AND 3Mixtatin:ti,ab) OR 3Mix:ti,ab) OR "modified 3Mixtatin" AND Biodentine:ti,ab) OR "Simvastatin with antibiotic":ti,ab) AND [mh ^"MTA Title"]) OR 3Mixtatin AND pain:ti,ab) OR discomfort:ti,ab.	**209**
Ovid	(((((((("Simvastatin MeSH Terms]") OR "Simvastatin material".tw.) AND 3Mixtatin.tw.) OR 3Mix.tw.) OR "modified 3Mixtatin" AND Biodentine.tw.) OR "Simvastatin with antibiotic".tw.) AND "MTA Title"/) OR 3Mixtatin AND pain.tw.) OR discomfort. tw..	**800**

Table 2. List of excluded studies at full-text review with reasons for exclusion

Reference	Reasons for the Exclusion
Zarabadi et al,PMID: 38448571	Not a Randomized Clinical Trial
Dianat et al, PMID: 29479026	Focused question not addressed.
Goel et al, PMID: 37496952	Focused question not addressed.
Karunakaran et al, PMID: 29284973	Focused question not addressed.
Rahimi et al, PMID: 35308444	Focused question not addressed.
Aripirala et al, PMID: 34810349	Focused question not addressed.
Mahendran et al, PMID: 33082659	Focused question not addressed.
Ghasemi et al, PMID: 35936929	Focused question not addressed.
Fawzy et al, PMID: 33363877	Focused question not addressed.
Jia et al, PMID: 27207592	Focused question not addressed.

Table 3. General Characteristics of Included Studies

Author	Year	Country	Study Design	Number of Participants	No. of teeth	Study Group	Control Group	Mean Age or age range	Male/Female	Duration of follow-up	Tooth Restored	Final Material used for restoration
Aminabadi NA et al. (Aminabadi et al., 2016)	2016	Iran	RCT	65 children	80 teeth	(Ciprofloxacin, metronidazole, Minocycline, simvastatin)	MTA	3–6-year-old	NR	2 years F/up: 4,6,12, 24 months	Primary molars	Teeth were restored with a stainless-steel crown, restorative glass ionomer, glass-ionomer reinforced amalgam, or composite resin restoration.
Asl Aminabadi et al. (Asl Aminabadi et al., 2016)	2016	Iran	RCT	83 children	160 teeth	(Ciprofloxacin, metronidazole, cefixime. simvastatin)	Group 1: MTA Group 2: Simvastatin Group 3:3Mix	3-6 years old	NR	1 year F/up: 12 months	Primary molars	The undermined cavity walls were reinforced with glass ionomer; the teeth were restored with amalgam.
Jamali et al. (Jamali et al., 2018)	2018	Iran	RCT	114 children	150 teeth	(Ciprofloxacin, metronidazole, simvastatin)	Group 1: MTA Group 2: Formocresol	3-6 years old	56 Males 58 Females	2 years F/up: 6, 12 and 24 months	Primary molars	Teeth were restored with amalgam in all three groups
Chak et al. (Chak et al., 2022)	2022	India	RCT	NR	64 teeth	(Metronidazole, ciprofloxacin, cefixime and simvastatin powder)	MTA Simvastatin	3-9 years old	NR	1 year F/up: 3, 6, 9, and 12 months simultaneously.	Primary molars	The pulpotomized teeth in all groups were given stainless-steel crowns cemented using luting glass ionomer cement.
Abdou et al. (Elsayed et al., 2023)	2023	Egypt.	Randomized and controlled prospective masked clinical trial	20 children	60 teeth	(Biodentine and Simvastatin)	Group 1: Biodentine. Group 2: Simvastatin	4-7 years old	NR	1 year F/up: Clinical follow-up was done after (1, 3, 6, 9, and 12) months. Digital Radiographic follow-up was done after 3, 6, 9 and 12 months.	Primary molars	First, it is restored with crowns made of stainless steel and then filled with restorative glass ionomer cement.
Mushtaq et al. (Mushtaq et al., 2023)	2023	India	RCT	48 children	50 teeth	(Ciprofloxacin, metronidazole, cefixime, simvastatin)	MTA	3-8 years old	NR	1 year F/up: 3, 6, and 12 months after treatment	Primary molars	The teeth were restored using universal restorative glass ionomer cement (GIC) and a full-coverage stainless steel crown.
Atteya et al. (Attia et al., 2023)	2023	Egypt	RCT	45 children	45 teeth	(Simvastatin, Ciprofloxacin, Metronidazole, Cefixime)	MTA Simvastatin	3-6 years old	NR	1 year F/up: 3, 6, 9, and 12 months after treatment.	Primary molars	The capping material was covered with high-viscous reinforced glass ionomer capsules, and then EQUIA™ Coat was applied to protect the glass ionomer surface.
Almarji et al. (Almarji et al., 2024)	2024	Syria	A single-center interventional, double-blinded RCT	38 healthy patients	NR	(Metronidazole, cefixime, ciprofloxacin, simvastatin	Zinc Oxide Eugenol	4-8 years old	22 males/ 16 females	1 year F/up: clinically evaluated after 1, 3, 6, and months, and radiographically at3,6, and months	Primary molars	The teeth in both groups were sealed with a glass ionomer cement and restored with a stainless-steel crown.

RCT- Randomized control trial, MTA- Mineral Trioxide Aggregate; NR- Not Reported

Table 4. General characteristics of the mixture (simvastatin and antibiotics)

Author	Tooth	Diagnosis	Dental Procedure	Component of the mixture (simvastatin and antibiotics)	Liquid used for making 3Mixtatin paste	The ratio of antibiotics or other materials in 3Mixtatin	The amount applied of 3Mixtatin	Thickness of 3Mixtatin	Other material in the Control group	Thickness of Other Material	The amount applied of other material
Aminabadi NA et al. (Aminabadi et al., 2016)	Primary molars	Interradicular or periapical root resorption and/or perforation	Conventional pulpectomy and restoration.	100 mg ciprofloxacin (Ruzdarou, Tehran, Iran), 100 mg metronidazole (Tehranshimi, Tehran, Iran, Minocycline + 2 mg of simvastatin	Normal saline	1:1:1	NR	NR	MTA	NR	NR
Asl Aminabadi et al. (Asl Aminabadi et al., 2016)	Primary molars	Small traumatic non-caries pulpal exposures	DPC	100 mg ciprofloxacin, 100 mg metronidazole, and 100 mg cefixime. Because of minocycline contraindication in children, it was replaced by cefixime. 2 mg of simvastatin	Normal saline	1:1:1	NR	1.5-2mm	Group 1: MTA Group 2: Simvastatin Group 3: 3 Mix	MTA: NR Simvastatin: 1.5-2mm 3 Mix: 1.5-2mm	NR
Jamali et al. (Jamali et al., 2018)	Primary molars	Teeth indicated for pulpotomy with pulpal exposure after caries removal	Pulpotomy	A total of 100 mg of ciprofloxacin, 100 mg of metronidazole, and 100 mg of cefixime + 2 mg of simvastatin	Normal saline	1:1:1	NR	1-2mm	MTA, Formocresol	NR	NR
Chak et al. (Chak et al., 2022)	Primary molars	Carious requires a pulpotomy procedure	Pulpotomy	Metronidazole, ciprofloxacin, cefixime and simvastatin powder	Normal saline	1:1:1	NR	2-3mm	MTA	3mm	NR
Abdou et al. (Elsayed et al., 2023)	Primary molars	Deep carious	Pulpotomy	Combination of Biodentine and Simvastatin	NR	1:1	NR	NR	Biodentine, Simvastatin	NR	NR
Mushtaq et al. (Mushtaq et al., 2023)	Primary molars	Deep dentinal caries approaching pulp in primary teeth	Pulpotomy	100 mg of ciprofloxacin, 100 mg of metronidazole, and 100 mg cefixime were mixed, and 2 mg of simvastatin	Normal saline	1:1:1	NR	2-3mm	MTA	NR	NR
Atteya et al. (Attia et al., 2023)	Primary molars	Deep carious with normal gingival and periodontal condition	DPC	2 mg of simvastatin to the triple antibiotic paste, which is composed of Ciprofloxacin, Metronidazole, and Cefixime	Normal saline	1:1:1	NR	1.5-2mm	MTA, Simvastatin	NR	NR
Almarji et al. (Almarji et al., 2024)	Primary molars	Necrotic pulp and evidence of pulp vitality loss	Non-instrumentation endodontic treatment (NIET)	100 mg of each of three commercially available antibiotics, metronidazole (Metronidazole®, Bahri), cefixime (CEF®, Bahri), and ciprofloxacin (CEPROXENE®, Bahri), with 2 mg of simvastatin (SIMVACOR®, Alfares	propylene glycol	Mixed in a ratio of 1:1:1	NR	NR	Zinc oxide eugenol	NR	NR

NR- Not Reported; MTA- Mineral Trioxide Aggregate; DPC-Direct pulp capping.

Table 5. Characteristics of the outcome's variables

Author	Pain Interval Evaluation	Clinical Criteria measurement	Radiographic Criteria measurement	P-value	Outcome	Adverse effects
Aminabadi NA et al. (Aminabadi et al., 2016)	Clinically and radiographically for 4, 6, 12 and 24 months	Clinical failure parameters were the presence of sinus tract, provoked or spontaneous pain, and pathologic tooth mobility	The radiographic failure parameter was expanding periapical or furcation radiolucency	P < 0.05	Radiographic and clinical healing occurred more successfully following 3Mixtatin treatment than with MTA treatment.	At 24-month follow-up, one tooth in the MTA group had extensive mobility because of early root resorption and was extracted. Although one tooth showed slight furcal rarefaction in the combination group (simvastatin and antibiotics), it was not considered a treatment failure.
Asl Aminabadi et al. (Asl Aminabadi et al., 2016)	Clinical and radiographic examinations were conducted 2, 6, and 12 months after treatment.	Pain, tenderness to palpation and percussion, sinus tract, and swelling	Presence of internal or external root resorption, inter-radicular radiolucency, and periapical lesion	P≤0.05	Radiographic and clinical outcomes in the 3Mixtatin group could suggest it as an acceptable alternative in DPC of primary molar teeth.	34 teeth were asymptomatic in the (simvastatin and antibiotics) group. In the MTA group, 30 teeth had no symptoms. One tooth failed because of pain, and one showed a sinus tract.

Author	Pain Interval Evaluation	Clinical Criteria measurement	Radiographic Criteria measurement	P-value	Outcome	Adverse effects
Jamali et al. (Jamali et al., 2018)	Radiographic and clinical examinations were conducted at 6, 12, and 24 months.	Sinus tract, tenderness to palpation and percussion, spontaneous pain, or pain of long duration, swelling	Presence of external or internal root resorption, inter-radicular radiolucency, and periapical lesion.	P≤0.05	The overall success rate was 78.9% for FC, 90.5% for 3Mixtatin, and 88.1% for the MTA group. 3Mixtatin may be considered an effective material in the pulpotomy of primary teeth because of its successful results	(simvastatin and antibiotics) combination group- Two (4.1%) teeth had pain at 12 months and one (2.3%) at 24-month follow-up. No tooth in this group showed radiographic failure in the follow-ups. MTA- Two teeth (4.4%) at 12-month follow-up and two (4.7%) teeth at 24-month follow-up had pain. One tooth (2.3%) had a fistula at the 24-month follow-up examination.
Chak et al. (Chak et al., 2022)	Clinical and radiographical analysis was done in the subsequent follow-up periods of 3, 6, 9, and12 months simultaneously	Clinical scoring criteria were based on the clinical signs, including spontaneous pain, swelling, abscess/fistula, abnormal mobility, tenderness on percussion, and soft tissue redness.	The radiographic signs included for evaluation are periodontal ligament widening, internal resorption, external resorption, furcal radiolucency/interradicular bone destruction, pulp canal obliteration, and periapical bone destruction.	P≤0.05	3mixtatin showed a similar clinical and better radiographical success rate to MTA	(simvastatin and antibiotics) combination group-. At the 12th month follow-up period, signs of periodontal length widening and pulp canal obliteration were seen in one patient each, and internal resorption was seen in two patients. MTA- At the end of the 12th month, there were two

Author	Pain Interval Evaluation	Clinical Criteria measurement	Radiographic Criteria measurement	P-value	Outcome	Adverse effects
						patients with periodontal length widening, one with pulp canal obliteration and one with internal resorption.
Abdou et al. (Elsayed et al., 2023)	Clinical follow-up was done after (1, 3, 6, 9, and 12) months. Digital Radiographic follow-up was done after 3, 6, 9 and 12 months	Pulpotomised teeth were deemed clinically successful if they fulfilled the following requirements: no tenderness, no pain on percussion, no pathological tooth mobility, no swelling/sinus	Radiographically successful if they fulfilled the requirements of no lamina dura loss, no external/ internal resorption, normal periodontal ligament space, and no periapical/furcation radiolucency.	P<0.05	A combination of Biodentine and simvastatin is a practical material in the pulpotomy of primary teeth because of its successful results.	At the end of the 12 months, no patient in group I had pain, tenderness on percussion, a swollen sinus, or pathological mobility. However, one patient in groups II and III had spontaneous pain and tenderness on percussion without a swollen sinus or pathological mobility.

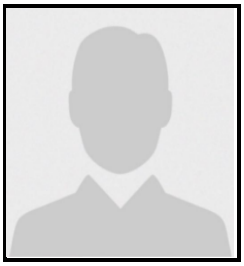
Author	Pain Interval Evaluation	Clinical Criteria measurement	Radiographic Criteria measurement	P-value	Outcome	Adverse effects
Mushtaq et al. (Mushtaq et al., 2023)	Clinical and radiographic examinations were conducted 3, 6, and 12 months after treatment.	Assessment of postoperative pain, sensitivity to palpation and percussion, mobility, and surrounding periodontium examination for any gingival inflammation, sinus tract, or fistula.	Assessment for the presence of external or internal resorption of the tooth, periodontal ligament (PDL) widening, furcation or periapical involvement, or evidence of internal resorption	$p<0.05$	Radiographic and clinical outcomes in the MTA and 3Mixtatin groups in this study show that 3Mixtatin is a suitable alternative to pulpotomy medicament in primary teeth.	(simvastatin and antibiotics) group - All the clinical signs of failure were absent among all the study participants at the 12th-month follow-up, except mobility and pocket formation, which were present among 2.2% of subjects.
Atteya et al. (Attia et al., 2023)	Clinical and radiographic evaluations were performed 3, 6, 9, and 12 months after treatment.	Clinical evaluation was done to ensure the success of the primary clinical outcome, which is the absence of pain, and the secondary clinical outcomes are swelling, mobility, fistula, gingival inflammation, tenderness to percussion, and functional impairment.	Evaluate the technique's success without internal resorption, external resorption, furcation involvement, and fracture.	$p\leq0.05$	Based on radiographic and clinical outcomes, 3Mixtatin can be used successfully as DPC material in primary teeth.	Swelling in simvastatin and 3Mixtatin External Resorption in simvastatin and MTA Furcation involvement in Simvastatin and 3Mixtatin
Almarji et al. (Almarji et al., 2024)	Clinically evaluated after 1, 3, 6, and 12 months Radiographically, at 3, 6, and 12 months	The absence of a fistula was detected visually. The absence of painful symptoms and abnormal mobility were evaluated by applying alternate pressure on the outer and inner aspects of the crown of the molar with the aid of two manual instruments. An intact gingival contour was detected by palpation.	The absence of pathological bone resorption was assessed by detecting any new radiolucency on radiographs, and the lack of pathological root resorption was analyzed on the follow-up radiographs to evaluate the changes in the extent of the radiolucent area.	$p<0.05$	NIET using 3Mixtatin seems to be a good choice for conventional pulpectomy, offering a less complex treatment approach	The total number of clinical failures was 2 out of 20 teeth in each group.

NIET: Non-instrumentation endodontic treatment, MTA: Mineral Trioxide Aggregate, DPC: Direct pulp capping, FC: Formocresol

Table 6. Risk of Bas (RoB) Assessment across individual studies using the Cochrane Risk of Bias Tool for Interventions

Author	Randomization Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias	Overall
Aminabadi NA et al. (Aminabadi et al., 2016)	Low	Low	High	Low	High	High	High	High
Asl Aminabadi et al. (Asl Aminabadi et al., 2016)	Low	Low	High	Low	High	Unclear	Unclear	Unclear
Jamali et al. (Jamali et al., 2018)	Low	Low	High	Low	High	Low	Unclear	Low
Chak et al. (Chak et al., 2022)	Low	Low	Low	Unclear	Low	Low	Low	Low
Abdou et al. (Elsayed et al., 2023)	Low	Low	Low	Unclear	Low	Low	Low	Low
Mushtaq et al. (Mushtaq et al., 2023)	Low	Low	Unclear	Unclear	High	Unclear	Unclear	Unclear
Atteya et al. (Attia et al., 2023)	Low	High	Low	Unclear	High	Low	Unclear	Unclear
Almarji et al. (Almarji et al., 2024)	High	High	High	Low	Low	High	Unclear	High

Biography of Authors



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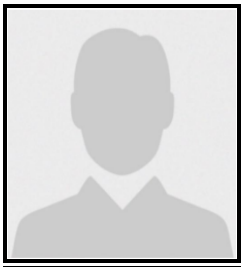

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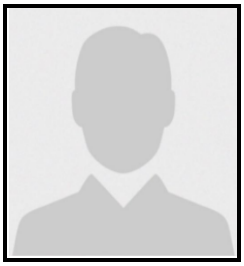

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