Review Article

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Herbal topical anesthetics in dentistry: an exploratory review

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Topical anesthetics are routinely used in dental practice for various purposes. They are usually available at higher dosages and have serious potential adverse reactions, such as seizures, anaphylaxis, and acquired methemoglobinemia. To date, the scope of application of herbal plants and their extracts, which have medicinal properties, has been elaborated in the field of dentistry. The growing interest in herbal medication can be attributed to the increased safety profile of herbal agents, in contrast to synthetic preparations that have a higher risk of systemic complications. Herbal preparations can induce topical anesthesia with minimal side effects. Recently, many studies have reported the use of topical herbal preparations. The current review aimed to evaluate data from various articles comparing the capacity of herbal topical anesthetic formulations and conventional synthetic anesthetics in reducing pain perception when used as local anesthesia before dental procedures.

Keywords: Dental Anesthesia; Herbal; Topical Administrations.

INTRODUCTION

In the field of dentistry, the most commonly encountered hurdle is managing patients' fear and anxiety before procedures, whether invasive or non-invasive [1]. Local anesthesia administration remains the most important precursor to any invasive dental procedure in alleviating pain perception. However, it also remains the single most important fear-inducing stimulus for children and adults, leading to anxiety and disruptive behavior during dental treatment, which may ultimately lead to the delivery of substandard treatment quality [1].

Although the words anesthesia and analgesia have different meanings, when it comes to dentistry, the terms topical anesthetic or topical analgesics are used interchangeably. Topical anesthetics or topical anesthetic agents are agents that induce surface analgesia. Their use is one of the most important pharmacological treatment strategies for alleviating pain and anxiety in children before the injection of local anesthetics [1]. Topical anesthetics increase the pain threshold by blocking signals transmitted from peripheral sensory nerve fibers [2]. Thus, it has always been a significant requirement prior

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to many dental procedures, especially in children [3]. Lignocaine and benzocaine are the most widely used agents for this purpose [2,4]. There has been a gradual increase in the number of adverse reactions associated with chemical topical anesthetic gels used in babies and very young children for treating various oral ailments [5]. The adverse effects of topical lignocaine gel 2% include seizures, respiratory arrest, Stevenson-Johnson syndrome, and rarely death in children below 3 years of age [6–14]. Seizures are the most common adverse effects reported in the literature for young children [15]. In 2014, the United States Food and Drug Administration (FDA) issued a black box warning against the use of chemical topical analgesic agents such as lignocaine for pain relief in children[16].

Benzocaine is also a potent topical anesthetic routinely used for pain relief in pediatric dentistry; however, acquired methemoglobinemia may develop from overdosage of the topical agent [17–21]. In 2018, the FDA issued a black box warning against the use of chemical topical analgesic agents such as benzocaine for pain relief in teething children. Due to concerns regarding the increased incidence of adverse reactions, investigators have resorted to exploring herbal formulations as alternatives to synthetic topical anesthetics.

Herbs have always been a very popular self-medication option for centuries due to their accessibility, trusted efficacy, and safety in relieving oral or dental problems without the systemic adverse effects encountered with synthetic preparations [22]. It has been found that a wide range of plants have anesthetic and analgesic properties, including clove (*Syzygium aromaticum*), neem leaves (Azadirachta indica), turmeric (*Curcuma longa*), lavender oil (*Lavandula* spp.) and betel leaves (*Piper betle*) [23]. Herbal medicines are not the most potent analgesic treatment available. However, they can also be highly beneficial for mild to moderate pain. Recently, some authors have compared the efficacy of herbal topical anesthetic agents with that of conventional synthetic gels and sprays. However, there is still an unexplored and growing area of research with very limited studies.

There is a need for consensus regarding the efficacy of natural medicaments as topical anesthetic agents in dentistry. Thus, this review aimed to compute and analyze the data from various articles comparing herbal topical anesthetic formulations with conventional synthetic anesthetics in reducing pain perception during the administration of local anesthesia before dental procedures.

METHODS

Protocol and registration: The protocol was registered under Prospero CRD42022301402 and compliant with PRISMA.

Eligibility criteria: The PICO strategy framework was adapted based on the pre-formulated question, “are herbal topical preparations equipotent in terms of analgesia during intraoral needle prick compared to conventional topical preparations such as lignocaine and benzocaine.” The search strategy of the current review was as follows: (P) patient: any patient requiring topical anesthesia to mitigate pain due to intraoral needle prick; (I) intervention: herbal topical preparations; (C) comparison: conventional topical preparations containing lignocaine or benzocaine; and (O) outcome: pain perception during intraoral needle prick.

Search strategy: Thorough electronic searches were performed using three databases: PubMed, Ovid SP, and Cochrane. The search was conducted until February 2022. There was ambiguity between the terms analgesia and anesthesia. Thus, a broader search strategy was used to prevent missing articles. The search was performed using broad terminology ([herbal] AND [topical]) AND (dental).

Eligibility criteria: Clinical trials related to studies that compared herbal topical preparations with conventional topical analgesia preparations were included. Case reports, narrative and systematic reviews, and articles that could not be translated into English were excluded. Any clinical study that evaluated and compared herbal topical

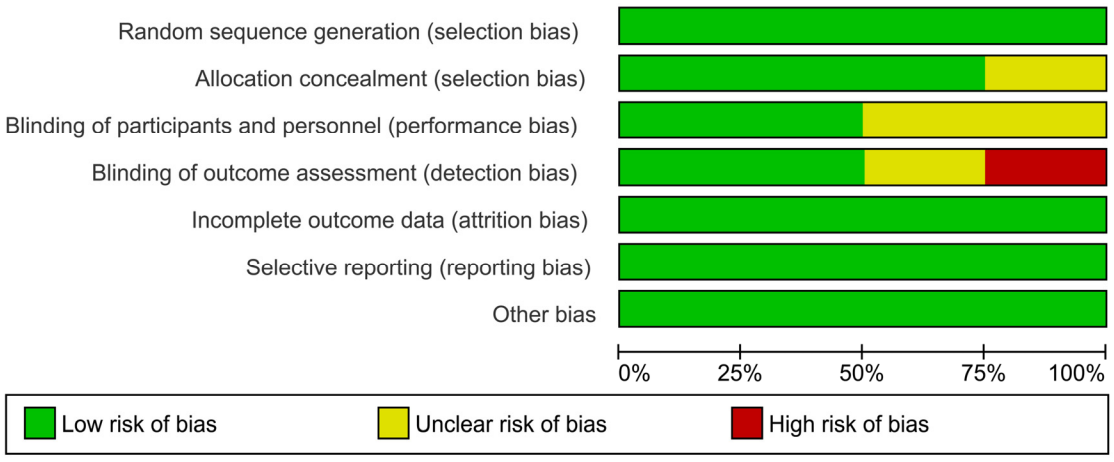

Fig. 1. Risk of bias

Table 1. Table showing the list of excluded studies with reasons

No	Excluded articles	Reasons for exclusion
1	Reddy SP et al., 2019	Gingivectomy procedure
2	Patil et al., 2014	Oral submucous fibrosis
3	Ghalayani et al., 2013	Recurrent aphthous stomatitis
4	Grbic et al., 2011	Gingivitis
5	Patel AS et al., 2020	Oral ulcers

anesthetics with conventional synthetic topical anesthetic preparations for reduced pain perception in dentistry was included in the current review. Article titles were carefully screened and then further evaluated by going through abstracts, and articles deemed fit were subjected to full-text evaluation and then further processed for qualitative analysis. Two reviewers independently evaluated quantitative and qualitative data. The data sheet included the name of the author, publication time frame, study design, number of participants, age, intervention, control, and outcome. The primary outcome measured was the pain score rated by the patient, and the secondary outcome evaluated was the pain reaction scored by the observer.

Risk of bias (RoB) assessment: Two independent reviewers individually assessed the methodological quality of the included articles using the Cochrane criteria (Fig. 1).

RESULTS

A total of 449 articles were retrieved, 440 of which remained after the exclusion of duplicates. Of these, nine studies were included for full-text review, and five articles were further excluded [24–28]. Reasons for exclusion are given in Table 1 (Fig. 2). Thus, four articles were included in the final analysis [4,29–31].

Characteristics of the included studies (Table 2): All included studies followed a randomized design [4,29–31]. Three studies followed a split-mouth design [4,29,30], and a parallel group design was used by Havale et al. [31]. Three studies were conducted in children [4,30,31], and one study was performed in adults [29]. The age range of the children in the included studies was 6–14 years [4,30,31], and the age range of the adults in the other study was 17–25 years [29].

Herbal topical preparations were clove-based and used for infiltration in three studies [29–31]. Two studies performed maxillary infiltrations [29,31]; however, Ananthraj et al. did not mention the type of infiltration [30]. Conversely, Mohite et al. [4] used herbal preparations containing Anacyclus pyrethrum and Spilanthes acmella extracts, and the preparations were used prior to inferior alveolar nerve block (IANB). The concentrations and combinations of herbal agents varied

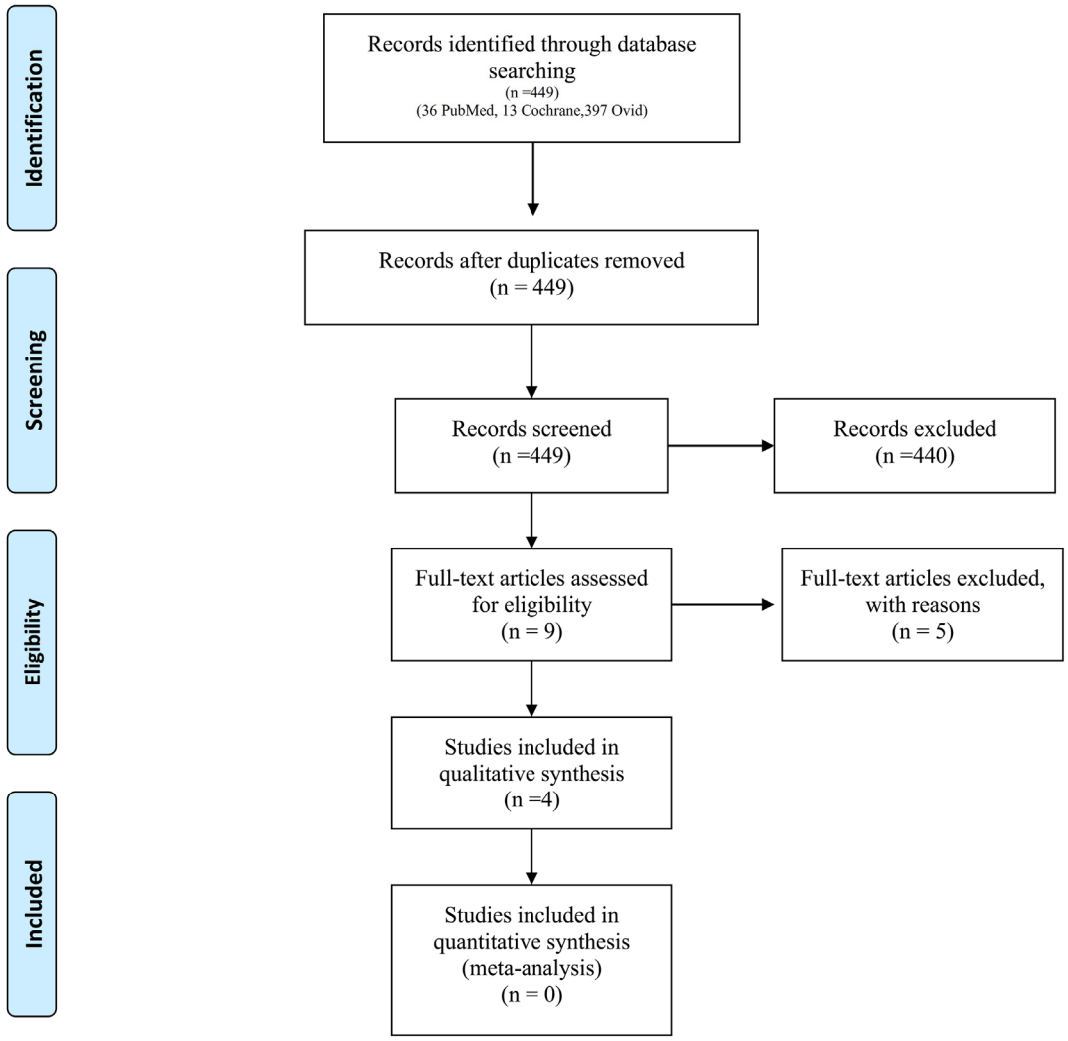

Fig. 2. Flow chart

across the studies. Alqareer et al. [29] used freshly prepared clove gel in glycerin base (2:3 concentration), Anantharaj et al. [30] used a clove and papaya gel combination, and Havale et al. [31] used a commercially available clove gel (Pain-out). The concentrations of clove used in these studies ranged from 3 to 4.7% [30,31]. However, clove extract concentration was not standardized in the study by Alqareer et al. [29]. The conventional topical anesthetics used in these studies were lignocaine [4,31], benzocaine [29,30], and pre-cooling with ice [30,31].

Outcome evaluation: Pain evaluation (subjective and objective) was performed for all studies but using different scales (Sound Eye Motor scale [SEM], Visual analog scale [VAS], and Wong-Baker faces pain scale [WB-FPSR]). Among the four studies, studies compared clove-based topical agents to benzocaine, and there was no significant difference in the pain scores between the two groups [29,30]. One study compared clove-based topical agents with lignocaine, and results showed that lignocaine was significantly better than clove-based gel in terms of reducing pain scores [31]. One study compared Anacyclus pyrethrum and Spilanthes acmella extracts to lignocaine and found no significant difference in the change in subjective and objective pain scores between the groups [4].

Table 2. Characteristics of included studies.

No	Author-year	Study design	Sample characteristics	Type of injection	Gauge of manual syringe used	Intervention	Control	Measuring scales	Outcomes
1.	Alqareer et al., 2006 [29]	Randomised control trial. Split mouth design.	73 adult volunteers aged 17-25. Each patient received both topical gel and placebo gel G1: Clove gel G2: Benzocaine 20% G3 and G4: Placebo	Infiltration in maxillary canine buccal space/muco buccal fold.	25 gauge needle	2:3 Clove-Glycerin gel	20% Benzocaine	100 mm VAS	Both clove and benzocaine gels had significantly lower mean pain scores than placebos (P = 0.005). No significant difference was observed between clove and benzocaine regarding pain scores.
2.	Anantharaj et al., 2020 [30]	Randomised clinical trial. Split-mouth	60 children aged 9–10 years who required local anesthestic injections for dental procedures were selected and divided into three groups of 20 patients each. G1: Ice G2: Benzocaine gel G3: Clove-papaya gel.	Infiltrations	Not mentioned	3% Clove and 10% papaya based gel	Ice and Benzocaine	WBFPS SEM	No significant difference between all the tested groups.
3.	Mohite et al., 2020 [4]	Bilateral split-mouth, single-blind, crossover study	Children aged 8–14 years were included in the study. G1: herbal topical gel G2: 2% lignocaine gel.	IANB block	26 gauge needle	Anacyclus pyrethrum and Spilanthes acmella extracts suspended in Carbopol (3:2)	2% Lignocaine gel.	SEM scale FPS-R scale Physiological parameters.	Both herbal gel and the conventional lignocaine gel there was no significant difference in the subjective, objective pain scales between both the groups.
4.	Havale et al., 2021 [31]	Randomised clinical trial. Parallel arm trial.	Sixty children requiring infiltration, aged 6-10 years were randomly divided into 4 groups. G1: 2% lignocaine G2: 4.7% Clove gel. G3: 10% betel leaf extract gel G4: Ice.	Maxillary buccal Infiltration	27 gauge needle.	4.7% clove gel and 10% betel leaf extract gel were used.	2% Lignocaine gel and ice	WBFPS SEM	2% Lignocaine was better than 4.7% clove gel and 10% betel leaf extract gel. No significant difference between 4.7 % clove gel and 10% betel leaf extract gel and ice.

Abbreviations: FPS-R, Faces pain scale revised; IANB, Inferior alveolar nerve block; SEM, sound eye motor scale; VAS, visual analog scale; WBFPS, Wong Baker faces pain scale.

DISCUSSION

Benzocaine and lignocaine are the most commonly used topical anesthetics in dental practice to reduce needle-prick pain [1]. The main disadvantage of conventional topical preparations is increased toxicity [6–15,17–21,32,33]. Dosage calculation is usually performed for injectable local anesthetics but not for topical anesthetic preparations [34]. Toxicity may result from topical absorption, ingestion, or aspiration of conventional topical anesthetic preparations.

Numerous herbal preparations have anesthetic properties. Herbal preparations such as clove, cinchona, datura, thymol, and jasmine have local anesthetic properties and are used in medicine and dentistry [23,35]. However, their use in dentistry is still not fully explored. The articles selected for the current scoping review reported the clinical use of only a few herbal preparations as topical anesthesia agents in dentistry. Clove extract (*Syzygium aromaticum*), betel leaf extract (*Piper betel Linn*), and pepper mint (*Mentha piperita*) are a few herbal preparations used as topical anesthetics in dentistry [35].

Piper betel leaf is an evergreen perineal creeper belonging to the *Piperaceae* family, the main constituents of which are betel oil, phenolic compounds chavibetol,

and chavicol. The analgesic efficacy of betel leaf is mainly due to the alkaloid compounds arakene and eugenol [36]. Clove extract (*Syzygium aromaticum L*), belonging to the family Myrtaceae, is a common spice used in Asian countries. Clove flower buds contain up to 18% essential oil, which consists of eugenol, eugenol acetate, and β-carioflavone. The analgesic efficacy of clove is conferred by eugenol, which acts by the activation of chloride and calcium channels in ganglion cells and through antagonist activity against capsaicin [37]. The FDA classified clove under the generally recognized as safe (GRAS) category, and the acceptable daily intake of clove for humans is 2.5 mg/kg body weight [37].

In all studies included in the current scoping review, three studies evaluated clove-based preparations for use as herbal topical anesthetic preparations [29–31]. Concentrations varied across the studies, ranging from 3 to 4.7%. The study by Havale et al. [31] used commercially available clove-based preparations containing 4.7% eugenol in addition to other ingredients, such as menthol and camphor. Alqareer et al. [29] used a home-based clove gel in a glycerin base, and another study by Ananthraj et al. [30] reported a clove-papaya-based preparation. The duration of application for effective action ranged between 1–5 minutes. The study by Alqareer et al. [29] used 5 minutes, while the studies by Havale et al. [31] and Anantharaj et al. [30] used a 1-minute application time.

In the studies by Alqareer et al. [29] and Ananthraj et al. [30], there was no significant difference between clove gel and topical benzocaine, both of which were comparable in terms of pain reduction during needle prick. However, Havale et al. [31] reported that topical lignocaine was slightly better than clove gel and betel leaf extract in terms of pain reduction during needle prick. This can be attributed to the short application time (one minute) compared to other studies. The compositions of the herbal preparations were also different in the studies by Havale et al. [31] and Anantharaj et al. [30], which can be attributed to the varied clinical performance in both studies. The main disadvantages of clove-based topical preparations are that eugenol can cause local irritation and mild cytotoxic and hypersensitivity reactions, as previously reported in the literature [38,39]. *Anacyclus pyrethrum* is a wild species belonging to the family Asteraceae that is used in traditional medicines to treat toothache. The root extract of this plant contains pyrethrin or pellitorine, which is believed to be responsible for its analgesic action [40]. *Spilanthes acmella* is commonly known as the toothache plant. The main constituents, spilanthol and acmellonate, reduce pain associated with toothaches and induce saliva secretion [41].

Conclusions and future prospects

Overall, eugenol-based topical anesthetic preparations are equipotent to conventional chemical topical preparations in reducing local anesthesia pain during intraoral needle pricks. In most of the studies mentioned, herbal topical preparations have comparable analgesic properties to those of conventional chemical analgesic properties, such as lignocaine or benzocaine. However, more research to investigate the active phytochemical agents in herbal topical preparations, dosages, local and systemic reactions, and interactions should be investigated further. More standardized clinical trials with a good methodologies should be carried out to establish a more acceptable consensus regarding the subject.

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AUTHOR CONTRIBUTIONS

Sunnypriyatham Tirupathi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing
Dharmarajan Gopalakrishnan: Writing - review & editing
Sanjeevani Deshkar: Writing - review & editing

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REFERENCES

1. Tirupathi S, Rajasekhar S. Topical anesthesia in pediatric dentistry: an update. Int J Clin Pediatr Dent 2022; 15: 240-5.
2. Lee HS. Recent advances in topical anesthesia. J Dent Anesth Pain Med 2016; 16: 237-44.
3. Peedikayil FC, Vijayan A. An update on local anesthesia for pediatric dental patients. Anesth Essays Res 2013; 7: 4-9.
4. Mohite VA, Baliga S, Thosar N, Rathi N, Khobragade P, Srivastava R. Comparative evaluation of a novel herbal anesthetic gel and 2% lignocaine gel as an intraoral topical anesthetic agent in children: bilateral split-mouth, single-blind, crossover in vivo study. J Indian Soc Pedod Prev Dent 2020; 38: 177-83.
5. Barea-Jiménez N, Calero J, Molina-Negrón D, López Del-Valle LM. Treatment for oral lesions in pediatric patients with Stevens-Johnson's syndrome: a case report and literature review. Int J Paediatr Dent 2020; 30: 489-96.
6. Sakai RI, Lattin JE. Lidocaine ingestion. Am J Dis Child 1980; 134: 323.
7. Garrettson LK, McGee EB. Rapid onset of seizures following aspiration of viscous lidocaine. J Toxicol Clin Toxicol 1992; 30: 413-22.
8. Hess GP, Walson PD. Seizures secondary to oral viscous lidocaine. Ann Emerg Med 1988; 17: 725-7.
9. Amitai Y, Whitesell L, Lovejoy FH Jr. Death following accidental lidocaine overdose in a child. N Engl J Med 1986; 314: 182-3.
10. Smith M, Wolfram W, Rose R. Toxicity--seizures in an infant caused by (or related to) oral viscous lidocaine use. J Emerg Med 1992; 10: 587-90.
11. Balit CR, Lynch AM, Gilmore SP, Murray L, Isbister GK. Lignocaine and chlorhexidine toxicity in children resulting from mouth paint ingestion: a bottling problem. J Paediatr Child Health 2006; 42: 350-3.
12. Giard MJ, Uden DL, Whitlock DJ, Watson DM. Seizures induced by oral viscous lidocaine. Clin Pharm 1983; 2: 110.
13. Gonzalez del Rey J, Wason S, Druckenbrod RW. Lidocaine overdose: another preventable case? Pediatr Emerg Care 1994; 10: 344-6.
14. Rothstein P, Dornbusch J, Shaywitz BA. Prolonged seizures associated with the use of viscous lidocaine. J Pediatr 1982; 101: 461-3.
15. Curtis LA, Dolan TS, Seibert HE. Are one or two dangerous? Lidocaine and topical anesthetic exposures in children. J Emerg Med 2009; 37: 32-9.
16. Teoh L, Moses GM. Are teething gels safe or even necessary for our children? A review of the safety, efficacy and use of topical lidocaine teething gels. J Paediatr Child Health 2020; 56: 502-5.
17. Bayat A, Kosinski RW. Methemoglobinemia in a newborn: a case report. Pediatr Dent 2011; 33: 252-4.
18. Bong CL, Hilliard J, Seefelder C. Severe methemoglobinemia from topical benzocaine 7.5% (baby orajel) use for teething pain in a toddler. Clin Pediatr (Phila) 2009; 48: 209-11.
19. Chung NY, Batra R, Itzkevitch M, Boruchov D, Baldauf M. Severe methemoglobinemia linked to gel-type topical benzocaine use: a case report. J Emerg Med 2010; 38: 601-6.
20. Trapp L, Will J. Acquired methemoglobinemia revisited. Dent Clin North Am 2010; 54: 665-75.
21. Melamed J, Beaucher WN. Delayed-type hypersensitivity (type IV) reactions in dental anesthesia. Allergy Asthma Proc 2007; 28: 477-9.
22. Kumar G, Jalaluddin M, Rout P, Mohanty R, Dileep CL. Emerging trends of herbal care in dentistry. J Clin Diagn Res 2013; 7: 1827-9.
23. Tsuchiya H. Anesthetic agents of plant origin: a review of phytochemicals with anesthetic activity. Molecules 2017; 22: 1369.
24. Patel AS, Patel SA, Fulzele PR, Mohod SC, Chandak M,

Patel SS. Evaluation of the role of propolis and a new herbal ointment in promoting healing of traumatic oral ulcers: an animal experimental study. Contemp Clin Dent 2020; 11: 121-5.
25. Patil S, Halgatti V, Maheshwari S, Santosh BS. Comparative study of the efficacy of herbal antioxdants oxitard and aloe vera in the treatment of oral submucous fibrosis. J Clin Exp Dent 2014; 6: e265-70.
26. Ghalayani P, Zolfaghary B, Farhad AR, Tavangar A, Soleymani B. The efficacy of Punica granatum extract in the management of recurrent aphthous stomatitis. J Res Pharm Pract 2013; 2: 88-92.
27. Grbic J, Wexler I, Celenti R, Altman J, Saffer A. A phase II trial of a transmucosal herbal patch for the treatment of gingivitis. J Am Dent Assoc 2011; 142: 1168-75.
28. Reddy SP, Koduganti RR, Panthula VR, Surya Prasanna J, Gireddy H, Dasari R, et al. Efficacy of low-level laser therapy, hyaluronic acid gel, and herbal gel as adjunctive tools in gingivectomy wound healing: a randomized comparative clinical and histological study. Cureus 2019; 11: e6438.
29. Alqareer A, Alyahya A, Andersson L. The effect of clove and benzocaine versus placebo as topical anesthetics. J Dent 2006; 34: 747-50.
30. Anantharaj A, Sabu JM, Ramakrishna S, Jagdeesh RB, Praveen P, Shankarappa PR. A comparative evaluation of pain perception following topical application of benzocaine gel, clove-papaya based anesthetic gel and precooling of the injection site before intraoral injections in children. J Indian Soc Pedod Prev Dent 2020; 38: 184-9.
31. Havale R, Rao DG, S PS, K MT, Tharay N, Mathew I, et al. Comparative evaluation of pain perception following topical application of clove oil, betel leaf extract, lignocaine gel, and ice prior to intraoral injection in children aged 6-10 years: a randomized control study. J Dent Anesth Pain Med 2021; 21: 329-36.
32. Balicer RD, Kitai E. Methemoglobinemia caused by topical teething preparation: a case report. Sci World J 2004; 4: 517-20.
33. Cannell H. Evidence for safety margins of lignocaine local anaesthetics for peri-oral use. Br Dent J 1996; 181: 243-9.
34. Becker DE, Reed KL. Local anesthetics: review of pharmacological considerations. Anesth Prog 2012; 59: 90-101.
35. Bhardwaj I, Sharma M. Herbal anesthetic agents: an overview on sources, uses and future perspectives. Asian J Pharm Pharmacol 2019; 5: 21-7.
36. Biswas P, Anand U, Saha SC, Kant N, Mishra T, Masih H, et al. Betelvine (Piper betle L.): a comprehensive insight into its ethnopharmacology, phytochemistry, and pharmacological, biomedical and therapeutic attributes. J Cell Mol Med 2022; 26: 3083-119.
37. Batiha GE, Alkazmi LM, Wasef LG, Beshbishy AM, Nadwa EH, Rashwan EK. Syzygium aromaticum L. (Myrtaceae): traditional uses, bioactive chemical constituents, pharmacological and toxicological activities. Biomolecules 2020; 10: 202.
38. Sarrami N, Pemberton MN, Thornhill MH, Theaker ED. Adverse reactions associated with the use of eugenol in dentistry. Br Dent J 2002; 193: 257-9.
39. Tammannavar P, Pushpalatha C, Jain S, Sowmya SV. An unexpected positive hypersensitive reaction to eugenol. BMJ Case Rep 2013; 2013: bcr2013009464.
40. Muralikrishnan K, Asokan S, Geetha Priya PR, Zameer Ahmed KS, Ayyappadasan G. Comparative evaluation of the local anesthetic activity of root extract of Anacyclus pyrethrum and its interaction at the site of injection in guinea pigs. Anesth Essays Res 2017; 11: 444-8.
41. Dubey S, Maity S, Singh M, Saraf SA, Saha S. Phytochemistry, pharmacology and toxicology of Spilanthes acmella: a review. Adv Pharmacol Sci 2013; 2013: 423750.