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REVIEW

Endodontic Applications of Propolis in Primary and Permanent Teeth: A Scoping Review of Clinical Studies

Hayat ALGHUTAIMEL,[1,2,3] Manal MATOUG-ELWERFELLI,[4] Venkateshbabu NAGENDRABABU,[5] Paul Michael HOWELL DUMMER[6]

[1]College of Dentistry, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[2]King Abdullah International Medical Research Centre, Riyadh, Saudi Arabia
[3]Ministry of the National Guard - Health Affairs, Riyadh, Saudi Arabia
[4]Department of Pre-clinical Oral Sciences, College of Dental Medicine, QU Health, Qatar University, Doha, Qatar
[5]Department of Preventive and Restorative Dentistry, University of Sharjah, College of Dental Medicine, Sharjah, United Arab Emirates
[6]School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK

ABSTRACT

The use of propolis-based materials within endodontics to promote pulp wound healing or disinfect the root canal system has been a recent focus of scientists and clinicians. This is mainly because of the well-documented antimicrobial, anti-inflammatory, immunomodulatory and wound healing properties of propolis. This scoping review critically appraises the literature on the clinical applications of propolis-based compounds during endodontic therapy of primary and permanent teeth. An electronic literature search was performed in Scopus, PubMed, and Web of Science up to and including October 2023 to identify studies assessing the use of propolis during endodontic therapy of primary and permanent teeth. A combination of relevant Medical Subject Headings (MeSH) terms and keywords was used. Only human clinical studies written in English were included. The identified manuscripts were screened and assessed for inclusion by two independent authors. Eligible manuscripts were then subjected to critical appraisal and data extraction with the information being summarised according to their clinical application. A total of 26 human clinical studies were identified and included in the analysis. Propolis was investigated for use in the primary and permanent dentitions as a direct pulp capping or pulpotomy material as well as in root canal disinfection and root canal filling material of teeth with non-vital pulps. Overall, the included studies reported that the use of propolis was associated with promising outcomes in terms of efficacy to control inflammation, enhance tissue repair, and disinfection of the root canal system. However, a critical appraisal of the studies revealed a range of methodological and reporting deficiencies, resulting in unreliable results and conclusions in terms of the clinical outcomes reported. Although the studies on the use of propolis-based materials in endodontics reported promising clinical outcomes, they had a range of methodological and reporting flaws. Therefore, further well-designed and properly reported controlled clinical studies are essential to derive sound evidence-based conclusions on propolis-based materials. Furthermore, guidelines for quality assurance and safe use of propolis-based materials are necessary to enhance their production for commercial use in endodontics.

Keywords: Bee wax, dental pulp, endodontic, flavonoids, propolis, root canal

HIGHLIGHTS

- The interest in propolis as a medicinal product is growing within dentistry.
- Propolis is a natural resinous substance with attractive antimicrobial, anti-inflammatory, and wound healing properties.
- Propolis use in endodontic therapy to promote pulp wound healing and/or disinfect the root canal system has been investigated in various formulations and delivery vehicles with promising reported outcomes.
- The studies published to date have substantial methodological and reporting deficiencies.

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Address for correspondence: Manal Matoug-Elwerfelli Department of Pre-clinical Oral Sciences, College of Dental Medicine, QU Health, Qatar University, Doha, Qatar
E-mail: melwerfelli@qu.edu.qa

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INTRODUCTION

Within the last decade, vital pulp therapy (VPT) for the management of teeth with deep caries has received significant attention and clinical translation from the bench-top to clinical use. The most common VPT strategies include direct pulp capping and pulpotomy, in which stringent control of infection and aseptic protocols are essential for a successful treatment outcome (1). Additionally, the outcomes of such treatments also depend on the pulpal diagnosis, operative procedure and the biomaterial used (2, 3). Indeed, the potential of biomaterials to control bacterial contamination and promote pulp wound healing is a critical factor in the success of VPT (2, 4).

Endodontic infections are polymicrobial and involve a mixture of gram-positive, gram-negative, facultative, and strict anaerobic bacteria (5). Clinically, chemical debridement of root canal infections using irrigants and/or medicaments is an essential step to reduce microorganisms and promote a positive outcome. Although various root canal disinfection agents and strategies are available with high clinical success rates, the development of natural disinfectant agents with appropriate antimicrobial properties and biocompatibility is of clinical and environmental importance (6). A recent review of the literature relating to alternative antimicrobial agents (such as, propolis and chitosan) concluded they had promising results and deserved further consideration (7). Furthermore, the development of safe materials that have sufficient antimicrobial properties and are not associated with antibiotic resistance is extremely relevant (8, 9).

Propolis (bee-glue or bee-wax) is a natural resinous substance produced by honeybees (e.g. Apis mellifera) and stingless bees (e.g. Tetragonisca angustula Illiger) from plant buds and exudates, and subsequently mixed with their salivary secretions (bee enzymes) and wax (10). Propolis consists of several components including resin, balsams, amino acids, aromatic compounds, pollens, minerals, and vitamins (11). The resinous component is mainly composed of flavonoids, phenolic acids and their esters, which are the main active components with broad-spectrum antimicrobial properties (12). The wide diversity in the botanical sources of propolis explains its complex and variable chemical composition (13).

Therapeutically, propolis-based materials are regarded as a promising natural antimicrobial agent with significant pharmaceutical potential, either to prevent or treat various conditions (14, 15). For centuries, propolis has been recognised as an antimicrobial and anti-inflammatory agent, to disinfect wounds and promote their healing (16). More recently, several studies have documented various properties of propolis, including antimicrobial (17), anti-inflammatory (18), antioxidant (19), immunomodulatory (20), biocompatibility (21), and wound healing properties (22). Indeed, this wide range of medicinal properties has attracted commercial and scientific attention towards the potential benefits of propolis in the development of medicinal products.

The use of propolis has expanded within the medical and dental fields with several propolis-based products (e.g. oral capsules, tablets, lozenges, syrups, ointments, mucoadhesive gels, and mouthwashes) being available as over-the-counter medications for topical or systemic use in various conditions, including the common cold, burns, acne, ulcers, viral infections, and skin problems (14, 15, 23). Specifically, within endodontics, various propolis formulations have been researched and compared to gold-standard clinical materials in the management of exposed dental pulps and disinfection strategies during root canal treatment.

Despite the potential of propolis-based materials, the clinical applications, efficacy, and safety of propolis use during vital and non-vital pulp therapy in primary and permanent teeth is controversial and unclear. Therefore, this scoping review aims to identify and critically appraise the literature on the applications of propolis-based materials in endodontics, summarise the available evidence and inform future research.

MATERIALS AND METHODS

This scoping review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis - Scoping Review extension (PRISMA-ScR) (24).

Research Question

The following research question was formulated: What is the clinical effectiveness of propolis use during endodontic therapy of primary and permanent teeth?

Search Strategy

An electronic literature search was conducted in three databases (Scopus, PubMed and Web of Science) up to and including October 2023 in order to identify relevant studies. The following MeSH terms and keywords were applied: (("root canal" OR "endodontic" OR "endodontology" OR "pulpectomy" OR "pulp capping" OR "pulpotomy" OR "periapical surgery" OR "periradicular surgery" OR "apicoectomy" OR "apicectomy" OR "dental pulp" OR "regenerative endodontics" OR "revitalisation") AND ("propolis" OR "bee glue" OR "flavonoids" OR "bee bread"). The detailed search strategy following individual databases syntax rules is presented in Appendix 1. Only human clinical studies written in English were included. No time restrictions were applied. Laboratory studies, animal studies, reviews, editorials, conference proceedings and letters were excluded. A further manual search was conducted through reference mining of the included studies.

All records identified through the search were initially imported into Endnote X9.3.3 (Clarivate Analytics) to remove duplicates. The records were then blindly screened for eligibility (title and abstract screening) by two independent authors using the Rayyan web-tool (25). Conflicts and discrepancies were resolved by discussion between the two authors until a consensus was reached or consultation with the third author. Full texts of eligible records were then retrieved and reviewed.

The included studies were subjected to critical assessment and data charting by two independent authors. Variables in study design, reporting of randomisation, allocation concealment, blinding, centres involved in the execution of each study, clinicians, and outcomes, in addition to the exact purpose of propolis use and the teeth on which they were tested

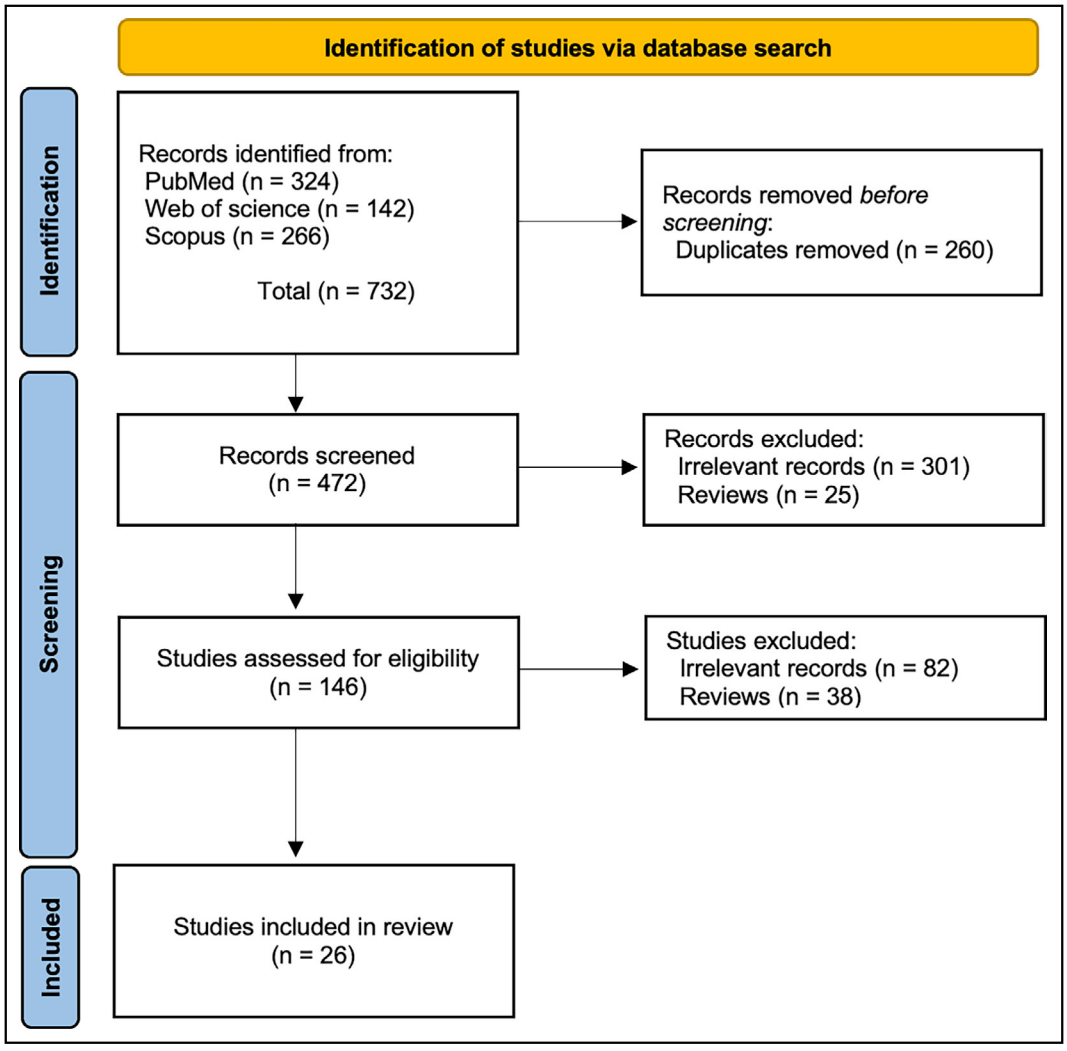

Figure 1. PRISMA 2020 flow diagram summarising the outcome of the electronic database search

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

were recorded. Furthermore, data on the origin of the specific propolis used, its extraction method, concentration, delivery vehicle, comparison groups, and controls were charted. Reporting of funding and conflicts of interest within the studies were also assessed. All extracted data were then synthesised and summarised in a narrative format and tables.

RESULTS

A total of 732 records were identified from the three databases. Following the removal of 260 duplicates, 472 records were eligible for title and abstract screening. Following initial screening, 326 records were excluded due to lack of relevance to the scope of the present review or reporting of non-primary studies. Following full-text screening, a total of 120 records were additionally excluded as they did not meet the inclusion criteria, resulting in a total of 26 studies eligible for inclusion and analysis (Fig. 1).

Studies Overview and Critical Appraisal

An overview and critical appraisal of the included studies are summarised in Table 1. A total of twenty-three clinical trials and three prospective cohort studies, testing a range of clinical endodontic applications of propolis were identified (Fig. 2). The identified studies were published between 2010–2023. The clinical use of propolis in primary teeth with vital pulps was investigated as a pulp-capping material during direct pulp capping (n=2) and pulpotomy (n=9). In primary teeth with non-vital pulps, propolis was assessed as an intra-canal irrigant (n=3) and root canal filling material (n=4) during pulpectomy. In permanent teeth, propolis was assessed as a direct pulp capping material (n=4) and intra-canal medicament (n=4).

Critical appraisal of the studies revealed a wide range of limitations in their methodological design and reporting of outcomes (Table 1). Briefly, in terms of quality assessment of the studies, several randomised clinical trials (RCT) failed to report the randomisation technique applied and allocation concealment (22, 26–36). Furthermore, several studies did not incorporate blinding in their design to minimise the risk of bias (26–28, 33, 36–40). Additionally, none of the studies reported the level of experience, knowledge and training of the clinicians who performed the intervention. Information on the origin of the propolis, its concentration and extraction method were loosely reported in all the studies. Incomplete reporting of the outcomes was evident in the majority of studies (32, 33, 37, 38, 41).

TABLE 1. Overview and summary of the critical appraisal of the included studies

Author (year)	Study design		Propolis usage					Teeth			Randomisation			Allocation concealment			Blinding				Outcome reporting		Centres		Treating clinician		Funding			Conflict of interest		
	RCT	Prospective cohort	Direct pulp capping	Pulpotomy	Root canal filling	Intra-canal medicament	Intra-canal irrigant	Primary	Immature permanent	Mature permanent	Reported	Not reported	Not applicable	Reported	Not reported	Not applicable	No blinding	Single-blinding	Double-blinding	Triple-blinding	Complete	Incomplete	Single-centre	Multi-centres	Reported	Not reported	No funding	Funding	Not reported	No	Yes	Not reported
Ahmad et al. (2022) (33)	□[N]		□						□		□			□			□					□	□		□		□		□		
Nasri et al. (2022) (34)	□		□						□		□			□				□			□		□		□		□		□		
Rasheed et al. (2021) (32)	□		□					□			□			□				□				□	□		□			□			□
Mohanty & Ramesh (2020) (49)	□		□						□		□			□					□		□		□		□		□		□		
Alafandy (2014) (37)		□[N]	□					□	□				□			□	□					□	□		□			□			□
Parolia et al. (2010) (41)	□[N]		□							□			□			□		□				□	□		□			□			□
Goinka et al. (2023) (35)	□[N]			□				□				□			□			□			□		□		□		□		□		
RojaRamya et al. (2022) (42)	□			□				□			□			□						□	□		□		□		□		□		
Madan et al. (2020) (43)	□			□				□			□				□				□		□		□		□		□		□		
Reddy et al. (2019) (45)	□[N]			□				□				□		□				□			□		□		□		□		□		
Aghazadeh et al. (2018) (46)	□			□				□			□				□			□			□		□		□			□			□
Hugar et al. (2017) (30)	□[N]			□				□				□			□			□			□		□		□		□		□		
Alolofi et al. (2016) (44)	□[N]			□				□			□			□				□			□		□		□			□			□
Alafandy & Barakat (2015) (38)		□[N]		□				□					□			□	□					□	□		□			□			□
Kusum et al. (2015) (47)	□[N]			□				□				□		□				□			□		□		□			□			□
RojaRamya et al. (2020) (48)	□				□			□			□			□						□	□		□		□		□		□		
Aguilar-Ayala et al. (2019) (39)		□			□			□					□			□	□				□		□		□			□			□
Divya et al. (2019) (40)	□				□			□			□			□			□				□		□		□		□		□		
Tirukkolluru et al. (2019) (36)	□					□				□	□			□			□				□		□		□		□		□		
Al-Ostwani et al. (2016) (29)	□				□			□				□			□			□			□		□		□			□			□
Lillygrace et al. (2021) (31)	□					□			□			□			□			□			□		□		□		□		□		
Shabbir et al. (2021) (50)	□					□				□	□			□				□			□		□		□		□		□		
Shabbir et al. (2020) (51)	□					□				□	□			□						□	□		□		□		□		□		
Kumar et al. (2014) (28)	□[N]						□	□				□			□		□				□		□		□		□		□		
Jolly et al. (2013) (27)	□						□	□				□			□		□				□		□		□			□			□
Shingare & Chaugule (2011) (26)	□[N]						□	□				□			□		□				□		□		□		□		□		

[N]: Not clearly stated, RCT: Randomised clinical trial

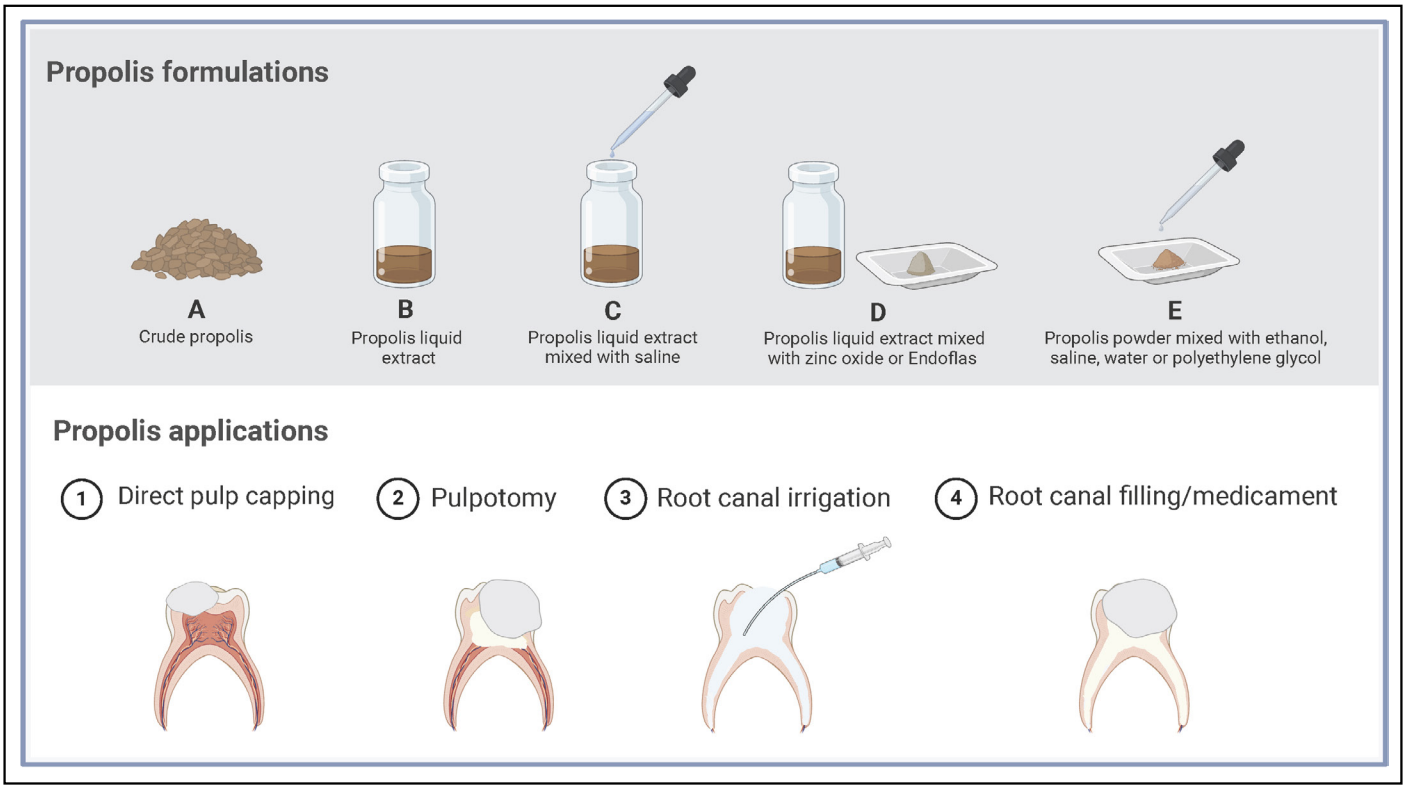

Figure 2. Schematic illustration of the reported formulations and applications of propolis in various endodontic therapies in primary and permanent teeth. A: Crude propolis, B: Propolis extract, C: Propolis extract mixed with saline, D: Propolis extract mixed with zinc oxide, E: Propolis powder mixed with ethanol, distilled water, saline, or polyethylene glycol

Funding was declared for only one study (29), in which the study was funded by Damascus University. However, the majority of the included studies reported no funding (n=16), while funding was not clearly reported in nine studies. Furthermore, the majority of the included studies clearly declared no conflict of interest, with only three studies not clearly documenting conflict of interest. None of the included studies reported a conflict of interest.

Propolis use in The Endodontic Therapy of Primary Teeth

Direct pulp capping material

The outcomes of direct pulp capping using propolis in primary teeth have been evaluated in a limited number of studies (Table 2). A prospective cohort study reported a clinical and radiographic success rate of 87.23% for crude propolis as a direct pulp capping material in asymptomatic primary teeth with deep dentine caries at the 12-month follow-up (37). Furthermore, a RCT reported histological evidence of minimal pulpal inflammation in sound primary teeth subjected to direct pulp capping using either a propolis-ethanol mixture, mineral trioxide aggregate (MTA, Angelus, Brazil) or calcium-enriched mixture (CEM, manufacturer not reported) for 15 days with no statistically significant difference between the three materials (32).

Filling material following pulpotomy procedures

A summary of the studies on the use of propolis as pulp capping material during pulpotomy procedures in primary teeth is presented in Table 2. Overall, the participants in the majority of the studies were healthy children with restorable primary molars and deep carious lesions close to the pulp without clinical and/or radiographic signs of irreversible pulpitis or pulp necrosis. Crude propolis (38), propolis tincture applied to the pulps using cotton pellets (30, 42, 43), propolis extract mixed with zinc oxide powder (44), and propolis powder mixed with either ethanol (35, 45), distilled water (46), or polyethylene glycol (47) were investigated. Following pulpotomy, several coronal restorations were used including stainless steel crowns placed at the same visit (36, 38) or next visit (1–7 days) (43, 45–47), polymer-reinforced zinc oxide-eugenol placed at the same visit (30, 35), or composite resin restorations placed at the same visit (38).

Clinical and radiographic outcomes of pulpotomy using propolis in primary teeth were assessed and compared to several materials, including MTA (Angelus, Brazil) (42, 43, 46), MTA (ProRoot MTA, Dentsply, USA) (47), Biodentine (Septodont, France) (47), Buckley's formocresol (1/5th dilution) (30, 44, 45), and calcium hydroxide [$Ca(OH)_2$] (manufacturer not reported) (30). Collectively, the clinical and radiographic success rate of pulpotomy using propolis in primary teeth was reported to be significantly lower than MTA and Biodentine over a follow-up period of up to 24 months, with MTA pulpotomy resulting in the highest success (42, 43, 46, 47). Furthermore, a comparison of propolis to formocresol revealed similar clinical and radiographic success for propolis-zinc oxide mixture and formocresol at 12 month follow-up (44). However, the clinical and radiographic outcomes of formocresol pulpotomy was reported inferior to propolis-ethanol paste-like pulpal dressing (45), and superior to propolis tincture (topically applied for 5

TABLE 2. Summary of clinical studies on propolis use as pulp capping material in primary and permanent teeth

Author (year)	Study design	Sample size-tooth type	Age in years	Propolis form	Study group (n)	Comparison group (n)	Follow-up	Assessment method: Outcomes assessed	Key findings
Usage	Direct pulp capping in primary teeth								
Rasheed et al. (2021) (32)	RCT	57-pr	8	Propolis powder mixed with ethanol to a thick consistency	Propolis (19)	MTA (19) Calcium Enriched Mixture (19)	15 days	Histological analysis using H&E staining: - Inflammation	No or only a few inflammatory cells were noted in 78.9% of propolis & CEM groups and 73.7% of MTA group
Usage	Direct pulp capping in primary and immature permanent teeth								
Alafandy (2014) (37)	Prospective cohort[N]	89-IP, pr	5–8	Crude propolis	Propolis (42 IP & 47 pr)	No comparison	1, 6 & 12 months	Clinical assessment: - Clinical symptoms, pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - PDL space widening, loss of lamina dura, interradicular or periradicular radiolucency, pathologic resorption	Clinical & radiographic success of 87.23%, & 100% in primary and immature permanent teeth, respectively
Usage	Direct pulp capping in permanent teeth								
Ahmad et al. (2022) (33)	RCT[N]	40-P	15–25	Propolis powder mixed with ethanol to a thick consistency	Propolis (20)	Biodentine (20)	15 & 45 days	Clinical assessment: - Postoperative pain Histological analysis using H&E staining: - Dentine bridge formation, architecture of odontoblast layer & Inflammation	- Dentine bridge formation was evident at the exposure site after 15 & 45 days in Biodentine & propolis groups, respectively - Mild inflammation in both groups
Nasri et al. (2022) (34)	RCT	41-P	15–25		Propolis (12)	MTA (12) Biodentine (12)	8 weeks	Clinical assessment: - Clinical symptoms, pain, TTP, swelling, sinus tract, mobility, thermal and electrical pulp test Radiographic assessment: - Periapical pathology Histological analysis using H&E staining: -Inflammation & dentine bridge formation	- 100% clinical and radiographic success in MTA group compared to 91.7% in both the propolis and Biodentine groups - Maximum inflammation in Biodentine group and the minimum in MTA group - Lower rate of dentine bridge formation in propolis group
Mohanty and Ramesh (2020) (49)	RCT	102-P	13–30		Propolis (34)	MTA (34) Biodentine (34)	12 weeks	Histological analysis using H&E staining: - Dentine bridge formation	- Dentine bridge formation was seen in 78.8%, 93.5%, & 19.4% of MTA, Biodentine and propolis groups, respectively - Less thickness of dentine bridge was evident in propolis group
Parolia et al. (2010) (41)	RCT[N]	36-P	15–25	Propolis powder mixed with ethanol to a thick consistency	Propolis (12)[N]	MTA (12[IN] $Ca(OH)_2$ (12)[N]	15 & 45 days	Clinical assessment: - Postoperative pain and sensitivity Histological analysis using H&E staining: - Inflammation & dentine bridge formation	- Superior inflammation control and dentine bridge formation in MTA followed by propolis

TABLE 2. Cont.

Author (year)	Study design	Sample size-tooth type	Age in years	Propolis form	Study group (n)	Comparison group (n)	Follow-up	Assessment method: Outcomes assessed	Key findings
Usage	Pulpotomy in primary teeth								
Goinka et al. (2023) (35)	RCT[N]	90-pr	5–10	Propolis powder mixed with titanium dioxide powder (2:1) & 70% ethanol to a thick consistency	Propolis (30)	FC (30) PDGF (30)	3 & 6 months	Histological analysis using H&E staining: - Inflammation, dentine bridge formation, pulpal soft tissue organization & repair	- Dentine bridge formation in propolis & PDGF but not in FC - Better inflammation control and pulp repair in propolis & PDGF compared to FC
RojaRamya et al. (2022) (42)	RCT	60-pr	4–8	Propolis solution applied to the pulp using cotton pellet for 5 minutes	Propolis (30)	MTA (30)	6, 12 & 24 months	Clinical assessment: - Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - PDL space widening, loss of lamina dura, interradicular or periadicular radiolucency, pathologic root resorption	- Success of pulpotomy with propolis and MTA was 80% & 93.1%, respectively
Madan et al. (2020) (43)	RCT	40-pr	4–9	Propolis tincture applied to the pulp using cotton pellet until a brownish to black discoloration is seen	Propolis (20)	MTA (20)	3, 6 & 12 months	Clinical assessment: - Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - Interradicular or periradicular radiolucency, pathologic root resorption	- Success rate of MTA (94.4%) was slightly higher than propolis (88.9%)
Reddy et al. (2019) (45)	RCT[N]	90-pr	5–10	Propolis powder mixed with titanium dioxide powder (2:1) & 70% ethanol to a thick consistency	Propolis (30)	FC (30) PDGF (30)	3 & 6 months	Clinical assessment: - Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - Interradicular or periradicular radiolucency, pathologic root resorption Histological analysis using H&E staining: -Inflammation, dentine bridge formation	- Clinical & radiographic success of propolis (88.4%) & PDGF (88.8%) were higher than FC (72%)* at 6 months - Thick and continuous dentine bridge formation with minimal inflammation were noted in propolis & PDGF but not FC
Aghazadeh et al. (2018) (46)	RCT	50-pr	4–8	Propolis powder mixed with distilled water to a thick consistency	Propolis (25)	MTA (25)	3, 6 & 12 months	Clinical assessment: - Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - Interradicular or periradicular radiolucency, pathologic root resorption	The incidence of clinical & radiographic signs of pathology was significantly higher in propolis
Hugar et al. (2017) (30)	RCT[N]	90-pr	4–9	Propolis tincture applied in cotton pellet for 5 minutes	Propolis ([N])	FC ([N]) Turmeric gel ([N]) $Ca(OH)_2$ ([N])	1, 3 & 6 months	Clinical assessment: - Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - Interradicular or periradicular radiolucency, pathologic root resorption	Success rate of 93.3%, 86.7%, 73.3%, & 100%* in propolis, turmeric gel, $Ca(OH)_2$ & FC, respectively
Alolofi et al. (2016) (44)	RCT[N]	60-pr	4–6	Drops of propolis extract were mixed with zinc oxide powder (1:1)	ZOP (20)	FC (20) ZOTV (20)	1, 6 & 12 months	Clinical assessment: Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: Interradicular or periradicular radiolucency, pathologic root resorption	- Clinical success of 88.2% in FC & ZOP and 94.4% in ZOTV at 12 months - Radiographic success of 73.3% in FC & ZOP and 87.5% in ZOTV at 12 months

TABLE 2. Cont.

Author (year)	Study design	Sample size-tooth type	Age in years	Propolis form	Study group (n)	Comparison group (n)	Follow-up	Assessment method: Outcomes assessed	Key findings
Kusum et al. (2015) (47)	RCT[N]	75-pr	3–10	Propolis powder mixed with polyethylene glycol to a thick consistency	ZOP (20) Propolis (25)	MTA (25) Biodentine (25)	3, 6 & 9 months	Clinical assessment: Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: Interradicular or periradicular radiolucency, pathologic root resorption	- Clinical success of 84%* in propolis compared to 100% success in the other groups at 9 months - Radiographic success at 9 months in MTA, Biodentine & propolis were 92%, 80% & 72%*, respectively
Usage	Pulpotomy in primary and immature permanent teeth								
Alafandy and Barakat (2015) (38)	Prospective cohort[N]	24-pr, IP	7.5–12	Crude propolis	Propolis (10 pr & 14 IP)	No comparison	1 & 3 months	Histological analysis using H&E staining: Inflammation & dentine bridge formation	- The majority of teeth (>60%) showed no or mild inflammation - Dentine bridge formation was evident as early as 1 month

*: Statistically significant difference reported. $Ca(OH)_2$: Calcium hydroxide, H&E: Haematoxylin and eosin, FC: Buckley's formocresol (1/5th dilution), IP: Immature permanent teeth, MTA: Mineral trioxide aggregate, N: Not clearly stated, P: Permanent teeth, PDGF: Platelet derived growth factor mixed with dry collagen powder, PDL: Periodontal ligament, pr: Primary teeth, RCT: Randomised clinical trial, TTP: Tenderness to percussion, ZOP: Zinc oxide propolis, ZOTV: Zinc oxide thymus vulgaris

minutes) at 6 months follow-up (30). The latter study reported the clinical and radiographic outcomes of pulpotomy using propolis tincture, although slightly better, were not statistically significantly different from $Ca(OH)_2$ (30).

Histological outcomes of pulpotomy using propolis in primary teeth were also assessed (38), and compared to Buckley's formocresol (35, 45). Overall, the histological outcomes analysis of pulpotomy in primary teeth using crude propolis or propolis-ethanol paste-like pulpal dressings revealed minimal pulpal inflammation compared to formocresol pulpotomy, with histological evidence of dentine bridge formation in propolis groups (35, 45).

Root canal irrigant during pulpectomy procedures

Studies assessing propolis use as an intra-canal irrigant during pulpectomy procedures in primary teeth are summarised in Table 3. In all included studies the participants were healthy children with restorable primary molars with non-vital (necrotic) pulps. Three formulations of propolis were tested as a root canal irrigant, including 4% dimethyl sulfoxide propolis extract (27), 25% water propolis extract (28), and 11% alcoholic propolis extract (26).

Intra-canal aerobic and anaerobic microbial colony forming units were assessed in primary teeth with non-vital pulps before and after exposure to intra-canal irrigation with propolis, and compared to 3% sodium hypochlorite (NaOCl) (26), 2% chlorohexidine (CHX) (27), 4% $Ca(OH)_2$ (27), and 0.9% isotonic saline (27, 28). Collectively, these studies reported a significant reduction of aerobic and anaerobic bacteria colony-forming units following propolis use. However, the efficacy of propolis was significantly less than NaOCl (21), and CHX (27); while superior to $Ca(OH)_2$ (27). The formulation of $Ca(OH)_2$ irrigant used in the latter study was not reported.

Root canal filling material following pulpectomy procedures

Studies assessing propolis use as a root canal filling material following pulpectomy procedures in primary teeth are summarised in Table 3. Various propolis formulations were tested as root canal filling materials in primary teeth, including 20% commercially available propolis paste (Yucamiel, Merida, Mexico) (39), a zinc oxide powder mixed with either 50% propolis extract (29) or 60% propolis extract (48), and Endoflas powder (Sanlor laboratories, Colombia) mixed with commercially available propolis extract (Brazilian Green Bee Propolis Liquid Extract, Uniflora®) (40). Following root canal filling, teeth were restored with stainless steel crowns in all the studies except one study (39), in which temporary coronal restorations were placed for 12 weeks.

Clinical and radiographic outcomes following the use of propolis as a root canal filling material in primary molars with non-vital pulps were assessed and compared to zinc oxide-eugenol, Endoflas-chlorophenol-free (ZOE, $Ca[OH]_2$ and iodoform), Metapex ($Ca[OH]_2$ and iodoform), and triple antibiotic paste (TAP; ciprofloxacin 200 mg, metronidazole 500 mg, and minocycline 100 mg mixed at a ratio of 1:3:3 in saline). Overall, zinc oxide-propolis resulted in more than a 90%

TABLE 3. Summary of the studies on propolis use in primary teeth with non-vital pulps

Author (year)	Study design	Sample size	Age in years	Propolis form	Study group (n)	Comparison group (n)	Assessment method: Outcomes assessed	Key findings
Usage	Intra-canal irrigant during pulpectomy							
Kumar et al. (2014) (28)	RCT[N]	70	4–7	Propolis extract	Propolis (35)	Saline (35)	Pre- and post-irrigation samples were collected using sterile paper points: - Microbial colony counts	Reduction in the mean bacterial colony counts (E. faecalis, E. coli, Streptococci & Staphylococcus) was evident in propolis group.
Jolly et al. (2013) (27)	RCT	60	6–12		Propolis (15)	CHX (15) $Ca(OH)_2$ (15) Saline (15)		A significant decrease in mean microbial colonies was seen in all groups. Maximum change was seen with CHX & the least was noted in $Ca(OH)_2$ & saline.
Shingare et al. (2011) (26)	RCT[N]	40	4–6	Propolis extract diluted with saline (2:1)	Propolis (10)	NaOCl (10) AEM (10) Saline (10)		Reduction in colony counts were 95.5%*, 89.7%*, 34.7% and 28.0% for NaOCl, AEM, propolis & saline, respectively.
Usage	Root canal filling material during pulpectomy							
RojaRamya et al. (2020) (48)	RCT	40	4–8	Propolis extract mixed with zinc oxide powder to a thick consistency	ZOP (20)	ZOE (20)	Clinical assessment: - Pain, TTP, swelling, sinus tract, mobility Radiographic assessment: - Interradicular or periradicular radiolucency, pathologic root resorption	95%* and 70%* success rate for ZOP & ZOE at 24 months, respectively.
Aguilar-Ayala et al. (2019) (39)	Prospective cohort	36	[N]	Propolis paste	Propolis (36)	No comparison		100% clinical & radiographic success over the follow-up period (1, 2, 4 & 12 weeks)
Divya et al. (2019) (40)	RCT	30	4–9	Propolis extract mixed with Endoflas powder (P-Endoflas)	P-Endoflas (15)	3Mix (15)		100%* clinical and radiographic success in P-Endoflas at 12 months, compared to 93% and 60% in the other group
Al-Ostwani et al. (2016) (29)	RCT	64	3–9	Propolis extract mixed with zinc oxide powder to a thick consistency	ZOP (16)	ZOE (16) ZOE, $Ca(OH)_2$, & iodoform (16) $Ca(OH)_2$-Iodoform (16)		ZOP achieved a clinical & radiographic success of 93.8%, while other groups (87.5%) at 12 months

*: Statistically significant difference reported. AEM: 12.5% alcoholic extract of miswak, $Ca(OH)_2$: 4% calcium hydroxide, CHX: 2% Chlorhexidine, N: Not clearly stated, N/A: Not applicable, NaOCl: 3% Sodium hypochlorite, RCT: Randomised clinical trial, TTP: Tender to percussion, 3Mix: Ciprofloxacin, metronidazole and minocycline in saline, ZOE: Zinc oxide eugenol, ZOP: Zinc oxide propolis

success rate over a follow-up period of up to 24 months and was reported to be superior to zinc oxide-eugenol, Endoflas-chlorophenol-free, and Metapex (29, 48). Furthermore, the clinical and radiographic outcomes of Endoflas powder-propolis mixture was reported to be remarkably better than those of TAP at 12 months follow-up (40). The resorption rate of the zinc oxide-propolis compound was reported to closely correspond to the physiological resorption of the roots of the primary teeth in 62.5% of the cases (29). However, the latter study did not report how the standardisation of radiographic angulation was controlled.

Propolis use in the Endodontic Therapy of Permanent Teeth

Direct pulp capping material

Studies assessing propolis use as a pulp capping material during direct pulp capping in permanent teeth are summarised in Table 2. Overall, the studies investigated the outcomes of propolis application to mechanically exposed dental pulps in healthy adults or children scheduled for orthodontic-related tooth extraction. In other words, the cavities and pulps were healthy and not infected with no existing carious lesions. Crude propolis (37) or propolis powder mixed to a paste-like consistency with ethanol were used (32–34, 41, 49). The size of pulp exposure was only reported in two studies as 1.2 mm (33), or equal/less than 1 mm (37).

Clinical, radiographic and histological outcomes of direct pulp capping using propolis in the permanent teeth were assessed and compared to MTA (ProRoot MTA, Dentsply, Switzerland) (32, 34, 41, 49), Biodentine (Septodont, France) (33, 34, 49), or $Ca(OH)_2$ (Dycal, Dentsply Caulk Milford, USA) (41). Descriptive qualitative histological evaluation was reported in one study (33), while various quantitative scoring systems for inflammation and dentine bridge formation were used in the evaluation of the histological outcomes in the three other studies (34, 41, 49). None of the studies reported the number of histological sections analysed per tooth, how they were selected nor the level at which the histological sections were selected from each tooth. Overall, the clinical and radiographic outcome of direct pulp capping using propolis in permanent teeth was reported to be similar to Biodentine (91.7%) and slightly lower than MTA (100%), with no statistically significant difference between the three materials at two months (34). Furthermore, several histological comparative studies reported the speed of dentine bridge formation in direct pulp capping using propolis in permanent teeth was inferior to MTA and Biodentine but superior to $Ca(OH)_2$ over follow-up periods of up to three months (33, 34, 41, 49).

Intra-canal medicament

Studies assessing propolis usage as an intra-canal medicament in permanent teeth with non-vital pulps are summarised in Table 4. Overall, only a limited number of clinical studies have been reported in the literature, each investigating different outcomes (31, 36, 50, 51). Comparison of the microbial colony counts in immature (31) and mature

TABLE 4. Summary of the studies on propolis use as intra-canal medicament in non-vital permanent teeth

Author (year)	Study design	Sample size-teeth type	Age in years	Propolis form	Study group (n)	Comparison group (n)	Assessment method: Outcomes assessed	Key findings
Lillygrace et al. (2021) (31)	RCT	30-IP	7–14	Propolis powder mixed with saline (1.5:1) to a thick consistency	Propolis (15)	TAP (15)	Sterile paper points were inserted after access cavity, after irrigation, and 3 - 4 weeks after medicament placement: Mean microbial colony counts	Propolis exhibited similar antimicrobial efficacy as TAP
Shabbir et al. (2021) (50)	RCT	80-P	20–40		Propolis (40)	$Ca(OH)_2$ (40)	Clinical assessment: - Incidence of flare-ups Pain visual analogue scale: - Postoperative pain Follow-up at 4, 12, 24, 48 & 72 hours	Outcomes from each group in addition to the inter-group comparison was not clearly reported - >78% of the participants experienced no or only mild pain in both groups at all time intervals - Slightly higher incidence of flare-up was noted in propolis (17%) compared to $Ca(OH)_2$ (12%)
Shabbir et al. (2020) (51)	RCT	80-P	20–40		Propolis (40)	$Ca(OH)_2$ (40)		
Tirukkolluru et al. (2019) (36)	RCT	45-P	35–50	Propolis powder mixed with moxifloxacin powder (1:1) in saline	Propolis (15)	TAP (15) $Ca(OH)_2$ (15)	Sterile paper points were inserted after chemo-mechanical preparation, and 7 days after medicament placement: Mean microbial colony counts	No differences between the three groups in terms of microbial colony counts reduction

$Ca(OH)_2$: Calcium hydroxide, IP: Immature permanent teeth, P: Mature permanent teeth, RCT: Randomised clinical trial, TAP: Triple antibiotic paste

permanent teeth (36) with non-vital pulps following application of propolis and TAP (Ciprofloxacin 500 mg, Metronidazole 400 mg and Minocycline 100 mg) as intra-canal medicaments revealed equal efficacy of both tested medicaments. Furthermore, postoperative pain control was reported to be similar in mature permanent teeth with non-vital pulps and apical periodontitis where the canal was disinfected using either propolis or $Ca(OH)_2$ (Calcipulpe, Septodont, France) as an intra-canal medicament (51). However, a slightly higher incidence of flare-ups was reported in the propolis cases (17%) compared to $Ca(OH)_2$ (12%) (51).

DISCUSSION

The present scoping review explored and critically appraised the literature on the clinical applications of propolis-based materials in endodontic therapy. The results of the review identified several human clinical studies investigating the effectiveness of propolis, incorporated into various formulations and delivery vehicles, in the endodontic therapy of primary and permanent teeth. Based on the reported outcomes of the studies, the use of propolis in VPT (i.e. direct pulp capping and pulpotomy), and root canal treatment on teeth with non-vital pulps (i.e. mainly primary teeth root canal disinfection and filling) appears at first sight to be promising. However, the majority of the evidence is derived from studies with flawed methodological designs and incomplete reporting. Lack of adequate reporting of propolis-related variables, including its origin, concentration, and extraction method, was evident within the studies. These critical variables are known to impact the chemical composition and biological activities of propolis (52–54), thus their reporting is essential. Furthermore, many aspects of the studies, including the various outcomes assessed and assessment methods, were not standardised and therefore failed to support the subsequent comparison and synthesis of evidence-based conclusions. Additionally, issues such as inadequate blinding, inter/intra-examiner variability, lack of adequate follow-up time, use of healthy teeth, and use of inappropriate coronal restorations were evident within the included studies. Collectively, the findings of the present review underline the need for further high-quality research in the area and the need for more rigorous editorial control over publications.

The positive results reported following propolis application in vital and non-vital pulp therapies can be directly related to the well-documented biological properties of propolis, such as its antimicrobial (55), anti-inflammatory (56), and wound healing properties (57). Furthermore, the biocompatibility of propolis is another advantageous property, for example, the superior cell viability of periodontal and pulpal fibroblast cells exposed to propolis compared to $Ca(OH)_2$ (58).

Despite its promising therapeutic potential, the clinical use of propolis-based materials has not been widely accepted due to its inconsistent composition that varies as a consequence of its geographical origin (52), and extraction method (54, 59), making the reproducibility of its therapeutic effects and quality control of the product challenging. To address this issue, chemical standardisation of propolis using marker compounds that characterise its biological activities has been suggested (12, 60). Chromatographic fingerprinting methods, such as high-performance liquid chromatography and thin-layer chromatography, can provide valuable information on the phytochemical composition of propolis compounds and aid chemical standardisation and reproducibility of their biological activities (12). Therefore, utilisation of these techniques as primary quality control parameters for propolis samples is suggested in future studies.

The interest in propolis as a medicinal product, to prevent and treat various conditions, is growing within the dental and medical fields (11, 15). Indeed, natural materials offer several advantages, including broad biological activity and a higher margin of clinical safety (61). Furthermore, natural materials with inherent antimicrobial activity could provide alternatives to antibiotics, thus limiting their use and contributing positively to the growing global health crisis of antibiotic resistance. Although the clinical use of antibiotics (such as triple/double antibiotic paste) to disinfect the root canal system has been commonplace in regenerative endodontic therapies in immature teeth with necrotic pulps (62–64), their continued clinical use has been questioned by the most recent European Society of Endodontology position statement on antibiotic use (65). Therefore, the development and use of alternative safer intra-canal disinfection strategies are essential.

Although this scoping review adopted a thorough and robust search strategy utilising two independent investigators to identify all potential studies, it has limitations. Inherent limitations such as the inclusion of clinical studies in English only are acknowledged. Additionally, only the three largest scientific databases were searched, which might have led to the exclusion of other studies not indexed in the searched database. Nevertheless, the authors undertook an extensive reference mining of included studies to reduce the risk of missing important studies. A scoping review design was selected over a systematic review due to the extent and heterogeneity of the evidence on the topic.

CONCLUSION

The use of propolis in various formulations and delivery vehicles to promote pulp wound healing and/or disinfect the root canal system has been investigated in a wide range of studies in primary and permanent teeth with overall promising clinical outcomes. However, the majority of the studies had various methodological limitations and reporting flaws. Study variations and lack of standardisation of reported outcomes and their assessment methods preclude the synthesis of evidence-based conclusions. Therefore, well-designed controlled clinical studies, with complete reporting of propolis-related variables, in addition to the use of consistent outcome sets relevant to the field of the study are recommended to support the subsequent comparison of future studies. Furthermore, researchers are advised to consider utilising standardised propolis formulations.

Disclosures

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