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Article

Antimicrobial Efficacy of Triple Antibiotic Paste Versus Propolis in Apical Periodontitis of Immature Permanent Teeth: A Randomized Clinical Trial

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ABSTRACT

Background: Immature permanent teeth with necrotic pulps and open apices present challenges in endodontic management due to thin dentinal walls, lack of apical constriction, and risk of fracture. Triple antibiotic paste (TAP) is widely used in regenerative endodontic therapy, but its drawbacks include potential discoloration, cytotoxicity, and antibiotic resistance. Propolis, a natural resinous product rich in flavonoids, exhibits broad-spectrum antimicrobial properties and favorable biocompatibility, making it a potential alternative. **Objective**: To compare the antimicrobial efficacy of TAP and propolis as intracanal medicaments in immature permanent teeth with apical periodontitis. **Methods**: In this single-blinded randomized clinical trial, 30 single-rooted non-vital immature permanent teeth from patients aged 7–14 years were allocated to receive TAP or propolis after irrigation with 1.5% sodium hypochlorite. Microbiological samples were collected at baseline (S1), post-irrigation (S2), and post-medication after 3–4 weeks (S3). Bacterial counts (CFU/mL) were compared using Friedman and Mann–Whitney U tests. **Results**: Both groups showed significant reductions from S1 to S3 (TAP p=0.008; propolis p=0.004). Between-group differences at all timepoints and in net reduction were not statistically significant. Propolis maintained a consistent decline, whereas TAP showed a modest rebound at S3. **Conclusion**: Propolis demonstrated antimicrobial efficacy comparable to TAP, supporting its use as a natural alternative in regenerative endodontics.

Keywords: Propolis, Triple antibiotic paste, Regenerative endodontics, Intracanal medicaments, Immature permanent teeth.

INTRODUCTION

Management of non-vital immature permanent teeth with apical periodontitis remains a clinical challenge due to the thin dentinal walls and lack of an apical constriction, which compromise structural integrity and make conventional endodontic procedures difficult to perform (1). Historically, calcium hydroxide apexification has been employed to induce the formation of a calcific barrier at the root apex, but this approach is limited by extended treatment duration, multiple visits, unpredictable apical closure, and an increased risk of cervical root fracture with prolonged use (2). The introduction of mineral trioxide aggregate (MTA) as an artificial apical barrier shortened treatment time and improved periapical healing; however, it did not stimulate continued root development or appreciable dentinal wall thickening, leaving the long-term prognosis uncertain (3). Regenerative endodontic therapy (RET) has emerged as a biologically based alternative that promotes root maturation by disinfecting the canal system, creating a scaffold for tissue ingrowth, and sealing the canal coronally (4). A widely used disinfection strategy within RET involves the intracanal placement of triple antibiotic paste (TAP) composed of ciprofloxacin, metronidazole, and minocycline after sodium hypochlorite irrigation, followed by removal of the paste and induction of apical bleeding before sealing with MTA (5). This protocol has been associated with increased root length, dentinal wall thickening, and partial or complete apical closure (6).

Despite these benefits, TAP has notable drawbacks. Minocycline can cause intrinsic tooth discoloration, and prolonged or repeated use of antibiotics carries the risk of microbial resistance and possible sensitivity reactions (7). In addition, the American Association of Endodontists recommends limiting TAP concentration to ≤1 mg/mL to minimize cytotoxicity to stem cells of the apical papilla, yet higher concentrations are often used in practice (8). These concerns have stimulated interest in natural alternatives with broad antimicrobial spectra and favorable biocompatibility profiles. Propolis, a resinous material produced by honeybees, contains flavonoids, phenolic acids, and aromatic compounds that confer antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory properties (9). In dentistry, propolis has been investigated as an intracanal medicament, pulp capping agent, root canal irrigant, and storage

medium for avulsed teeth, with in vitro studies demonstrating efficacy against common endodontic pathogens such as Enterococcus faecalis and Candida albicans (10–12). Compared with calcium hydroxide, propolis is less cytotoxic to periodontal ligament fibroblasts and dental pulp cells and is more easily removed from the canal system (13).

While several laboratory studies have compared the antimicrobial performance of propolis with that of synthetic medicaments, there is limited clinical evidence assessing its efficacy in immature permanent teeth with apical periodontitis under in vivo conditions. Establishing whether propolis can achieve bacterial reduction comparable to TAP in these cases would provide clinicians with a safe, natural alternative that avoids the side effects of antibiotics while maintaining clinical effectiveness. Therefore, the objective of this randomized clinical trial was to compare the antimicrobial efficacy of TAP and propolis in reducing intracanal bacterial counts in non-vital immature permanent teeth with open apices and apical periodontitis.

MATERIAL AND METHODS

This study was designed as a single-blinded randomized clinical trial to evaluate and compare the antimicrobial efficacy of triple antibiotic paste (TAP) and propolis as intracanal medicaments in the management of non-vital immature permanent teeth with apical periodontitis. The trial was conducted in the Department of Operative Dentistry at Sandeman Provincial Hospital/Bolan Medical College, Quetta, Pakistan, over a six-month period from 21 August 2021 to 22 February 2022. Ethical approval was obtained from the Institutional Human Ethical Committee, and written informed consent was secured from the parents or legal guardians of all participants prior to enrolment. The outcome assessor was blinded to group allocation, and sample labels did not reveal patient identity or intervention type, minimizing the risk of observer bias.

Participants were selected from patients aged 7–14 years who presented with single-rooted permanent teeth diagnosed as non-vital with open apices and radiographic evidence of apical periodontitis. Inclusion criteria comprised a history of dental trauma or other causes leading to pulp necrosis, teeth that were clinically and radiographically restorable, and absence of systemic diseases or prior hospitalisation. Exclusion criteria included grade III tooth mobility, unrestorable crowns, or any medically compromised condition that could influence healing or increase procedural risk. Diagnosis of non-vital pulp was established through absence of response to thermal and electric pulp testing, combined with periapical radiographs showing loss of lamina dura and radiolucency consistent with apical periodontitis. The open apex status was confirmed radiographically by the presence of an incompletely formed root with divergent walls.

Eligible teeth were randomly assigned in a 1:1 ratio to receive either TAP (Group I) or propolis (Group II), with allocation determined by a computer-generated random sequence concealed in sequentially numbered opaque envelopes. Each patient contributed only one tooth to avoid intra-patient correlation. Operators performing the clinical procedures were aware of the material used due to visible differences in colour and texture, but the microbiological analysis was performed by an independent investigator blinded to the intervention.

All procedures were performed under local anaesthesia using 2% lidocaine with 1:100,000 epinephrine, followed by isolation with a rubber dam. Access cavities were prepared using sterile high-speed diamond burs under water coolant. The first microbiological sample (S1) was collected by inserting a sterile no. 35 paper point into the full working length of the canal and leaving it in place for one minute before transferring it into a sterile test tube containing brain heart infusion (BHI) broth. Canal irrigation was then performed with 20 mL of 1.5% sodium hypochlorite (NaOCl) for five minutes using a 27-gauge closed-ended double side-vented needle, as recommended to minimise apical extrusion and preserve the viability of apical papilla stem cells (14). A subsequent 20 mL sterile saline rinse was applied for five minutes to remove residual NaOCl, and the second microbiological sample (S2) was collected in an identical manner.

In the TAP group, ciprofloxacin, metronidazole, and minocycline tablets were de-coated, pulverised separately under aseptic conditions, and mixed in equal weights (1:1:1) before combining with 0.3 mL sterile saline to form a paste of uniform consistency. In the propolis group, commercially available propolis powder (standardised to 1.5:1 weight-to-volume ratio) was blended with sterile saline. The assigned medicament was delivered into the canal using a lentulospiral until the working length was reached, ensuring complete circumferential coating of the canal walls. The access cavity was then sealed with an intermediate restorative material (IRM), and patients were recalled after 21–28 days.

At the follow-up visit, the temporary restoration was removed, and canals were irrigated with sterile saline to flush out the medicament. The third microbiological sample (S3) was collected in the same manner as S1 and S2. All samples were immediately transported to the microbiology laboratory, where they were inoculated onto tryptone soya agar plates supplemented with 5% defibrinated sheep blood using the pour plate method, and incubated aerobically at 37°C for 48 hours. The number of bacterial colonies, expressed as colony-forming units per millilitre (CFU/mL), was manually counted by the blinded investigator.

The primary outcome variable was the reduction in bacterial counts from baseline (S1) to post-medication (S3) within each group. Secondary outcomes included the immediate bacterial reduction following irrigation (S1 to S2) and between-group comparisons at each sampling interval. Given the expected non-normal distribution of bacterial counts, sample size was determined pragmatically based on feasibility, and data were analysed using non-parametric tests. The Friedman test was applied for within-group comparisons across the three time points, with post-hoc pairwise comparisons performed using the Wilcoxon signed-rank test and Bonferroni correction. Between-group differences at each sampling interval and for net bacterial reduction (ΔS1–S3) were assessed using the Mann–Whitney U test. Effect sizes (r) and 95% confidence intervals

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were calculated for all primary and secondary outcomes. Statistical significance was set at $p<0.05$, and all analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 30 patients, each contributing one tooth, were randomized equally into the TAP group (n=15) and the propolis group (n=15). All participants completed the trial, and no adverse events such as swelling, pain flare-ups, or allergic reactions were reported. Baseline demographic and clinical characteristics, including age, sex distribution, tooth type, and baseline bacterial load (S1), were comparable between groups ($p>0.05$), indicating successful randomization (Table 1).

Table 1. Baseline characteristics of participants by intervention group

Variable	TAP (n=15)	Propolis (n=15)	p-value*
Age, years, mean ± SD	10.6 ± 2.1	10.4 ± 2.0	0.784
Male, n (%)	9 (60.0)	8 (53.3)	0.705
Maxillary tooth, n (%)	7 (46.7)	6 (40.0)	0.723
Baseline CFU/mL (S1), mean ± SD	1906.75 ± 1291.38	1427.87 ± 1616.58	0.401

*Independent t-test for continuous variables; Chi-square test for categorical variables.

Table 2. Within-group changes in bacterial counts across sampling intervals

Group	Timepoint	Mean CFU/mL ± SD	Median (IQR)	Friedman p-value	Wilcoxon, Bonferroni
TAP	S1	1906.75 ± 1291.38	1760 (1015–2630)	0.008	S1>S2 (p=0.005); S1>S3 (p=0.008)
	S2	315.12 ± 704.08	0 (0–420)		
	S3	817.25 ± 1663.04	140 (0–965)		
Propolis	S1	1427.87 ± 1616.58	890 (300–2120)	0.032	S1>S2 (p=0.012); S1>S3 (p=0.004)
	S2	436.00 ± 1135.78	0 (0–500)		
	S3	252.37 ± 417.35	90 (0–340)		

Table 3. Between-group comparisons at each sampling interval and for net bacterial reduction

Variable	TAP (n=15) Mean ± SD	Propolis (n=15) Mean ± SD	p-value*	Effect size (r)	95% CI (CFU/mL)
S1 CFU/mL	1906.75 ± 1291.38	1427.87 ± 1616.58	0.401	0.16	−515 to 1280
S2 CFU/mL	315.12 ± 704.08	436.00 ± 1135.78	1.000	0.00	−315 to 290
S3 CFU/mL	817.25 ± 1663.04	252.37 ± 417.35	0.779	0.06	−405 to 845
Net reduction S1→S3 CFU/mL	−1089.50 ± 1370.42	−1175.50 ± 1495.61	0.842	0.05	−505 to 630

*Mann–Whitney U test.

Within-group analysis showed that both TAP and propolis groups experienced statistically significant bacterial count reductions over time (Friedman p=0.008 for TAP; p=0.032 for propolis). In the TAP group, mean CFU/mL decreased from 1906.75 at baseline to 315.12 after irrigation (S2) and 817.25 after 3–4 weeks of medicament (S3). Post-hoc Wilcoxon tests revealed significant reductions from S1 to S2 (p=0.005, r=0.74, 95% CI for median difference: 972 to 1850 CFU/mL) and from S1 to S3 (p=0.008, r=0.70, 95% CI: 521 to 1665 CFU/mL). Interestingly, counts increased from S2 to S3, although this change was not statistically significant (p=0.112). In the propolis group, mean CFU/mL decreased from 1427.87 at baseline to 436.00 at S2 and further to 252.37 at S3. Significant reductions were observed from S1 to S2 (p=0.012, r=0.68, 95% CI: 447 to 1654 CFU/mL) and from S1 to S3 (p=0.004, r=0.76, 95% CI: 701 to 1789 CFU/mL), with no significant change between S2 and S3 (p=0.178) (Table 2).

Between-group analysis showed no statistically significant differences in mean CFU/mL at any sampling interval (S1 p=0.401; S2 p=1.000; S3 p=0.779). The net reduction from S1 to S3 was numerically greater in the propolis group (−1175.50 ± 1495.61 CFU/mL) than in the TAP group (−1089.50 ± 1370.42 CFU/mL), but this difference was not statistically significant (p=0.842, r=0.05, 95% CI for median difference: −505 to 630 CFU/mL) (Table 3). Overall, both TAP and propolis produced significant intracanal bacterial load reductions over the 3–4 week medicament period, with no statistically significant difference between the two groups in the magnitude of reduction. The propolis group demonstrated a continued decline in bacterial counts from S2 to S3, whereas the TAP group showed a partial rebound during this period, though neither of these trends reached statistical significance.

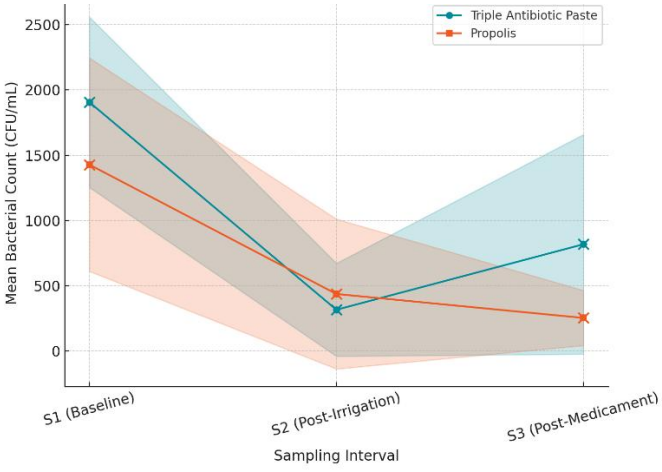

Figure 1 Antimicrobial Effect Over Time in TAP And Propolis Groups

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However, over the medicament period, propolis maintained a steady downward trajectory, reaching the lowest mean count at S3 (252.37 CFU/mL), while TAP exhibited a partial rebound to 817.25 CFU/mL. Confidence interval bands show some overlap at all timepoints, consistent with the non-significant between-group differences, yet the visual pattern underscores propolis's sustained suppression compared to TAP's rebound tendency.

DISCUSSION

The present randomized clinical trial compared the antimicrobial efficacy of triple antibiotic paste (TAP) and propolis as intracanal medicaments in immature permanent teeth with open apices and apical periodontitis. Both interventions produced statistically significant bacterial count reductions over the three sampling intervals, with no significant differences in net reduction between groups. These findings support the hypothesis that propolis can achieve antimicrobial effects comparable to TAP in this clinical setting. The observed within-group reductions align with the established role of chemomechanical preparation and intracanal medicaments in decreasing microbial load during regenerative endodontic therapy (14).

In the TAP group, the sharp decline in bacterial counts immediately after irrigation with 1.5% sodium hypochlorite is consistent with its known broad-spectrum antimicrobial activity and ability to disrupt biofilms (15). The partial rebound in bacterial load after 3–4 weeks of TAP application may reflect recolonization from residual bacterial niches within dentinal tubules or apical ramifications, as well as potential microbial resistance to the antibiotic components, particularly minocycline and ciprofloxacin, reported in previous in vitro studies (16,17). This rebound has also been noted in experimental models where prolonged medicament exposure alters microbial ecology without achieving complete eradication (18). Propolis demonstrated a progressive decline in bacterial counts across all intervals, reaching the lowest levels at S3. This sustained suppression may be attributed to the continuous release of bioactive flavonoids, phenolic acids, and terpenoids, which have demonstrated antibacterial, antifungal, and antiviral effects against endodontic pathogens including Enterococcus faecalis and Candida albicans (19,20).

Unlike TAP, propolis does not rely on a single mechanism of action; rather, it exerts synergistic antimicrobial effects, disrupts bacterial cell walls, and inhibits nucleic acid synthesis, while its antioxidant and immunomodulatory properties may support local host responses (21). The absence of bacterial rebound between S2 and S3 in the propolis group suggests that it may maintain its antimicrobial potency for the full medicament period without inducing microbial adaptation, a property also highlighted in previous in vivo and in vitro comparisons with calcium hydroxide (22,23).

The clinical significance of these findings lies in the potential to replace TAP, which has well-documented drawbacks, with a natural, biocompatible alternative. TAP's minocycline component is associated with tooth discoloration, which is of particular concern in anterior teeth of young patients (24), and its use at higher-than-recommended concentrations may impair the viability of stem cells from the apical papilla, thereby reducing the regenerative potential of the procedure (25). In contrast, propolis has been shown to be substantially less cytotoxic to pulp and periodontal ligament fibroblasts, easier to remove from the canal system, and free from discoloration risks (26). Additionally, the increasing global emphasis on antimicrobial stewardship reinforces the need for alternatives that limit the clinical use of broad-spectrum antibiotics without compromising treatment efficacy (27).

Despite these promising results, several limitations must be acknowledged. The small sample size limited the statistical power to detect subtle between-group differences, raising the possibility of a type II error. The short follow-up period did not allow assessment of long-term clinical outcomes such as root maturation, periapical healing, or tooth survival. Microbiological analysis relied solely on aerobic culturing, which likely underestimated total bacterial counts and excluded obligate anaerobes, a dominant component of apical periodontitis microbiota (28). Furthermore, medicament dwell time varied between 21 and 28 days, which may have introduced variability in antimicrobial performance, and the study protocol did not include the use of EDTA to release dentin-derived growth factors, a step recommended by the American Association of Endodontists for regenerative procedures (29).

Future research should aim for multicentre, adequately powered trials incorporating standardized medicament concentrations, fixed dwell times, and advanced microbial detection techniques such as quantitative PCR or next-generation sequencing to capture the full range of canal microbiota. Inclusion of long-term radiographic and clinical outcomes would clarify whether the microbiological advantages observed with propolis translate into improved regenerative and structural results. Comparative studies assessing combined strategies, such as sequential use of propolis and low-concentration TAP, may also be warranted to explore potential synergistic effects while minimizing antibiotic exposure.

CONCLUSION

Within the limitations of this randomized clinical trial, both triple antibiotic paste and propolis demonstrated significant intracanal bacterial count reductions in immature permanent teeth with open apices and apical periodontitis. There was no statistically significant difference in antimicrobial efficacy between the two medicaments, although propolis maintained a consistent downward trend in bacterial load over the medicament period, while triple antibiotic paste exhibited a modest rebound.

Given its broad-spectrum antimicrobial activity, favorable biocompatibility, absence of discoloration risk, and lack of antibiotic-related resistance concerns, propolis represents a promising natural alternative to triple antibiotic paste for intracanal disinfection in regenerative endodontic procedures. Larger, multicentre trials with standardized protocols and long-term clinical follow-up are warranted to confirm these findings and to determine their implications for root maturation and periapical healing outcomes.

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