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EFFICACY OF ASIATICOSIDE AS AN INTRACANAL MEDICAMENT ON BACTERIAL LOAD REDUCTION IN PRIMARY INFECTED ROOT CANALS: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Objective: This research aimed to clinically study the effectiveness of asiaticoside as intracanal medication compared to the commonly used medicaments (Ledermix and $Ca(OH)_2$) in the reduction load of bacteria in necrotic teeth.

Materials and Methods: This study comprised 36 patients with single-rooted, single-canal necrotic teeth who suffered from chronic periapical periodontitis.

Before any clinical procedures, aseptic control measures were implemented. Access cavities were made, and pre-disinfection samples (S1) were obtained immediately afterward, before root canal cleaning and shaping.

The subjects were divided into three groups depending on the nature of the intracanal medicament utilized ($Ca(OH)_2$), Ledermix, and asiaticoside. A second set of samples (S2) was collected one week after administering the intracanal medicaments. Both samples were transported in blood agar dishes for anaerobic culturing in the microbiology lab. The evolution of bacterial growth was measured as colony-forming units (CFUs) and Calculated by manual counting technique. The antibacterial effectiveness of intracanal medicaments was assessed by calculating the percentage reduction in bacterial colonies from S1 to S2.

Results: All evaluated intracanal medicaments showed a significant reduction in CFUs from S1 to S2 ($P<0.05$). Asiaticoside and Ledermix had significantly lower CFUs than Ca(OH)2 ($P < 0.05$), however, there was no significant difference between them ($P > 0.05$).

Conclusion: Asiaticoside might be considered a potential root canal medicament due to its equivalent anti-microbial impact with Ledermix and greater efficacy than $Ca(OH)_2$ medicament.

KEY WORDS: Asiaticoside, $Ca(OH)_2$, Intracanal medicaments, Ledermix.

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INTRODUCTION

Bacteria play a central role in causing apical periodontitis. Consequently, endodontic treatments focus on eliminating these microbes in the system of root canals. This microbial removal is accomplished through chemomechanical debridement.[1] The use of an instrument panel and irrigation only does not eliminate microorganisms from the root canal. However, using an interappointment medicament has significantly improved cleaning after chemomechanical processes. Calcium hydroxide ($Ca(OH)_2$) is one commonly used substance in the canal for treating medical conditions because it effectively eliminates most root canal bacteria due to its high pH,[2] ability to dissolve tissue, and capacity to promote the formation of mineralized tissue. Additionally, it is biocompatible.[3] Nevertheless, it is incapable of eliminating definite resistant bacteria, such as Enterococcus faecalis. [4] Besides may decrease root fracture resistance.[5] Ledermix is a useful intracanal medication that comprises 1% triamcinolone (TAA) and 3% demeclocycline (DOC). This formulation was initially recommended for endodontic applications by Schroder and Triadan. Its main advantage appears to be linked to the anti-inflammatory effects of the corticosteroid, rather than its antibacterial properties. [6]

Root canal treatments require medicaments that are both highly effective against bacteria and compatible with body tissues, as they can interact with the surrounding periapical area. When choosing these medications, it is crucial to assess their therapeutic benefits about any potential toxicity to cells. An ideal medicament should have strong antibacterial properties while minimizing harm to the host's tissues.

For centuries, herbs have been utilized in clinical practices. Recently, researchers have employed scientific methods to validate certain herbs' efficacy and explore how they function.[7-18]

Tropical areas have been famous for their favorable climate asiatica is one of the most widely producing herbs.[19] Asiaticoside (AC) is a major bioactive metabolite with a triterpenoid saponin, which is defined by a 30-carbon skeleton that forms a pentacyclic shape and has a glycosylated side chain.[20] Centella asiatica is a herbal medicine that has been widely used and is known to be effective in healing skin conditions,[21] which possess antioxidative, and anti-inflammatory properties.[22] [23] Asiaticoside has high antibacterial activity regarding E. faecalis in periapical infections which has been investigated by Wahdany et al.[24]

Alazemi et al. studied and highlighted AC's potential as a beneficial complementary to traditional intracanal medicaments such as Ca $(OH)_2$ and TAP, specifically in improving the possibility and production of DPSCs. Asiaticoside properties, containing its antioxidant, osteogenic variation capabilities, and anti-inflammatory, it's recommended for its suitability in utilizing endodontic recovery, specifically in young teeth with wide apical foramina. [13]

Therefore, this comparative research aimed to clinically study the antibacterial effectiveness of Asiaticoside in the form of an intracanal medicament compared to the commonly used medicaments (Ledermix and $Ca(OH)_2$) on the decrease of bacterial count in necrotic teeth.

METHODOLOGY:

Sample size Determination:

In a prior work (19), the sample size was calculated using G*Power 3.1 software given by Heinrich Heine University in Dusseldorf, Germany. The study aimed to include at least 10 patients in each group with an α-type error of 0.05 and power β of 0.80. Hence, a total of 36 teeth (from 36 patients) exhibited clinical and radiographic signs of pulp necrosis (Figure 1). This research involved individuals with asymptomatic apical periodontitis. In addition, these teeth were picked among patients seeking treatment at Mansoura University's endodontic clinic.

Study Design:

This study with approved by the Ethical Committee of the Faculty of Dentistry, Mansoura University (ID: A0209023RC) and registered in Clinical Trials.gov (ID: NCT06566508). This study was done in the Faculty of Dentistry, Department of Endodontics, Mansoura University, from January 2024 to July 2024.

Eligibility criteria:

The teeth that were used in the trial were chosen according to strict inclusion/exclusion guidelines. Inclusion criteria included teeth with straight roots and a straight canal in anterior and premolar necrotic teeth suffering from apical periodontitis related to chronic necrosis of pulp tissue in people aged 20 to 60. Exclusion criteria included patients who took antibiotics in the previous three months, complaining of systemic disease or even the inability to apply a strict rubber dam isolation, and periodontally affected teeth with a periodontal pocket greater than 3mm.

Randomization and blinding:

During the microbiological analysis, a blinded assessment was used, and sample identities were anonymized such that the analyst had no idea which sample belonged to which individual or phase. The envelope approach was employed to randomize. This is performed by employing an opaque sealed envelope with a code identifying a patient and the group's name. For the new case, the in-line envelope was chosen and opened to begin the intervention.

Gel preparation:

Prof Dr Fareed Badria's liver research lab at the Faculty of Pharmacology, Department of Pharmacognosy, Mansoura University, developed our Asiaticoside gel. The gel was made using the specified amount of Carbopol and the concentration of Asiaticoside employed was 25ug/mL.

Informed consent:

Each patient was presented with a signed consent document from the ethics committee of Mansoura University's dentistry faculty, which confirmed that the patient completely understood the study methods and associated dangers.

Collection of samples and clinical procedures:

Scaling and root planning effectively removed all plaque and calculus from the tooth structure. The initial stage of access cavity preparation involved removing previous restorations and caries with sterile quick burs and appropriate cooling. The operative site was sterilized with 30% hydrogen peroxide and 3.5% sodium hypochlorite, which was deactivated with 5% sodium thiosulfate before proceeding for the second stage, which comprised exposing the pulp chamber and complete deroofing under strict rubber dam isolation and utilizing new sterile fast burs.

Pre-disinfection sample (S1):

The cavity was filled with a sterile saline solution, and a #15 K-file from Dentsply-Sirona, Balaigues, Switzerland, was utilized to verify the previously determined working length as computed radiographically with the help of an apex locator. A small #15 H-file (also from Dentsply-Sirona, Balaigues, Switzerland) was then introduced into the root canal up to the determined working length, employing a gentle filling motion to eliminate debris and necrotic tissue, which was subsequently collected in the saline solution.[25]

Cleaning and Shaping:

The root canals were prepared using Protaper Gold files [10] (Dentsply-Sirona, Ballaigues, Switzerland) up to the F4 instrument (40/06). This was followed by irrigation with 5 mL of 2.5% NaOCl via a 27-gauge side-vented needle (Endo-Eze; Ultradent). The root canals were irrigated with ten mL of saline solution, followed by three minutes

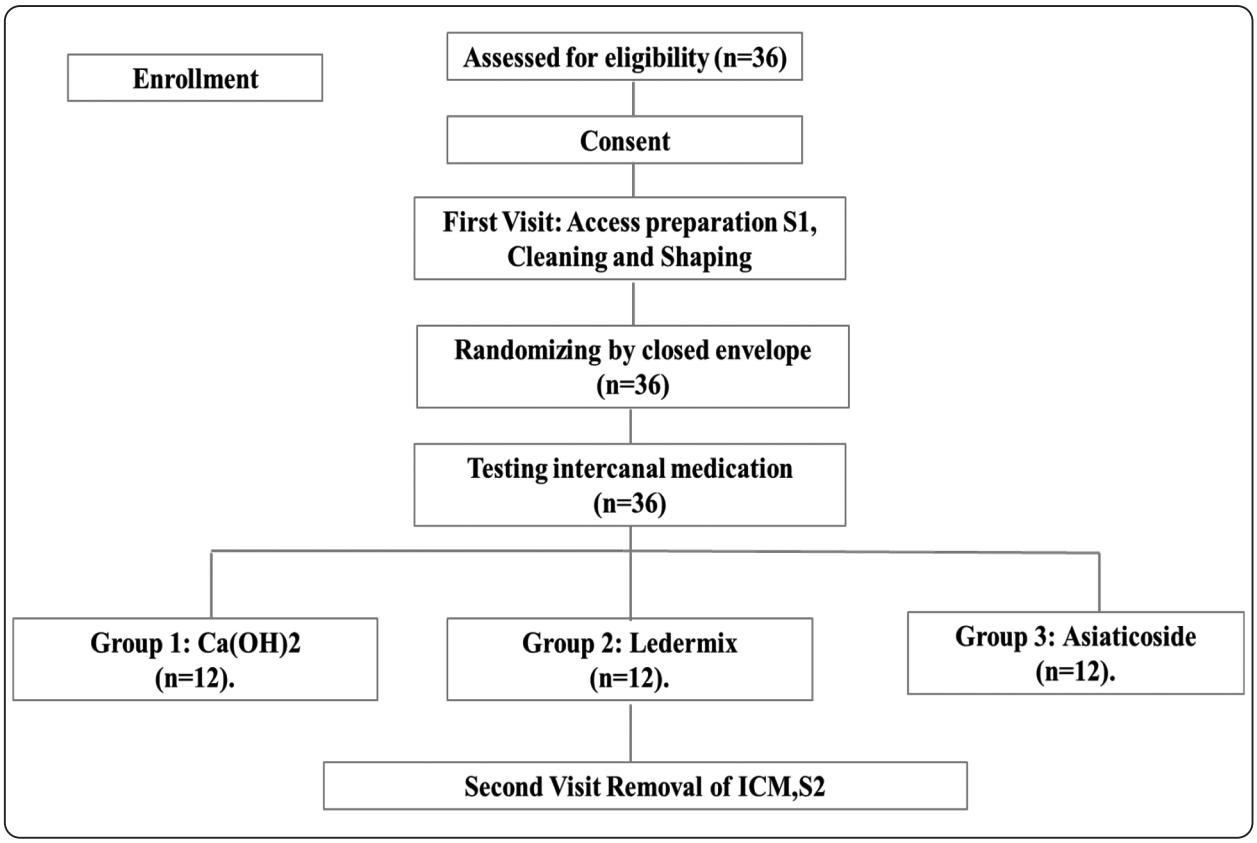


Fig. (1): Flow chart showing a summary of study design and treatment procedures.

of treatment with 17% ethylenediaminetetraacetic acid (EDTA) to cease the impact of NaOCl before placing intracanal medicaments.[26]

Placement of Intracanal medication:

After the chemo mechanical preparation, A study was conducted after the division of the thirty-six teeth with pulpal necrosis and chronic periapical periodontitis, categorizing the subjects randomly into three distinct groups based on the intracanal medication applied. Group 1 (n=12) received Calcium Hydroxide (MetaBiomed., LTD, Cheong-won-gun, Chungcheong-do, Korea). Group 2 (n=12) was treated with Ledermix paste (Lederle Laboratories, Wolfatshausen, Germany). Group 3 (n = 12) was administered Asiaticoside, which was prepared at the Faculty of Pharmacy, Mansoura University.

The root canals were dehydrated by utilizing sterile paper points and placing the previously mentioned intracanal medicaments was taken place according to the group selection. Lentulo spiral was utilized to place the intracanal medicaments. Sealing of access cavity with Cavit (ESPE, Seefeld, Germany) and light-cured resin (Z-250, 3 M Dental Products, St. Paul, MN, USA).

Second Sampling (S2):

Following a week, the patients were called back, and stringent rubber dam isolation along with sterile control measures were put in place. The teeth were made accessible, and the medications were flushed out using a saline solution (5 mL) before the second sampling (S2), as documented earlier. After all signs and symptoms had resolved and the canals were clean and dry, a single Protaper Gold gutta-percha

cone along with Bioceramic sealer was utilized for obturation. The access cavities were then restored.[27]

Anaerobic culture method:

The test tube lids were partly opened, and paper points were quickly inserted into the BHI broth media to maintain anaerobic conditions. The collected specimens were delivered to the microbiology lab at Mansoura University's Faculty of Medicine within 10 minutes. The broth medium was inoculated onto blood agar media plates (Oxoid) using a bacteriological loop. The culture plates were placed inside the anaerobic gas jar, together with the attachments, which included an anaerobic indicator strip and an anaerobic gas bag. The jar was then incubated at 37°C for 24 hours.[28] After 24 hours, CFUs were counted manually to determine bacterial proliferation. The bacterial count in anaerobic culture was calculated using CFUs, considering the dilution and inoculation conditions CFU= Count on plate * inoculation factor * Dilution factor = CFU / 0.1 ml.

Analysis of microbiology:

To assess the effectiveness of the antibacterial properties of the materials being studied, samples taken from the root canals (S2 and S1) were analyzed through anaerobic bacterial culture to determine the bacterial count present. To explore this, CFUs were manually counted, and the percentage of bacterial reduction was calculated before and after chemomechanical preparation and medication delivery.

Statistical analysis:

GraphPad Prism was used to carry out statistical analyses. Data normality was evaluated using the Shapiro-Wilk test. The data was non-parametric. The Wilcoxon test was used to measure the efficacy of each root canal disinfectant. Kruskal Wallis, followed by post-hoc Dunn, was used to determine the difference between S1 and S2 of the three materials evaluated.

RESULTS

The study included patients aged between 27 and 52 years, with an average age of 34.5 years. A total of 36 patients participated, comprising 12 females and 24 males. The teeth examined throughout this research were central and lateral incisors, canines, and bicuspids, all having a single root canal. Notably, there were no reported dropouts during the study. Microbiological analysis of samples from the dental crown and surrounding tissues revealed no signs of bacterial growth.

Comparison of CFUs within the intragroup:

The CFUs decreased significantly following the application of the ICM. Asiaticoside decreased bacterial counts from 4.15 * 104 CFU/mL to 100 CFU/mL. Ledermix reduced CFUs from 7.95*103 to 450 CFU/mL. Ca (OH)2 reduced bacterial burden from 8.85*103 CFU/mL to 1900 CFU/mL (Figure 2).

Intergroup comparison of CFUs:

As to S1 there was no significant difference in all three tested groups ($p > 0.05$) (Figure 3). Regarding S2, Asiaticoside and Ledermix showed significantly lower CFUs than Ca $(OH)_2$ ($p < 0.05$). There was no significant difference between Asiaticoside and Ledermix ($p > 0.05$) (Figure 4). There was no significant difference in the percentage of bacterial reduction between Asiaticoside and Ledermix. Asiaticoside decreased bacterial populations by 99.98%, while Ledermix achieved a reduction of 99.79%. In contrast, calcium hydroxide (Ca(OH)2) lowered bacterial counts within the root canals by 93.43% (see Table 1).

TABLE (1) Median and range values (CFU/mL) of bacteria prior to and following ICM treatment.

	$Ca(OH)_2$	Ledermix	Asiaticoside	Test of significance
S1	41500^{Ab} (900-5600000)	7950^{Ab} (800-1000000)	8850^{Ab} (900-3200000)	Kw=0.7281 P=0.6948
S2	$1900(0\text{-}7000)^{Aa}$	$450(0\text{-}1100)^{Ba}$	$100(0\text{-}1000)^{Ba}$	Kw=12.92 P=0.0016
Bacterial reduction Percentage	93.43% (77.78%-100%)	99.79% (91.76%-100.0%)*	99.98% (97.70%-100.0%)*	Kw=11.53 P=0.0031
S1&S2 Comparison	P<0.001*	P<0.001*	P<0.001*	

The parameters are described as median (minimum to maximum). KW: Kruskal Wallis test.

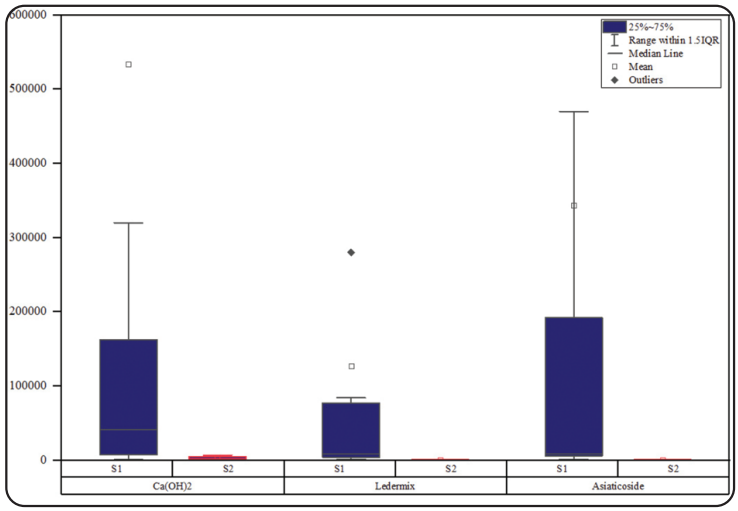
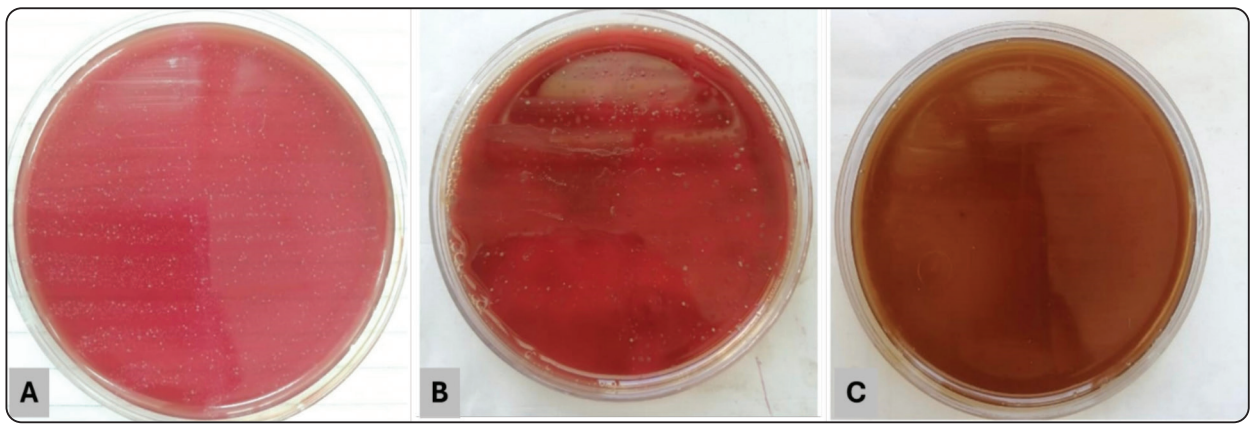


Fig. (2) Box plot showing the change in the number of CFUs before and after application of (Ca (OH)2, Ledermix, and Asiaticoside).



Figs (3) A to C: Bacterial growth on the culture plates of the first samples. (A) Calcium hydroxide; (B) Ledermix; (C) Asiaticoside.

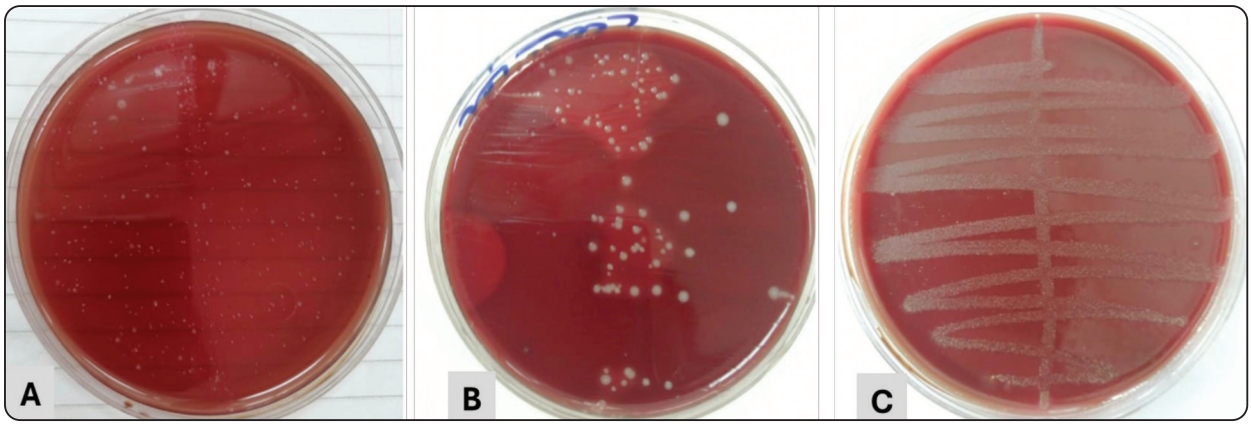


Fig (4) A to C: Bacterial growth on the culture plates of the second samples. (A) Calcium hydroxide; (B) Ledermix; (C) Asiaticoside

DISCUSSION

Intracanal medication is critical to root canal therapy success. As bacteria become more resistant to antibiotics, there is a huge increase in the need for the development of other antimicrobial classes to battle illnesses. It is widely acknowledged that natural resources have a substantial impact on human survival. Recently, there has been a strong emphasis on testing many plant extracts for their capacity to battle bacteria that cause tooth decay and periradicular illness. Researchers are exploring herbal alternatives in endodontics due to the continual rise in antibiotic-resistant germs and the harmful effects caused by current drugs.[29] The primary benefits of using herbal derivatives in dentistry include cost-effectiveness, ease of access, lower toxicity, and no documented incidences of pathogen resistance thus far. After evaluating the available literature, it was revealed that Asiaticoside can be employed as a safe medicament and a potential complement to bone healing in the field of endodontics.[28]

This work aimed to clinically analyze the effect of Asiaticoside as an intracanal medicine in reducing bacterial load in necrotic teeth, evaluated to the regularly used medicaments like $Ca(OH)_2$ and Ledermix.

This research employed microbiological bacterial culture techniques to assess the antibacterial effectiveness of the medications being tested. This method is widely accepted as the gold standard for microbiological counting and identification of colony-forming units (CFU). While the culture method has its limitations, multiple investigations have proven a definite relationship between treatment effectiveness and a reduction in the quantity of bacteria.[30, 31] A rubber barrier was used to separate the teeth, reducing the possibility of erroneous positive results. Both the rubber dam and the tooth were cleaned, and specimens were collected to ensure sterility. Following that, an aseptic bur was used to access the pulp chamber.

Typically, clinical studies gather bacteria samples from the canals at three distinct stages, known as S1. The first stage happens following the initial access to determine the presence of infection in the canal at the time of therapy. S2 refers to the period following the cleaning and shaping treatment but before the canal medication is applied. S3 refers to when the canal is entered again after the medicine has been discontinued. There was no significant difference found between S2 and S3.[32] Thus, in our study, we prefer to employ S1, which consistently produces positive findings in 100% of cases involving teeth

with periradicular lesions, as these teeth are more likely to have infected canals. S2 shows the effect of intracanal medication on the bacterial burden.

Furthermore, a recent study discovered that bacteria levels decreased continuously as the therapy progressed. S1 showed a progressive deterioration at each stage of the treatment. Following the construction of the access cavity at S1, all sampled teeth tested positive for germs. There was no significant statistical variation observed between the groups, indicating that the subjects were similar at the start of the experiment.

In this research, teeth from the anterior and premolar categories that possess a single root canal were chosen for the study. These teeth were selected due to their typically larger, straight canals, which could lower the chances of errors occurring during the cleaning and shaping process. Besides, according to Smith et al, [33] reported that avoiding infection from other canals in multi-rooted teeth is challenging.

The findings of this investigation revealed that Asiaticoside had a greater effect on bacterial load reduction than Ca $(OH)_2$, whereas Asiaticoside and Ledermix had a comparable effect. Bacterial presence has a substantial impact on the development of post-treatment problems because persistent bacteria can cause infection, inflammation, and, eventually, treatment failure. Thus, reducing bacterial load is an important sign of clinical effectiveness in root canal therapy. Effective bacterial reduction reduces the danger of reinfection and promotes better healing results, hence contributing to the procedure's long-term success.

In our investigation, Ca $(OH)_2$ demonstrated minimal antibacterial effects compared to other medications. This conclusion was drawn from earlier research indicating that Ca(OH)2 was ineffective in eliminating bacterial territory within the system.[34] Furthermore, a study claimed that using a Ca (OH)2 paste was not effective in eliminating E. faecalis from the outer surface of the dentinal tubules. The buffering activity of dentin hydroxyapatite on the hydroxyl ions of $Ca(OH)_2$ can explain this matter adequately. This buffering action works by giving the proton in the hydroxyl layer of hydroxyapatite.[34] Another researcher found that the pH level of Ca(OH)2 might not be high enough to effectively eliminate certain bacteria, such as E. faecalis, which can resist pH levels of up to 11.5.[35]

According to the findings, utilizing Ledermix as an intracanal medicine resulted in fewer microbiological colonies on the experimental plates than Ca $(OH)_2$. This is demonstrated by the demeclocycline hydroxide and triamcinolone acetonide presence,[36] The activity of Ledermix, known for its antibacterial properties and recognized as an anti-inflammatory agent, is released into the root canal and diffuses through the dentinal tubules to enter the systemic circulation, accessory canals, and apical foramina.[37] These results are individuality from the research by Hegde et al, [38] which determined that Ledermix had higher capability as an antimicrobial intracanal medication than $Ca(OH)_2$. Asiaticoside, a key triterpene derivative found in Centella asiatica, serves as a unique therapeutic agent that encourages the development of both soft and hard tissues, as well as the osteogenic differentiation of human periodontal ligament cells (HPDLCs).[39]

There are various studies have shown the proper antimicrobial activity of Asiaticoside against intracanal microorganisms.

Soyingbe et al. demonstrated that C. asiatica extracts had good antibacterial activity as well as anti-proliferative effects on selected cancer cells. Given the extracts' high antibacterial activity, the plants may work as an immunological booster, preventing infection in immunosuppressed cancer patients. This is further supported by the plants' antiproliferative potential, bacteriostatic and bactericidal properties, and their capacity to block bacterial efflux pump systems.[40]

Xie et al demonstrated flavonoids' antibacterial mechanisms, including inhibition of nucleic acid synthesis, inhibition of cytoplasmic membrane function, inhibition of energy metabolism, inhibition of attachment and biofilm formation, inhibition of the porin on the cell membrane, alteration of the permeability of the membrane, and attenuation of pathogenicity.[41] There are regulated studies conducted for the evaluation of Asiaticoside against endodontic pathogens. Further longitudinal studies can be carried out with microbial evaluation to justify the results obtained, focusing on exploring the long-term effect of Asiaticoside on periapical healing, its impact on different bacterial strains, and its performance in more complex root canal systems would valuable direction for future studies.

CONCLUSION

Our study upholds the usage of Asiaticoside as a potential root canal medicament owing to its low-cost availability and antibacterial properties.

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Data availability:

This study is part of an MSc thesis at Mansoura University. The information underlying the results of this research can be obtained from the corresponding author upon a reasonable request.

Declarations of Ethics approval and consent to participate:

The Ethical Committee of the Faculty of Dentistry, Mansoura University, approved this study (protocol ID: A0209023RC). All selected participants were requested to provide written informed consent following the guidelines ethical, the Faculty of Dentistry, Mansoura University.

Competing Interests:

The authors declare no conflicts of interest.

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