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Murraya koenigii (L.) Spreng and Tinospora cordifolia (Willd.) : Potential antimicrobials against Treponema denticola - an Invitro analysis

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ABSTRACT

BACKGROUND & OBJECTIVE: Endodontic infections are polymicrobial in nature and commonly involve anaerobic bacteria such as Treponema denticola, a spirochete also associated with periodontal disease. Increasing interest in herbal alternatives has led to the investigation of traditional medicinal plants for dental infections. However, the antibacterial activity of Murraya koenigii (L.) Spreng and Tinospora cordifolia (Willd.) against T. denticola has not been previously reported. This study aimed to evaluate the antibacterial efficacy, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) of ethanolic leaf extracts of M. koenigii and T. cordifolia against T. denticola.

METHODOLOGY: An in vitro experimental study was conducted using the Kirby–Bauer disc diffusion method to assess the zone of inhibition (ZOI) of M. koenigii (Group 1) and T. cordifolia (Group 2) extracts against T. denticola. Triple antibiotic paste (Group 3) served as the positive control, while sterile water was used as the negative control. MIC and MBC values were determined using the serial dilution method.

RESULTS: Group 1 exhibited a greater ZOI (18.09 ± 1.99 mm) compared to Group 2; however, both were significantly lower than the positive control ($p < 0.001$). MIC results indicated bacteriostatic activity for M. koenigii, whereas T. cordifolia demonstrated bactericidal effects.

CONCLUSION: Both Murraya koenigii (L.) Spreng and Tinospora cordifolia (Willd.) showed promising antibacterial activity against T. denticola, suggesting their potential use as intracanal medicaments for reducing root canal pathogens.

KEYWORDS: Anti-Bacterial Agents, Murraya, Tinospora, Treponema denticola.

INTRODUCTION

In primary teeth, root canals harbor more bacterial species, and the increased prevalence of anaerobic species leads to irreversible pulp damage and, subsequently, pulp necrosis. The various clinical signs and symptoms are due to a combination of aerobic and anaerobic bacterial species in the infected root canals. The final goal of endodontic therapy is to remove all pathogenic bacteria from the root canal system. Unfortunately, it cannot completely remove most bacteria that cross the apical foramen and reach the periapical tissue. They consequently lead to failure of endodontic treatment [1].

A study highlights that Fusobacterium nucleatum is the most prevalent bacterial species in endodontic infections of primary teeth, with other obligate anaerobes, such as Treponema denticola, also common. Prevotella intermedia, Porphyromonas gingivalis, and Enterococcus faecalis are strongly associated with teeth exhibiting past pain and pulpal necrosis [2]. Additionally, microbiological similarities between the root canal microbiome and periodontal pockets suggest that these species may contribute to periradicular lesions after endodontic failure. This indicates a complex microbial interplay in the etiology of such conditions [3].

Treponema spp., a Gram-negative spirochete, is a key periodontal pathogen prevalent in subgingival plaque. Beyond endodontic infections, it is among the 49 Treponema species in the oral microbiome most strongly linked to periodontal disease, signifying its role in oral microbial pathogenesis [4].

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To reduce bacterial infections during endodontic treatment of primary teeth, Triple Antibiotic Paste (TAP) has been used as an intracanal medicament because it requires no instrumentation, is non-invasive, and is less time-consuming. It is a combination of antibiotics, minocycline 100mg, metronidazole 400 mg, and ciprofloxacin 200 mg in a ratio of 1:1:1 that can sterilize infected root canals. Nevertheless, TAP's disadvantages include tooth discolouration. These altered dentin mechanical properties make teeth more brittle and reduce dentin microhardness [5,6].

Therefore, using natural plant-based medications is a good alternative to address the drawbacks of existing medications, given their easy availability, greater tolerance, and lower incidence of side effects. Due to their effective antibacterial, anti-inflammatory, analgesic, and bio active properties, herbs are increasingly used in dentistry to treat various infectious disorders. Among various medicinal plants, Murraya koenigii and Tinospora cordifolia are widely used herbs in Ayurveda. Curry leaf, or M. koenigii, is a member of the Rutaceae family. It is a relatively small, evergreen tree native to South Asian nations. Several medical conditions are treated with different components of M. koenigii. This plant has been reported to have antimicrobial, antioxidant, antiulcer, cytotoxic, and cholesterol-lowering properties [7].

Meanwhile, T. cordifolia, commonly called heart-leaved moonseed plant, is a herbaceous vine belonging to the Menispermaceae family and is extensively employed for therapeutic purposes in Australia, Africa, and Asia. The plant is of great significance in medicine because of its anticancer, antifungal, antibacterial, anti-inflammatory, antispasmodic, antidiabetic, antiarthritis, and antineoplastic properties [8].

Despite substantial research into their antimicrobial activity, there is limited evidence of antibacterial activity against Treponema denticola.Considering the medical significance of these plant leaves, the present study aimed to compare and assess the antimicrobial properties of M. koenigii and T. cordifolia against T. denticola using TAP.

METHODOLOGY

The investigation was conducted for 6 months in a lab at Universiti Teknologi MARA using an in vitro experimental study design, which the institution's ethical committee approved (REC/10/2022 (PG/MR/251). The sample size was estimated using the G Power software. **Preparation and culturing of bacteria :** A bacterial strain of T. denticola ATCC 35405 was obtained from the American Type Culture Collection (ATCC, USA). A freeze-dried bacterial preparation was retrieved from the vial and reconstituted in BHI broth. The BHI broth was kept in an anaerobic jar with gas packs (AnaeroGen system Oxoid) in an incubator for a week at 37°C. The stock was subcultured onto BHI agar plates and incubated anaerobically in an AnaeroGen incubator (Oxoid) at 37°C for 48 hours using anaerobic gas packs. **Preparation of ethanolic extract from herbal leaves:** The mature leaves of M. koenigii and T. cordifolia plants were obtained from the nursery. Species confirmation was received from the Herbarium Universiti Kebangsaan Malaysia, with voucher numbers ID064/2023 (M. koenigii) and ID067/2023 (T. cordifolia). The ethanolic extracts of both herbal plants' leaves were prepared, as they yield higher levels of bioactive compounds with antimicrobial and antioxidant properties. The technique described by Troung et al. was used for the preparation with minor modifications [9]. **Preparation of positive control (TAP):** The coating was removed from the pills containing ciprofloxacin (Ciprodac ® 500 mg, Cadila Pharmaceuticals Ltd.), metronidazole (Axcel ® 400 mg, Kotra Pharma), and doxycycline (100 mg, Duopharma). Using a sterile mortar and pestle, the tablets were powdered and mixed evenly with sterile water in a 1:1:1 ratio to obtain a final concentration of 1.0 mg/mL [5]. **Disc diffusion method:**The antibacterial effects of herbal plant leaves, including Group 1 (M. koenigii), Group 2 (T. cordifolia), and TAP (Group 3), were assessed by using the Kirby disk diffusion method. Sterile water was used as a negative control (Figure-I).

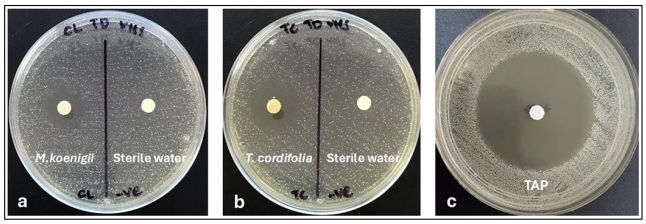
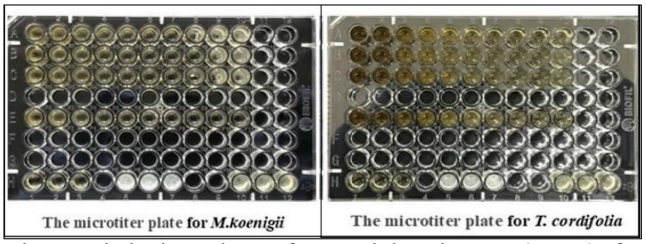


Figure - I (a, b, and c): The antibacterial activity of Murraya Koenigii, Tinospora Cordifolia and Triple antibiotic paste respectively against Treponema denticola. Sterile water was used as negative control.

Minimal inhibition concentration (MIC) and Minimal bacterial concentration (MBC):The serial dilution method determined the Minimal Inhibition Concentration (MIC) of M. koenigii and T. cordifolia against T. denticola [10] (Figure II). Meanwhile, 100 µl of BHI broth was added to each well in rows A, B, and C of the 96-well plate, with a maximum of 10 wells. Next, 100 µl of plant extract with its initial concentration of 500 mg/ml was placed in the first well of rows A, B, and C. Two-fold serial dilutions were performed from well 1 to well 10, resulting in a final concentration range of 0.49 to 250 mg/ml. Finally, 10 µl of bacterial culture was added to each well. In row E, a blank control was done by serial diluting the extract in broth without bacteria. As the growth control, triplicate wells containing BHI broth with bacteria were used, whereas triplicate wells containing only BHI broth served as the sterility control. Furthermore, triplicate wells containing TAP with bacteria serve as the positive control. After completing the two-fold serial dilution, the plates were incubated in the anaerobic jar with the gas pack for 24 hours at 37°C. The same procedure was repeated for another plant extract. After 24 hours of incubation, the OD at 600 nm was measured in the wells using a microplate reader. The MIC was defined as the minimum extract concentration with a difference in OD value (experimental group-blank control group) of less than 0.05 [11].

Following the MIC evaluation, the MBC was determined. Ten microlitres were taken from the wells that preceded the extract's MIC to inoculate the BHI-agar plates. The plates were then placed in an anaerobic jar with a gas pack and incubated for 24 hours at 37°C. After a day, colonies were observed. The MBC refers to the lowest concentration of the extract where no bacterial colonies are detected on the agar plate, suggesting complete bacterial eradication rather than just inhibition.

Figure – II: MIC Plates for M. koenigii, and T. cordifolia Against T. denticola.



The Statistical Package for Social Sciences (SPSS) for Windows, Version 22.0 (launched in 2013), Armonk, NY: IBM Corporation, was used to conduct statistical analyses. The expression of the inhibitory zone in millimetres, along with each group's mean and standard deviation, is included for a microbe in the descriptive analysis. The mean Zone of Inhibition (ZOI) across the four groups was compared using one-way Analysis of Variance (ANOVA) and Tukey's post hoc test. The statistical significance level was set at $P<0.05$.

RESULTS

The mean ZOI (in mm) for T. denticola in Group 1 was 18.09 ± 1.99, Group 2 was 12.91 ± 1.20, and Group 3 was 62.11 ± 1.62. This difference in the mean ZOI (in mm) for T. denticola among the three groups was statistically significant ($p<0.001$; Table I). Multiple comparisons of mean ZOI differences between groups revealed that Group 3 had the highest mean ZOI for T. denticola, followed by Group 2 and Group 1. The mean differences were statistically significant at $p<0.001$, respectively. This was followed by Group 1, which showed a significantly higher mean ZOI for T. denticola than Group 2 ($p<0.001$). This infers that the mean ZOI for T. denticola was significantly highest in Group 3, followed by Group 1 and Group 2 (Table-II).

Table-I: Comparison of mean Zone of Inhibition (in mm) for T. Denticola b/w 4 groups using One-way ANOVA Test.

Groups	n	Mean±SD	Min	Max	P-Value
Group 1	9	18.09±1.99	14.2	20.8	<0.001*
Group 2	9	12.91±1.20	11.0	14.2	
Group 3	9	62.11±1.62	60.0	65.0	

Table - II: Multiple comparison of mean difference in the Zone of Inhibition (in mm) for T. Denticola b/w groups using Tukey's Post hoc Test

(I) Groups	(J) Groups	Mean Diff. (I-J)	95% CI for the Diff.		p-value
			Lower	Upper	
Group 1	Group 2	5.1778*	3.253	7.102	<0.001*
	Group 3	-44.022*	-45.947	-42.098	<0.001*
Group 2	Group 3	-49.20	-51.124	-47.276	<0.001*

Table-III: Minimum inhibitory and bacterial concentrations for Murraya koenigii, and Tinospora cordifolia against Treponema denticola.

Herbal extracts	MIC (mg/ml)	MBC (mg/ml)	MBC/MIC Ratio
Murraya koenigii	7.81	31.25	4
Tinospora cordifolia	3.91	3.91	1

DISCUSSION

With the increasing prevalence of antibiotic side effects and multidrug resistance among microorganisms, it is essential to identify novel antimicrobial sources. Natural remedies derived from medicinal plants rich in bio active compounds have been used as traditional medicine to treat various infectious diseases in humans.

The current investigation was the first in which the T. denticola microbe was targeted by assessing the antibacterial efficacy of M. koenigii and T. cordifolia with TAP against the microbe. The results showed that the ethanolic extract of M. koenigii showed better ZOI as compared to T. cordifolia. Other than endodontic infections, T. denticola is strongly involved in periodontal diseases. In another study, M. koenigii effectively inhibited periodontal pathogen P. gingivalis by triggering the aberrant membrane vesicle formation on the bacterial cell surface [12]. This property is attributed to the presence of carbazole alkaloids present in the organic extracts Similarly, its ethanolic extract showed antibacterial activity against Streptococcus mutans due to the presence of phenolics and gallic acid [13].

The ethanolic extract of M. koenigii leaves and its formulated topical cream have demonstrated antimicrobial activities against S. epidermidis, S. aureus, methicillin-resistant S. epidermidis, and S. aureus [14]. It has been demonstrated that the antibacterial activity of methanolic extract against the organisms, including Klebsiella pneumoniae, Bacillus subtilis, Staphylococcus aureus, and Psuedomonas aeruginosa could be mainly due to the presence of quercetin, a bioactive component in the plant leaves [15]. As compared to chlorhexidine, curry leaf was effective in reducing plaque and gingivitis [16]. It has shown that the polyphenols with antiviral effects present in the plant may help manage SARS-CoV-2 infection [17]. The phytochemical screening of hexane, ethyl acetate, and methanol extracts of M. koenigii (L.) Spreng leaves showed the presence of terpenoids. They proved to be a potent cytotoxic activity agent against HeLa cancer cells [18].

Although in the present study, M. koenigii exhibited better ZOI compared to T. cordifolia, both the herbal extracts have exhibited bactericidal activity against T. denticola as their MBC/MIC ratio is ≤ 4 (Table-III). In the present study results, T. cordifolia at its 250 mg concentration showed 12.91mm of ZOI against T. denticola, which is comparable to the study results that have better antimicrobial activity against S. mutans with the ZOI of 25.6 mm with its ethanolic concentration of 3 mg [19]. The ethanolic extract of T. cardifolia at its 500mg/ml concentration showed maximum antibacterial activity on B. subtilis, Bacillus cereus, Escherichia coli and Salmonella typhi [20].

The T. cordifolia leaf extracts in methanol and ethanol demonstrated an effective ZOI against E. coli. This can be explained by the solvent's inherent and natural microbicidal properties [21]. Along with the antimicrobial properties, the aqueous extract of T. cordifolia showed its antifibrotic activity against oral submucous fibrosis [22]. An aqueous extract of T. cordifolia was found to induce apoptosis-mediated cell death in the oral cancer cells in a concentration-dependent manner [23].

T. cordifolia's gel formulation showed clinically significant antimicrobial and anti-inflammatory effects in periodontitis patients with scaling and root planning [24]. The tinosponone chemical found in the T. cordifolia plant was discovered as a potential lead molecule in the fight against SARS-CoV-2 [25]. TAP was used as a positive control in the present study. It showed a significant inhibition of 62.11mm compared to both extracts. Its drawbacks may limit its long-term use as difficulty in removing the paste from the root canal area and tooth discolouration [5].

LIMITATIONS

One of the current study's distinguishing features is that we tested the efficacy of TAP, a standard intra canal medicament, and a single concentration of 250 mg/ml extract of two distinct herbal leaves against T. denticola. However, it does not accurately imitate the actual state in a root canal environment, as established in vitro. The herbal leaves of M. koenigii and T. cordifolia were employed in this study using ethanol as a solvent. However, phytochemical screening of the leaves was not carried out as it was not within the scope of the study. Additionally, this study will keep looking at the exact mechanism of action that gives them antimicrobial properties. Nevertheless, additional investigation in clinical trials is necessary to evaluate their antimicrobial qualities and possible long-term detrimental impacts on the diverse ecology of the oral cavity. Despite extensive research on the plant's medicinal properties, its potential in dentistry remains largely unexplored. Limited data exists on human trials involving different extraction methods. It is advised to determine the effective dose of each plant component and its associated chemicals for future clinical trials.

Furthermore, future clinical research ought to examine at the antimicrobial effects of varied concentrations of these herbal extracts in combination to determine how they work synergistically to suppress the root canal bacterial infections. The findings of these future investigations may lead to the development of novel, low-cost natural formulations with minimal side effects that are successful in endodontic treatment. These formulations could supplement current commercially available intracanal medicaments that are resistant to bacterial strains in the teeth.

CONCLUSION

Although the findings from the present investigation showed that the 250 mg/ml ethanolic extract of M. koenigii has a better ZOI, both the herbal extracts of M. koenigii and T. cordifolia have exhibited potential bactericidal activity against T. denticola. Hence, both extracts could be used as medicaments against endodontic pathogens. Further studies on these herbal extracts are recommended to explore their synergistic effects.

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Authors Contributions:

Vanishree Shivakumar: Substantial contributions to the conception and design of the work.

Anand S Tegginamani: The acquisition and analysis of data for the work.

Annapurny Venkiteswaran: Interpretation of data for the work.

Nurhayati Mohamad Zain: Drafting the work .

Nurul 'Izzah Mohd Sarmin: Reviewing it critically for important intellectual content

Eddy Hasrul Hassan: Final approval of the version to be published.

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