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RESEARCH ARTICLE

FABRICATION OF TRIPLE ANTIBIOTIC AND CISSUS QUADRANGULARIS CONJUGATED LYOPHILIZED GUIDED TISSUE REGENERATION MEMBRANE AND ITS CHARACTERISATION

Srivarsha R[1], Balaji Ganesh S[1*], Chitra Shivalingam[2], Gurumoorthy Kaarthikeyan[1]

[1]Department of Periodontics, Saveetha Dental College and hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India
[2]Green lab, Saveetha Dental College and hospitals Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India

*** Corresponding author**: **Dr. Balaji Ganesh. S** Reader, Department of Periodontics, Saveetha Dental College and hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India, Email id: balajiganeshs.sdc@saveetha.com

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ABSTRACT

Background: Periodontitis is a severe gum infection that damages the soft tissue and, if untreated, can destroy the bone that supports your teeth.Cissus quadrangularis, a medicinal plant known for its bone healing properties, has been used in traditional medicine for centuries. Antibiotic-laden membranes have gained significant attention due to their ability to prevent infections, which are a major challenge in orthopedic surgeries and bone grafting procedures. The main aim of the study is to fabricate and characterize the triple antibiotic and Cissus quadrangularis conjugated lyophilized membrane for periodontal bone regeneration.

Materials and Methods: 10mg of Cissus quadrangularis was weighed and dispersed in 100 ml of deionised waste and heated at 50 degree centigrade for 24 hrs then the extract was collected using filtration method with wattmann filter paper. 1 g of PEG and Carrageenan (2 g) was dissolved in 100 mL of cissus quadrangularis extract at 60 ◦C using magnetic stirrer under 400 rpm . Triple antibiotics were also added. Following a 24-hour period, the petri plate was dried for 12 hours at 50°C. The membrane was then removed from the petri dish and placed in a desiccator. Following membrane formation FTIR, contact angle, Antimicrobial activity were compared between Cissus quadrangularis membrane and carrageenan (control group) and Group 2 consisted of Cissus quadrangularis membrane, triple antibiotic, and carrageenan (test group).

Results: Tensile strength of the control group is 14.62 N and Test group is 32.13 N. Hence the control group membrane has more tensile strength than the test group membrane. The Test group membrane showed an contact angle average of 75.27 degree and Control group membrane showed an contact angle average of 46.51degree. Hence the control group membrane indicates the better hydrophilic nature of the material. The control group membrane showed better antimicrobial activity than the test group membrane against the tested bacteria (Streptococcus mutans).

Conclusion: The present study results showed a higher tensile strength, good antimicrobial property and enhanced wettability in the prepared novel membrane when compared to the control group. By addressing both the prevention of infection and the promotion of bone healing, this novel membrane builds on existing research and offers a promising solution for use in guided tissue regeneration.

Keywords: Triple antibiotics, Cissus quadrangularis, Guided tissue regeneration, Membrane, Periodontal regeneration

INTRODUCTION

Periodontitis is a severe gum infection that damages the soft tissue and, if untreated, can destroy the bone that supports your teeth[1] It can lead to tooth loss or increased risk of other serious health complications. Periodontitis is usually caused by poor oral hygiene. It begins with plaque, a sticky film of bacteria that forms on the teeth.[2] If plaque is not removed, it can harden into tartar, which is harder to remove. This can cause the gums to become inflamed, leading to gingivitis, the earliest stage of gum disease. Without treatment, gingivitis can progress into periodontitis.[3]Symptoms of periodontitis are swollen, tender, or bleeding gums, receding gums and persistent bad breath.[4] Periodontal bone regeneration is a treatment approach aimed at restoring lost bone and supporting structures in the jaw that have been destroyed due to advanced periodontal disease, like periodontitis.[5] When periodontitis progresses, the bone that supports teeth deteriorates, leading to tooth mobility and, ultimately, tooth loss if not treated. Bone regeneration aims to reverse this damage and rebuild the lost bone. In periodontal bone regeneration, various materials are used to stimulate and support the growth of new bone and tissue. These materials typically act as scaffolds for natural bone regeneration or directly encourage tissue repair. The main categories of materials include bone grafts, barrier membranes, and biologics/ growth factors.[6] Bone regeneration is a complex process that involves the restoration of bone tissue lost due to trauma, disease, or surgical interventions.[7] The search for effective materials and strategies to enhance bone healing has led to the development of innovative biomaterials.[8] Among these, guided tissue regeneration membranes play a crucial role by providing a barrier that protects the site of injury, promotes bone regeneration, and minimizes complications such as infection and delayed healing. One emerging approach is the use of lyophilized membranes, which are dehydrated at low temperatures to preserve the bioactive components and enhance the stability of the material.

Antibiotic-laden membranes have gained significant attention due to their ability to prevent infections, which are a major challenge in orthopedic surgeries and bone grafting procedures. The use of broad-spectrum antibiotics, such as triple antibiotic combinations, has proven effective in reducing the risk of bacterial contamination and post-operative infections.[9] However, beyond infection control, promoting the actual regeneration of bone tissue remains a critical goal.[10] In this regard, herbal and natural compounds have shown potential as bioactive agents that can stimulate bone growth and repair. Cissus quadrangularis, a medicinal plant known for its bone healing properties, has been used in traditional medicine for centuries. Recent scientific studies have demonstrated its ability to promote bone formation and enhance the healing process.[11] The bioactive compounds in Cissus quadrangularis, such as flavonoids and triterpenoids, have been shown to stimulate osteoblast differentiation and mineralization, key processes in bone regeneration.[12] In this context, the combination of a triple antibiotic formulation with Cissus quadrangularis in a lyophilized membrane presents a novel strategy for bone regeneration. This conjugated membrane offers dual functionality: protection against bacterial infection and enhance bone healing.[13] By integrating these two therapeutic agents into a single scaffold, the membrane can provide an ideal environment for bone repair while mitigating the risk of infection- a critical factor in the success of bone grafts and implants. This study aims to fabricate and characterize the triple antibiotic and Cissus quadrangularis conjugated lyophilized membrane for periodontal bone regeneration.

MATERIALS AND METHODS

PREPARATION OF CQ EXTRACT AND MEMBRANE

10mg of Cissus quadrangularis was weighed and dispersed in 100ml od deionised waste and heated at 50 degree centigrade for 24 hrs then the extract was collected using filtration method with wattmann filter paper. 1 g of PEG and Carrageenan (2 g) was dissolved in 100 mL of cissus quadrangularis extract at 60 ◦C using magnetic stirrer under 400 rpm . This pure biopolymer solution is kept as control. Triple antibiotics (Erythromycin, Penicillin, and Amoxicillin) were infused into the biopolymers to create the corresponding membranes in order to fabricate drug-infused membranes. Before being added to the biopolymer solution for membrane casting, a triple antibiotic was combined with double-distilled water. A polystyrene petri dish (90 mm in diameter) was filled with drug solutions (25 mL) in a biopolymer matrix, and the dish was left to dry at room temperature. Following a 24-hour period, the petri plate was dried for 12 hours at 50°C. The membrane was then removed from the petri dish and placed in a desiccator. Group 1 consisted of Cissus quadrangularis membrane and carrageenan (control group); Group 2 consisted of Cissus quadrangularis membrane, triple antibiotic, and carrageenan (test group).

CHARACTERIZATION-STRUCTURAL PROPERTY

Fourier transform infrared (FTIR) spectroscopy

The functional group analysis for the prepared group 1 and group 2 lyophilized guided tissue regeneration

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membrane was done using FTIR spectroscopy (Perkin elmer, USA). The guided tissue regeneration membrane samples were placed to an attenuated total reflectance crystal surface and the spectra were captured within the range of 400-4000 cm-1. Scans were performed across different areas of the sample to investigate the presence of various elements within it.

Field emission Scanning electron microscopy (FE-SEM) analysis

A JEOL JSM-IT800 SEM was used to perform FE-SEM analysis on the newly prepared group 1 and group 2 lyophilized guided tissue regeneration membranes in order to investigate the structural morphology of the membrane. Samples were made after the membranes were cut into tiny pieces with scissors. Following a vacuum-sprayed application of platinum to the sections, FE-SEM analysis was performed at a 500× magnification.

PHYSICAL PROPERTY

Tensile strength

The universal testing machine (Instron Electroplus E3000, USA) was used to evaluate the tensile strength of the newly prepared group 1 and group 2 lyophilized guided tissue regeneration membranes. 10 × 15 mm test samples were used for analysis, with a crosshead speed of 5 mm/min. Forces were applied to the specimens in groups 1 and 2 after the membranes were fitted onto the analyzer. The breaking force was defined as the force at which the scaffold broke. Tensile stress was calculated by multiplying this breaking force by the specimens' area, and tensile strain was defined as the deformation at the breaking force.

Swelling Analysis

To measure the degree of swelling and fluid absorption, the samples from groups 1 and 2 were dry weighed, submerged in 5 mL of 10% PBS solution for an hour, and then wet weighed. After blotting the membrane with tissue paper to get rid of extra PBS solution, it was weighed. Swelling Ratio (SR) = ((W - W0) / W0) × 100% was the formula used to determine the swelling ratios, where W stands for the initial wet weight and W0 for the initial dry weight.

Contact angle analysis

The wettability of the guided tissue regeneration membranes in groups 1 and 2 was assessed using the sessile drop method. Using a micropipette, a droplet of distilled water (2 µL) was applied horizontally to the guided tissue regeneration membrane. The contact angle of the water drop that formed at the interface with the guided tissue regeneration membrane sample was measured using an Ossila goniometer.

ANTIMICROBIAL PROPERTY

Minimum inhibitory concentration

The extract of Cissus quadrangularis was tested for minimum inhibitory concentrations (MICs) using the broth microdilution method. In the assay, the MIC of the Cissus quadrangularis extract containing carageenan and triple antibiotic against S. mutans was evaluated at a distinct concentration level. By adding 2,3,5-triphenyl tetrazolium chloride (TTC) salt, which serves as an indicator, the growth of the bacteria was seen.

RESULTS

Carrageenan is extracted from Seaweeds that contain repeatable units of anhydro galactose and sulfated or non-sulfated galactose repeating units, which is a high molecular weight polymer. Together, carboxylic and sulfate vibrations in the FTIR spectra are reported to validate the formation of carrageenan. Peak indicated in 1100 in carrageenan and 1200 in triple antibiotic.(Figure 1) FE-SEM parameters included 300 X magnification, scale bar was 10 micrometer, working distance was 4.2mm and KV value was set to 3.00KV.

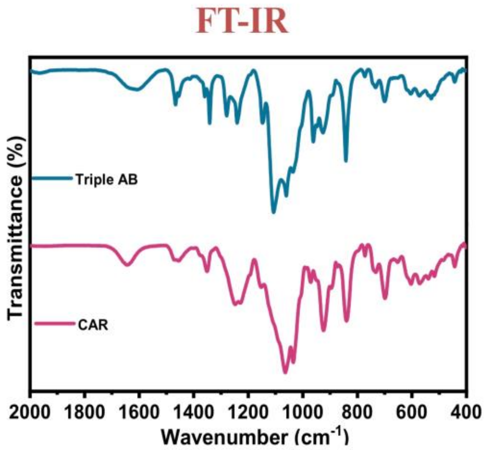

Figure 1. FTIR analysis

The group 1 sample image displays a rough, uneven surface texture with interconnected structures.(Figure 2) The group 2 sample image displays a rough, variable surface texture with interconnected structures.

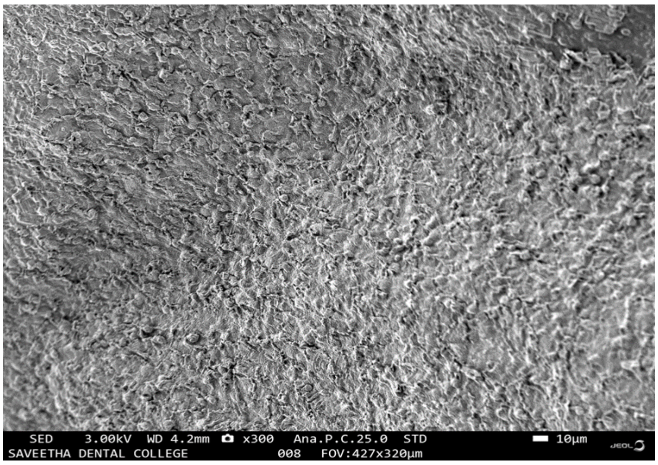

Figure 2. FE SEM image of group 1 membrane

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(Figure 3) Contact angle measurement was used to express the guided tissue regeneration membrane's wettability.

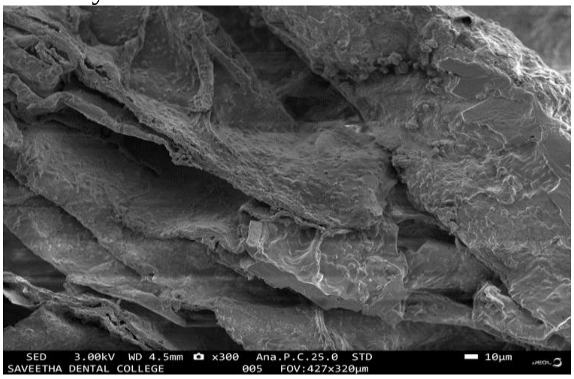


Figure 3. FE SEM image of group 2 membrane

The material's hydrophilicity or hydrophobicity is determined by the contact angle. A lower contact angle suggests that the material is more hydrophilic. In this study, the group 1 membrane showed an contact angle average of 75.27 degree and group 2 membrane showed an contact angle average of 46.51degree. (Figure 4)

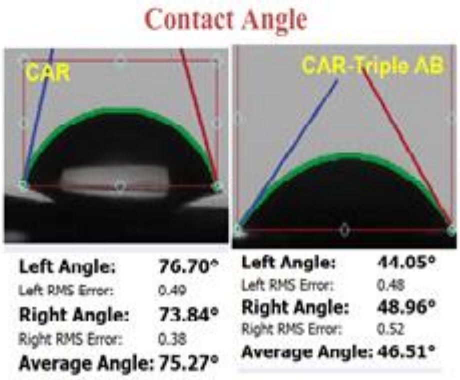
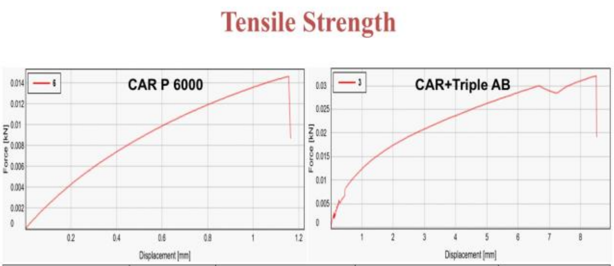


Figure 4. Contact angle analysis

Tensile strength of the group 1 was 14.62 N and group 2 was 32.13 N. Hence the group 2 membrane has more tensile strength than the group 1 membrane.(Figure 5).



Materials Name	Maximum Force [N]	Tensile stress at Tensile strength [MPa]	Tensile strain (Displacement) at Break (Standard) [%]	Tensile stress at Break (Standard) [MPa]
CAR	14.62	10.44	2.89	2.89
CAR+Triple AB	32.13	22.93	21.24	21.24

Figure 5 Tensile strength analysis

The group 2 membrane showed a good antimicrobial activity against the tested bacteria (Streptococcus mutans). Zone of inhibition was found to be an average of 0.358, 0.312, 0.264 at different concentrations of 25µl, 50µl and 100µl; compared to the average value of 0.192 of the control group. (Figure 6&7) This shows an enhanced antimicrobial activity that can be attributed to the triple antibiotic component in the membrane.

Figure 6. The anti-microbial activity

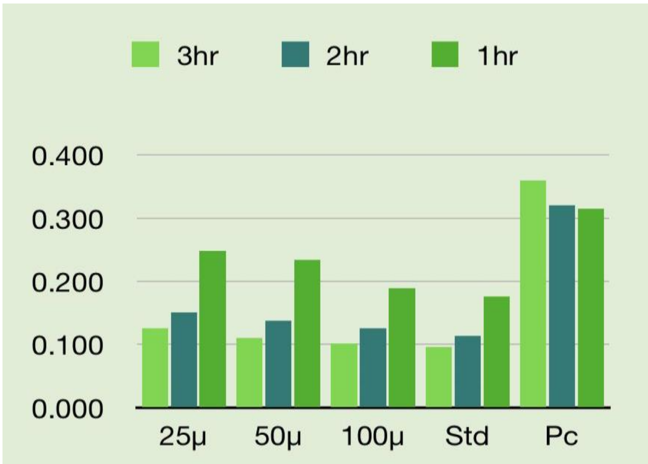


Figure 7. The anti-microbial activity with MIC assay

DISCUSSION

The development of a triple antibiotic and Cissus quadrangularis conjugated lyophilized membrane for bone regeneration is a promising strategy that integrates both periodontal infection control and enhanced bone healing. To fully appreciate the potential impact of this approach, it is important to analyze how it compares and builds upon findings from other research studies in related fields. Several studies have focused on the use of antibiotic-loaded membranes for infection prevention in bone regeneration applications. Wu et al. (2021) explored membranes impregnated with vancomycin and gentamicin for bone regeneration and infection control, showing a dual-functionality membrane similar to the one proposed in this study.[5] However, while these studies focus on bacterial control, they often lack an osteogenic component, limiting their direct role in enhancing bone regeneration.[14] The current study addresses this gap by introducing Cissus quadrangularis, a bioactive plant extract known for its bone healing properties, into the membrane matrix. This dual-action approach could prove superior, offering not only infection control but also active stimulation of bone formation.The use of herbal extracts like Cissus quadrangularis for bone regeneration has gained interest due to their osteogenic potential. Few Studies have explored the efficacy of Cissus quadrangularis in bone fracture healing, demonstrating accelerated bone formation and increased mineralization in experimental models.[15] The flavonoids and triterpenoids present in Cissus quadrangularis have been shown to enhance the proliferation and differentiation of osteoblasts, the cells responsible for bone formation.[16] The inclusion of Cissus quadrangularis in the lyophilized membrane developed in this study adds a unique bioactive component that enhances its bone regeneration capabilities, distinquishing it from purely antibiotic or synthetic membranes.[17]

Tetracycline or amoxicillin significantly decreased the adherence of S. mutans or A. actinomycetemcomitans on the ePTFE, glycolide fiber, or collagen membranes, according to the earlier paper by Chi-Fang Cheng et al. This result suggests that using antibiotic-loaded GTR membranes for periodontal regeneration therapy is beneficial and efficient.[18] Gabriel et al concluded that Four bacterial strains were used to assess the antibacterial activity of the AMX-loaded membranes, which varied depending on the drug and nAp concentrations. SEM/EDX examination revealed extensive mineralization in the simulated bodily fluid (SBF) after 21 days. For dentistry and tissue engineering applications, the investigated electrospun nanocomposite membranes coated with amoxicillin may be a viable fibrous-based antibiotic delivery system.[19] Kalluri et al concluded that The maximum tensile strength of 3.1 MPa and modulus of 39.9 MPa could be achieved at membrane compositions of 8.9 weight percent PLGA, 7.2 weight percent SEP, and 2 weight percent HAp, according to optimization utilizing response surface approach. HPLF proliferative activity was higher in optimized PLGA/SEP/HAp membrane specimens electrospun on a static collector than in tissue culture polystyrene and commercial collagen membrane.[20] Naoyuki kaga et al concluded that the PLGA membranes with pillar and hole patterns had a greater contact angle, which suggested that they were more hydrophobic. However, compared to the non-patterned PLGA membrane, a considerably greater number of MC3T3-E1 cells attached to the grooves, pillars, and holes of the patterned PLGA membranes.[21]

Lyophilization is a widely used technique in tissue engineering for developing scaffolds with enhanced stability and preservation of bioactivity. The process allows for the incorporation of both natural and synthetic materials into a highly porous structure, providing an ideal environment for cell infiltration and tissue growth. The conjugation of antibiotics and Cissus quadrangularis in a lyophilized membrane leverages these advantages.[22]

The porous structure created by lyophilization facilitates the controled release of antibiotics, ensuring sustained antimicrobial activity, while also providing a scaffold conducive to cell attachment and proliferation. This dual-functionality membrane draws on earlier work that developed lyophilized chitosan- based membranes for wound healing, noting their success in creating an environment that promotes both tissue growth and infection control.[23]

The concept of a dual-action membrane that addresses both infection control and bone regeneration is supported by recent research trends. Few authors investigated the combination of bioactive molecules and antibiotics in scaffolds for bone repair, noting that a synergistic approach could significantly improve outcomes in bone regeneration, especially in infection-prone environments.[24] Their findings align with the current study's hypothesis that combining a triple antibiotic with a bone-promoting agent like Cissus quadrangularis could enhance both the speed and quality of bone healing. Comparatively, other dual-action scaffolds, such as those developed by Srinivasan et al. (2020) using antibiotic and growth factor combinations, emphasize infection control but lack the natural osteogenic stimulation provided by Cissus quadrangularis.[25] By integrating both antimicrobial and osteogenic agents in one membrane, the proposed lyophilized membrane may offer a more holistic solution for bone regeneration, particularly in clinical scenarios where infection risk is high, such as in osteomyelitis or post-traumatic bone defects. It is important to acknowledge potential limitations in our study which includes only characterization of the membrane; further nano ct and animal trials are necessary to know the efficacy of the membranes. Future research should also focus on optimizing the concentration of both antibiotics and Cissus quadrangularis to balance antimicrobial action with osteogenic promotion. Moreover, clinical trials will be necessary to confirm the membrane's safety and effectiveness in humans, as much of the current evidence is based on in vitro or animal models.

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CONCLUSION

In conclusion, the integration of a triple antibiotic combination with Cissus quadrangularis in a lyophilized membrane represents a novel and potentially superior approach. Our study results showed a higher tensile strength, good antimicrobial property and enhanced wettability in the prepared novel membrane when compared to the control group. By addressing both the prevention of infection and the promotion of bone healing, this novel membrane builds on existing research and offers a promising solution for use in guided tissue regeneration.

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CONFLICT OF INTEREST

The authors have none to declare.

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