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Evaluating the Bioactive Potential of Cinnamomum Verum Against Staphylococcus Aureus And Methicillin-Resistant Staphylococcus Aureus

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ABSTRACT

Staphylococcus aureus and Methicillin-resistant *Staphylococcus aureus* are the most common causes of skin infections globally. Due to the increase in antibiotic-resistant strains and the numerous side effects caused by conventional synthetic drugs, new antimicrobials must be developed. One such promising source is *Cinnamomum verum, which is* cultivated mainly in the southern regions and northeastern states of India. This research utilizes the potential antibacterial activity of cinnamon, particularly its active component, cinnamaldehyde, which can suppress the production of toxins by disrupting the integrity of bacterial cell membranes. Cinnamon crude extract was prepared from the cinnamon bark using organic solvent extraction. Phytochemical tests of the cinnamon extract revealed the presence of active secondary metabolites, namely alkaloids, saponins, resins and terpenoids. A comparative analysis evaluated the antibacterial efficacy of cinnamaldehyde and ampicillin against Staphylococcus aureus and methicillin-resistant Staphylococcus aureus (MRSA). The results demonstrated that cinnamaldehyde exhibited antibacterial activity comparable to ampicillin, highlighting its potential as an effective alternative for combating these pathogens. The minimum inhibitory concentration (MIC) study of the extract was also determined for further applications. Crude extract was incorporated into different formulations with oil, petroleum jelly, starch and carboxymethyl cellulose, among which starch and petroleum jelly gave positive results. In the future, cinnamaldehyde-infused hydrogel-based topicals could serve as a safer and more accessible alternative for managing *Staphylococcus aureus* infections, particularly in regions where these infections pose significant public health challenges.

Keywords: *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus,* antibiotic-resistant, *Cinnamomum verum,* formulations, oil, petroleum jelly, starch and carboxymethyl cellulose

1. INTRODUCTION

Skin conditions significantly impact quality of life, for which effective and safe therapy is crucial. Researchers are looking for biologically active natural compounds as alternatives to conventional drugs causing a several side effects. *S.aureus* most frequently causes skin infections globally colonizing the skin in approximately 20–30% of the global population. Between 2005 and 2010, a large retrospective cohort

study of 50 million insured individuals identified 2.3 million ambulatory and hospital encounters for skin and soft tissue infections among patients aged 0–65 years[2-5].

There are two kinds of localized *S. aureus* skin infections: primary and secondary. A primary or "spontaneous" cutaneous infection develops as a result of an insignificant skin lesion such as impetigo, furuncles, folliculitis and primary abscesses[2]. The primary lesion for *S. aureus* **impetigo** is a fragile bulla that bursts producing an oozing erosion or crust after rapidly becoming inflammatory and pustular. Staphylococcal impetigo is characterized by the local production of exfoliatin toxins A and B[2]. An **abscess** develops from a sensitive, inflammatory, and highly painful erythematous nodule whose consistency becomes soft gradually, indicating a pus collection. *S. aureus* produces Panton-Valentine leucocidin (PVL), which causes the majority of primary or spontaneous abscesses[2]. *S.aureus* causing **folliculitis** is characterized by hair follicle inflammation manifesting acutely as clusters of red papules typically affecting the face, but it can occur anywhere on the body[6].

Secondary skin infections occur as a result of an existing cutaneous lesion including cellulitis, lymphangitis, secondary wound infections, toxic shock syndrome and secondary abscesses. **Toxic shock syndrome** (TSS) is a severe, toxin-mediated condition that can lead to multi-organ failure, with a reported mortality rate of ~8% in the U.S. (2023). Its incidence ranges from 0.03 to 0.50 cases per 100,000 people[7, 8]. A North Indian study found that 60.3% of pediatric TSS cases had a clear infection source, with 44.5% involving skin and soft tissue infections and 17.5% showing *Staphylococcus aureus* growth[9]. TSS is triggered by superantigen toxins from *S. aureus* and *Streptococcus pyogenes*, leading to cytokine storms and symptoms like high fever, rash, hypotension, and organ failure. Methicillin-resistant Staphylococcus aureus (MRSA) strains are significant contributors, often producing Toxic Shock Syndrome Toxin-1(TSST-1), which drives the exaggerated immune response[7,10]. Enterotoxins have the potential to produce **Staphylococcal scalded skin syndrome** when they spread systemically. This widespread blistering condition primarily affects newborns, young children, and, in rare cases, adults who have underlying medical conditions[2].

Staphylococcus aureus is a nonmotile, Gram-positive, coagulase-positive cocci which expresses a large number of cell surface-associated and external proteins such as cytolytic proteins (T super antigenic factors), immune evasion molecules, and cell wall-anchored proteins. It expresses surface proteins that facilitate attachment to host proteins such as laminin and fibronectin, which are part of the extracellular matrix. *S. aureus* can produce proteases, lipases, deoxyribonucleases (DNase), and fatty acid modifying enzymes (FAME)[11]. Several *Staphylococcus aureus* clones have grown into MRSA through horizontal gene transfer of staphylococcal cassette chromosome mec (SCCmec), a mobile genetic element that encodes the genes mec A or mec C, providing resistance against methicillin, most β-lactam drugs and a variety of other antibiotic classes[12].

In 2023 and early 2024, reports indicate that approximately 13.8 infections per 100,000 population were associated with MRSA, with substantial contributions to hospital-associated infections (HAIS)[3, 4, 5]. Due to the increase in antibiotic-resistant strains such as MRSA and decreased efficiency of existing antibiotics, new antimicrobials must be developed. Cinnamon due to its distinct scent and potent antibacterial properties is one of the most studied plant whose essential oils are extracted from different plant parts of several trees in the genus *Cinnamomum*.

Cinnamomum verum in India is mainly cultivated in the southern regions and northeastern states which comprises active components such as cinnamaldehyde inhibits the growth and suppresses the production of toxins by microorganisms, including MRSA. The major active components include cinnamaldehyde

(85.50%), stigmasterol (3.69%), cadinene (1.37%), (E)-cinnamaldehyde (1.35%), α-amorphene (1.33%), hydrocinnamaldehyde (1.28%), α-cubebene (1.25), and ergosterol (1.09%)[15]. Cinnamaldehyde can be loaded into or conjugated with polymers for sustained or controlled release, which will extend the biological activities' effective action time, reactivity and production of cellular reactive oxygen species and overcome its drawbacks like poor water solubility and light sensitivity[16, 17]. Cinnamaldehyde, a hydrophobic molecule, can disrupt the integrity of bacterial cell membranes by introducing itself into the lipid bilayer. This alters membrane fluidity, disrupting normal functions like transport and signal transduction. It can also cause cellular content leakage and interfere with membrane-bound enzymes, impairing bacterial growth and survival. Sequential soxhlet extraction can produce the crude stem-bark extract of *Cinnamomum verum*[13], which exhibits lethal effects when supplemented with 7.5% NaCl[1].

2. MATERIALS

All the chemicals, glassware and equipment were provided by the Department of Biotechnology, K.C. College

Sample and Chemicals: *Cinnamomum verum* bark, Chloroform (98% purity), Sodium chloride, Ethanol, Sulphuric acid (H_2SO_4), Potassium hydroxide, Sodium dihydrogen phosphate, Disodium phosphate, Ferric chloride, Hydrochloric acid (HCL), Glacial acetic acid, Distilled water, Dimethyl Sulfoxide (DMSO), Carboxymethyl cellulose, Starch, Glycerol, Picric acid

3. METHODOLOGY

3.1 PREPARATION OF CRUDE EXTRACT

The crude cinnamon extract was prepared by solvent extraction using chloroform. 240 ml of Chloroform and 20 g of cinnamon powder were used for preparing crude extract by solvent extraction in a Soxhlet apparatus at 31°C for 5 hours, and the final extract was obtained by evaporating the chloroform overnight.

Figure 1. Crude extract obtained by solvent extraction from *Cinnamomum verum* bark.

3.2 CHARACTERISATION OF CRUDE EXTRACT

- **Phytochemical analysis of the crude extract**

Sr. No	Test	Procedure	Expected Observation
1.	Detection of alkaloids	100 µL extract + 50 µL dil. HCL+ filter it + add a few drops of Hager's reagent to the filtrate	A yellow precipitate
2.	Detection of glycosides	100 µL extract + 50 µL of glacial acetic acid, H_2SO_4 and ferric chloride	A green-blue colour
3.	Detection of flavonoids	100 µL extract + a few drops of NaOH Yellow colour is observed + add 50 µL dil. HCL	Yellow color changes to colourless.
4.	Detection of tannins	100 µL extract + 100 µL ferric chloride solution	Green grey, or dark blue colour.
5.	Detection of saponins	100 µL extract + 100 µL distilled water and shake vigorously	Foam layer formation.
6.	Detection of resins	250 µL extract + 500 µL distilled water	Precipitate formation.
7.	Detection of phenols	100 µL extract + 50 µL ferric chloride solution	Deep blue-black colour.
8.	Detection of terpenoids	50 µL extract + 50 µL chloroform + few drops of conc. H_2SO_4 Shake well and allow to stand for some time.	Formation of the yellow colour layer.

Table 1: Different phytochemical tests for checking presence of alkaloids, tannins, saponins, phenols, terpenoids, resins and glycosides

Fourier Transform Infrared Spectroscopy (FTIR) of the crude extract

In this study, FTIR analysis was carried out to characterize the functional groups present in the crude extract of *Cinnamomum verum* stem bark obtained using chloroform solvent by subjecting a small quantity of the crude extract to FTIR analysis.

3.3 ANTIMICROBIAL ACTIVITY DETERMINATION

Determining the antimicrobial susceptibility of extract against S. *aureus* and MRSA by agar well diffusion

20% and 40% concentration crude extract solution in DMSO and 1:1 ratio concentration Ampicillin antibiotic solution in phosphate buffer saline (pH 6.7) was prepared. Two 20 mL sterile Mueller Hinton (MH) agar butts were prepared. 1 mL of 0.1 optical density (OD) culture of *S. aureus* and MRSA were

added separately in the two molten MH agar butts. The pour-plate method was performed along with punching 4 wells in each agar plate using a sterile cork borer. 50 µl of DMSO (negative control), Ampicillin solution (positive control), and 20% and 40% crude extract were loaded separately in each well on the agar plates. The plates were refrigerated for 10 minutes for pre-diffusion and later incubated at 37˚C for 24 hours. The zones of inhibition were observed and measured after 24 hours of incubation.

Determining Minimum Inhibitory Concentration (MIC) of the crude extract

The crude extract was first prepared at a 40% concentration in DMSO. Serial two-fold dilutions of the stock solution were performed across the wells to achieve decreasing concentrations of the extract. As diluent, 100 µL of sterile nutrient broth was added to each well of the 96-well microtiter plate along with 50 µL of the bacterial culture (either *S. aureus* or MRSA adjusted to an optical density (OD) of 0.1 at 540 nm), and 50 µL of the stock solution were added. The positive control wells contained 50 µL of the bacterial culture and 50 µL of nutrient broth without the crude extract to confirm normal bacterial growth in the absence of treatment. The Negative Control Wells contained 50 µL of nutrient broth, and 50 µL of the stock solution (without bacterial culture) was added to ensure that the extract or DMSO did not cause turbidity or interfere with the results. The Media Control Wells contained 100 µL of nutrient broth alone to confirm the sterility of the medium and absence of contamination. The plates were incubated at 37°C for 24 hours.

Figure 2 96 well microtiter plate containing serial dilutions of crude extract along with the positive and negative controls.

3.4 FORMULATIONS CONTAINING CRUDE EXTRACT

Formulation developed with Oil and Petroleum Jelly

Equal amounts of oil and crude extract were added to an Eppendorf to make a 1:1 concentration formulation. The same was repeated for petroleum jelly. 0.1 O. D. culture of MRSA was swabbed onto a Nutrient agar plate aseptically. The two formulations containing the extract, along with controls (only oil and petroleum jelly), were streaked using an inoculating loop separately onto the swabbed plates. The plates were incubated at 37˚C for 24 hours and checked for their zone of clearance after 24 hours.

Formulation developed with Starch and Carboxymethylcellulose

5 g of starch and carboxymethylcellulose powder were added to two separate glass beakers. 50 mL of distilled water was added to both the beakers and kept boiling and stirred continuously until both the powders were completely digested. Finally, 1 mL of glycerol was added to both the beakers and then poured into petri dishes to create a colloidal patch and kept for drying for 48 hours. The formulations can be stored at room temperature in sterile containers.

Figure 3 Starch- based patch containing crude cinnamon extract and glycerol.

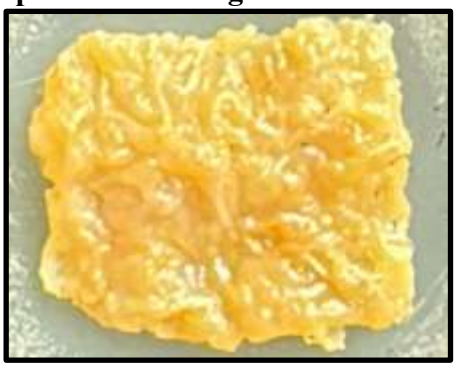
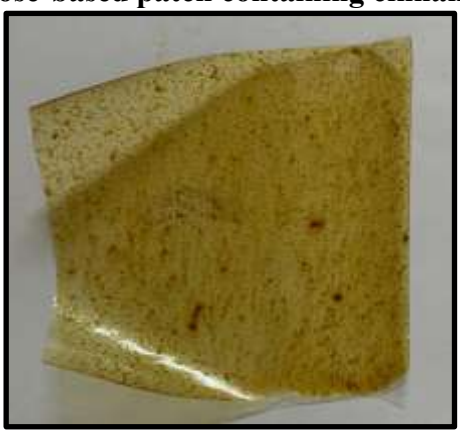


Figure 4 Starch-based patch containing glycerol (control).

Figure 5 Carboxymethyl cellulose-based patch containing glycerol (control).

Figure 6 Carboxymethyl cellulose-based patch containing cinnamon crude extract and glycerol.



4 RESULTS

4.1 CHARACTERISATION OF CRUDE EXTRACT

- **Phytochemical analysis of crude extract**

Phytochemical analysis is essential for identifying the bioactive compounds present in plant extracts that contribute to their therapeutic properties, including antimicrobial activity[18, 19].

Figure 7 Qualitative tests evaluate presence of phytochemicals in crude extract.
A- Alkaloids B- Resins C-Saponins D- Terpenoids E- Glycosides

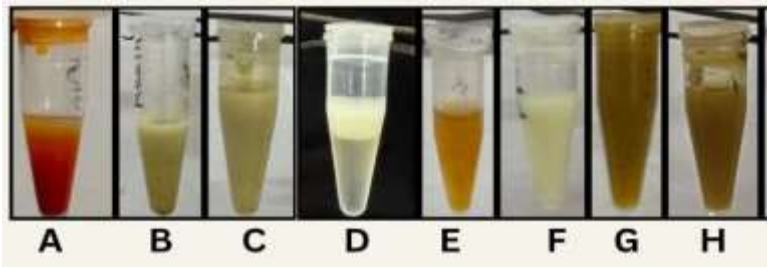


Table 2 : Different phytochemical tests show the presence of alkaloids, saponins, terpenoids and resins

Phytoconstituents	Crude Cinnamon extract
Alkaloids	+
Glycosides	-
Steroids	-
Resins	+
Flavonoids	-
Phenols	-
Tannins	-
Saponins	+
Terpenoids	+

- **Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR analysis was conducted to confirm the presence of bioactive compounds in the crude extract of *Cinnamomum verum* stem bark, focusing on the identification of cinnamaldehyde. The spectra were recorded in the range of 4000–450 cm^{-1}, and the characteristic absorption bands corresponding to various functional groups were identified[20, 21].

Figure 8 Absorption peaks obtained by Fourier Transform Infrared Spectroscopy (FTIR) on testing the crude extract.

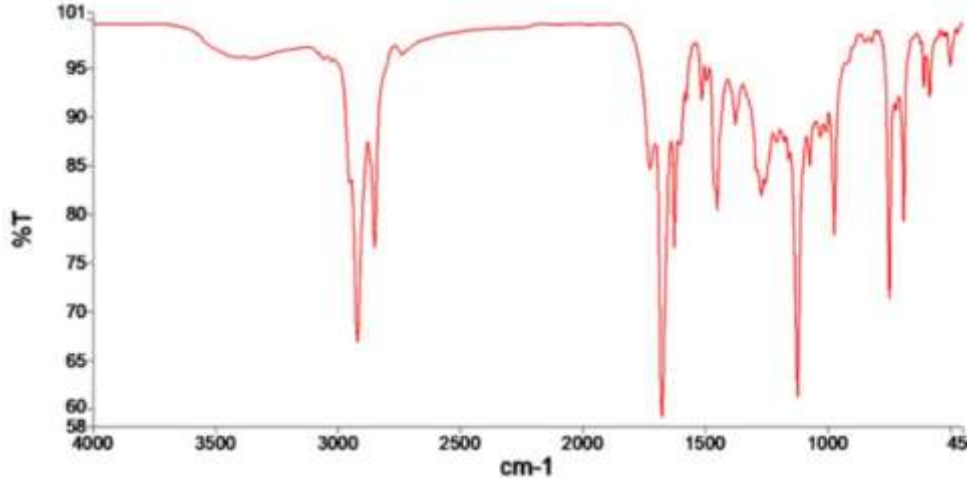


Table 3 Absorption peaks of functional groups present in the crude extract at different wavelengths

Compounds	Wavelength (cm^{-1})	Transmittance (%)
Aromatic C-H stretch	2922.61	66.89
Aldehyde C-H stretch	2852.35	76.58
Aldehyde C=O stretch	1676.54	59.22
Alkene C=C stretch	1625.92	76.59

4.2 ANTIMICROBIAL ACTIVITY DETERMINATION

- **Antimicrobial Susceptibility Testing by agar well diffusion**

The antimicrobial activity was determined by measuring the diameter of the clear zones of inhibition around each well, where bacterial growth was suppressed. The size of these inhibition zones serves as an indicator of the extract's efficacy in preventing bacterial proliferation [19,21].

Figure 9 Nutrient agar plate swabbed with *S.aureus* and loaded with the crude extract, positive control and negative control.

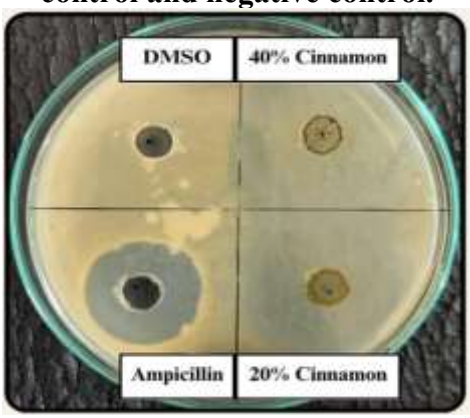
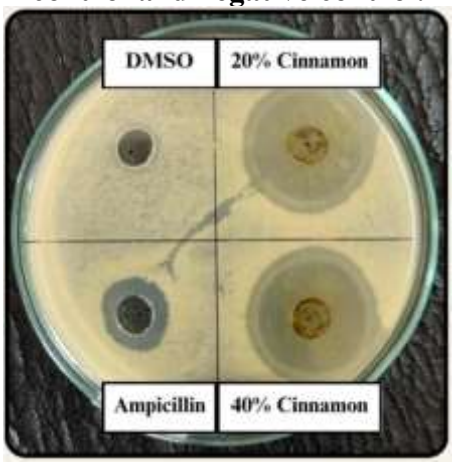


Figure 10 Nutrient agar plate swabbed with MRSA and loaded with the crude extract, positive control and negative control.



For *Staphylococcus aureus*, the 20% cinnamon extract produced a zone of inhibition measuring 34 mm, while the 40% extract exhibited a slightly larger zone of 37 mm. In comparison, the standard antibiotic Ampicillin (10 µg) showed a 25 mm zone, and the negative control (DMSO) showed no inhibition (0 mm). In the case of MRSA, the 20% extract resulted in a 30 mm inhibition zone, while the 40% extract showed a 31 mm zone. Ampicillin was less effective against MRSA, producing only a 15 mm zone, and DMSO again showed no activity.

Determining Minimum Inhibitory Concentration of the crude extract

Following incubation, bacterial growth was assessed using an ELISA plate reader at 490 nm to measure turbidity. The MIC was recorded as the lowest concentration of the crude extract at which significantly reduced turbidity was seen. The MIC for **MRSA** was found to be **5%**, indicating that a relatively higher concentration of the crude extract was needed to inhibit this more resistant strain. The MIC for ***Staphylococcus aureus*** was **2.5%**, suggesting that *S. aureus* was more susceptible to the extract compared to MRSA.

***Figure* 11 Effect of crude extract on growth of *MRSA* indicated by MIC values in the graph**

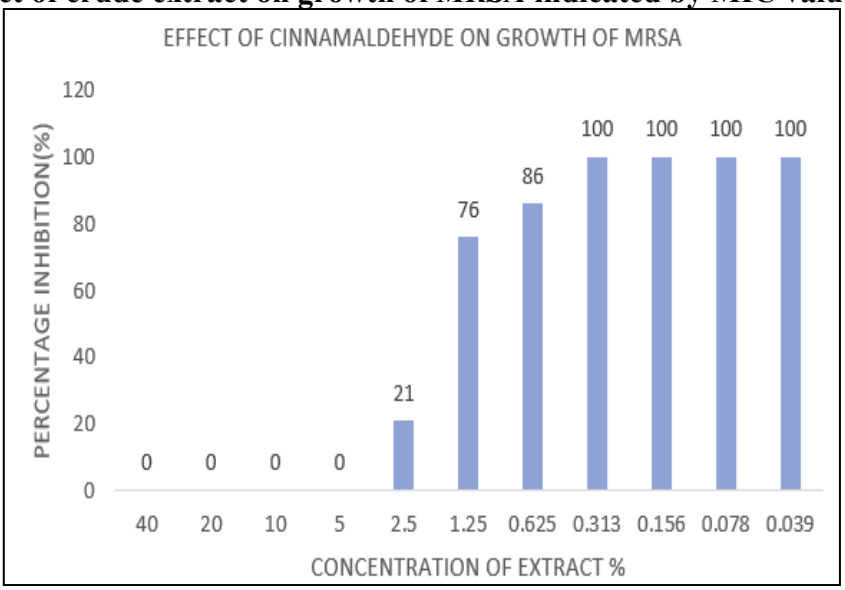
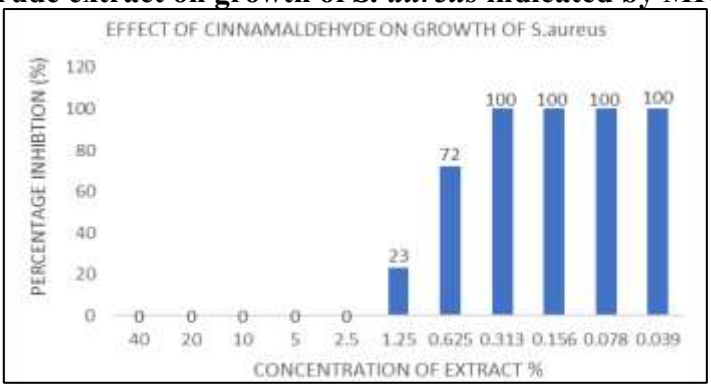


Figure 12 Effect of crude extract on growth of *S. aureus* indicated by MIC values in the graph



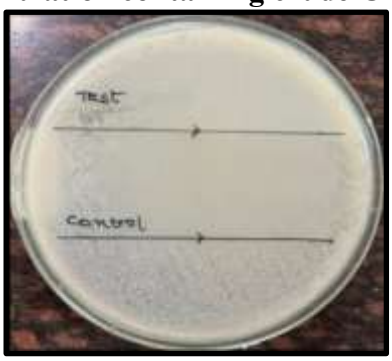
4.3 FORMULATIONS CONTAINING CRUDE EXTRACT

Petroleum jelly-Based Formulation: The formulation exhibited a **clear line of inhibition** against MRSA, indicating that the bioactive compounds within the extract retained their antimicrobial efficacy in the petroleum jelly matrix. The control sample containing only petroleum jelly showed **no inhibition**, confirming that the antibacterial effect was solely due to the *C. verum* extract.

Coconut Oil-Based Formulation: The coconut oil formulation yielded **inconclusive results** against MRSA. This could be attributed to several factors. The extract's bioactive compounds may not have dispersed effectively in the coconut oil due to its higher viscosity, reducing their availability to act against MRSA. Moreover, Coconut oil contains natural fatty acids with mild antimicrobial properties, which could interfere with or mask the effects of the *C. verum* extract.[23]

Figure 13 Petroleum jelly-based formulation containing crude Cinnamon extract against *S.aureus*

Figure 14 Coconut oil-based formulation containing crude Cinnamon extract against *S.aureus*



Starch-based formulation: The starch formulation containing *C. verum* extract exhibited a **clear zone of inhibition** against *S. aureus* and MRSA, though the zones on the MRSA plate were smaller, suggesting that a higher concentration of the extract might be required to combat the drug-resistant strain. The control sample containing only petroleum jelly showed **no inhibition**, confirming that the antibacterial effect was solely due to the *C. verum* extract[24].

Figure 15 Starch based formulation containing crude Cinnamon extract and Glycerol against *S.aureus* (Test)

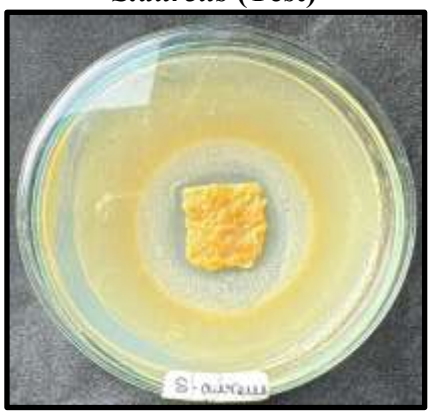


Figure 16 Starch based formulation containing Glycerol against *S.aureus* (Control)

Figure 17 Starch based formulation containing crude Cinnamon extract and Glycerol against MRSA (Test)

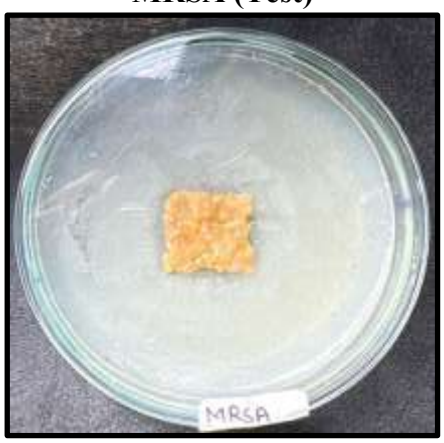
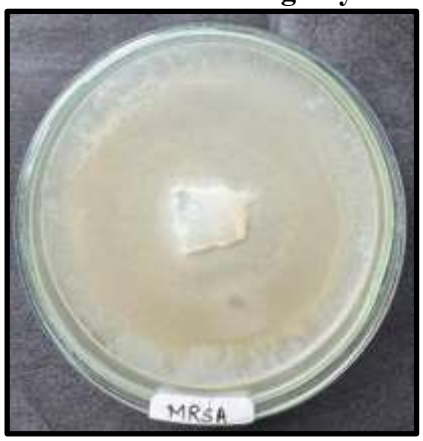


Figure 18 Starch based formulation containing Glycerol against MRSA (Control)



Carboxymethyl cellulose-based formulation: The antibacterial activity of carboxymethylcellulose (CMC) based formulation containing cinnamon extract was determined. Both the test (extract + CMC) and control (CMC) showed **no zone of inhibition**. The ineffective results may be due to the instability of the formulation as it completely dissolved in the agar as a result, the colonies were displaced[24].

Figure 19 Carboxymethylcellulose-based formulation containing Cinnamon extract and Glycerol (top) and containing only Glycerol (bottom) against MRSA

5 DISCUSSION

Due to the escalating global concern of antimicrobial resistance, coupled with the reduced efficacy of conventional antibiotics, it is important to explore and develop novel therapeutic antimicrobial agents derived from natural sources. This study aims to evaluate the antibacterial potential of *Cinnamomum verum* bark extract against both *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA).

The chloroform-based solvent extraction of *C. verum* bark yielded a mixture of bioactive compounds, confirmed through phytochemical analysis and FTIR spectroscopy[25]. Phytochemical analysis revealed the presence of key bioactive compounds in the extract, specifically alkaloids, resins, terpenoids, and saponins, each contributing towards the antimicrobial activity[18, 19]. The FTIR spectroscopy confirmed the presence of cinnamaldehyde, cinnamic acid and other aldehydes through characteristic peaks at 1676.54 cm^{-1} (aldehyde carbonyl groups), along with other significant bioactive compounds indicated by peaks at 1625.92 cm^{-1} (alkenes), 2852.35 cm^{-1} (aldehyde C–H stretch), and 2922.61 cm^{-1} (aromatic C–H stretch)[20,21].

The antimicrobial susceptibility testing showed particularly promising results, with the cinnamon extract showing superior inhibition compared to the conventional Gram-positive antibiotic ampicillin. The 20% and 40% extract concentrations produced larger zones of inhibition against both *S. aureus* and MRSA as compared to ampicillin's zone. These results suggest that the extract possesses potent antibacterial properties even at lower concentrations[19, 21].

Minimum Inhibitory Concentration (MIC) studies determined that the extract effectively inhibited *S. aureus* at 2.5% concentration and MRSA at 5% concentration, indicating its potential therapeutic efficacy at relatively low concentrations, which is particularly significant for developing topical formulations.

To check cinnamon's compatibility in different formulations and choose the most optimal formulation, antimicrobial studies were performed. The starch-based formulation showed the most promising results among the various delivery systems tested (oil, petroleum jelly, starch, and carboxymethylcellulose). The starch-based formulation demonstrated clear zones of inhibition against both organisms, with notably stronger activity against *S. aureus* compared to MRSA. While petroleum jelly showed minimal efficacy, oil-based and carboxymethylcellulose formulations proved ineffective, likely due to poor diffusion characteristics and formulation instability, respectively[23, 24].

These findings suggest that *Cinnamomum verum* bark extract, particularly when incorporated into appropriate delivery systems like starch-based formulations, could serve as a viable alternative to conventional antibiotics for treating *S. aureus* and MRSA infections. The study also indicates that the extract's effectiveness stems from the synergistic action of multiple bioactive compounds, primarily cinnamaldehyde, which disrupts bacterial cell membranes and inhibits microbial growth[13].

However, further research is required to optimize the formulations, particularly the starch-based formulation, and conduct stability and toxicity studies to validate these findings.

6 CONCLUSION

Hence, the crude extract can serve as a natural alternative or adjunct to conventional antibiotics, especially in the fight against multidrug-resistant bacteria. The starch-based formulation demonstrated not only effective antibacterial activity but also favorable moisture-absorbing characteristics, which can help maintain an optimal environment for wound healing. The formulation forms a protective barrier over the affected area, preventing secondary infections while promoting natural healing. Moreover, unlike synthetic antibiotics, which can cause skin irritation or systemic side effects, the natural extract is less likely to induce adverse reactions. This makes the formulation especially suitable for sensitive skin and long-term use. In addition, the formulation is based on natural, biodegradable ingredients, reducing the environmental impact compared to synthetic antibiotics and chemical-laden skincare products, meeting the increasing consumer demand for eco-friendly and sustainable healthcare solutions.

7 FUTURE PROSPECTS

To ensure the safe and effective use of the extract in topical formulations, future studies should focus on comprehensive toxicity and skin irritation testing, along with stability assessments under varying pH, temperature, humidity, and light conditions. Further research should aim to isolate and purify key bioactive compounds using chromatography, supported by advanced spectroscopic techniques like mass spectrometry and nuclear magnetic resonance for structural characterization. Additionally, exploring synergistic combinations with other antimicrobial agents such as lysozyme may enhance therapeutic efficacy by targeting multiple bacterial mechanisms.

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