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EVALUATION AND COMPARATIVE ANALYSIS OF ANTIBACTERIAL ACTIVITY OF ETHANOLIC EXTRACTS OF MALE AND FEMALE TREE LEAVES OF CARICA PAPAYA LINN. AGAINST CLINICAL ISOLATES

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Abstract

Background: The significant emergence of antimicrobial resistance has sparked considerable interest in plant-based alternatives for managing infections. As resistant bacteria continue to spread rapidly, current antimicrobial treatments offer limited therapeutic options **Objectives**: This study investigates the antibacterial potential of ethanolic extracts of Carica papaya male and female tree leaves against clinically isolated strains of Escherichia coli, Staphylococcus epidermidis, Staphylococcus aureus, and Klebsiella pneumoniae. **Methodology:** Varying concentrations of the extract (25–100 mg/mL) were tested using the agar well diffusion method, with Moxifloxacin serving as the positive control and DMSO as the negative control. **Results**: Among the four bacterial strains tested, both male and female Carica papaya leaf extracts showed concentration-dependent antibacterial activity, with female extracts demonstrating consistently stronger effects. At 100 mg/mL, female extracts produced the largest zones of inhibition, particularly against Gram-positive bacteria (S. epidermidis and S. aureus). MIC and MBC tests confirmed significant antibacterial activity of female extracts at higher concentrations (≥75 mg/mL), especially against Gram-positive strains. In contrast, male extracts exhibited weaker antibacterial effects, with limited activity

observed only at 100 mg/mL for S. epidermidis and S. aureus, and no detectable activity against Gram-negative bacteria. **Conclusions**: The findings suggest that Carica papaya male and female leaf extract holds promise as a natural antimicrobial agent, especially against Gram-positive pathogens. Further phytochemical and pharmacological studies are needed to isolate the active compounds and explore their therapeutic potential.

INTRODUCTION:

Carica papaya Linn, a member of the family **Caricaceae**, is widely cultivated in Pakistan, particularly in the Sindh province and certain regions of Punjab. The plant is easily recognized by its soft, unbranched stem and long-stalked leaves. It can reach heights of up to 20 meters and exhibits a rapid growth rate [1] Traditionally, Carica papaya leaves have been employed in folk medicine for the treatment of various conditions, including pyrexia, vitamin deficiency disorders such as beriberi, asthma, colic pain, and malaria, particularly across Asian countries [2]. The leaves are also reported to possess **antiviral** properties and **immunomodulatory** activity [3].

Phytochemical analysis reveals that papaya leaves are rich in **alkaloids**, predominantly **carpaine** and **pseudocarpaine**, as well as **enzymes** such as **papain**, **chymopapain**, and **cystatin**. They also contain a variety of **vitamins and derivatives**, including **tocopherol** and **nicotinic acid**, along with **tannins** and **saponins** [4]. Important **phenolic acids** such as **caffeic acid**, **p-coumaric acid**, and **protocatechuic acid** are among the core bioactive compounds present. Moreover, the leaves are a rich source of **flavonoids** like **kaempferol** and **myricetin** [5]. Young leaves and fruits also contain **carotenoids**—notably **lycopene** and **β-carotene**—as well as **glycosidic anthraquinones**. Carica papaya leaves exhibit a broad spectrum of **pharmacological properties**, including **anti-inflammatory**, **hypoglycemic**, **anti-fertility**, **abortifacient**, **hepatoprotective**, **wound-healing**, and **antitumor** activities [6]. In the current global context, where **bacterial infections** continue to pose significant challenges to clinical practice, the emergence and rapid spread of **antimicrobial resistance** have severely limited effective treatment options. This scenario underscores the urgent need for alternative therapeutic strategies, such as plant-based antimicrobials, to combat resistant bacterial strains [7.8].

MATERIALS AND METHOD

Collection of specimens of clinical isolates

Clinical isolates of Escherichia coli, Staphylococcus epidermidis, staphylococcus aureus and Klebsiella pneumoniae were collected from Civil Hospital Karachi, Pakistan. These pathogenic strains were recovered from a diverse range of clinical specimens, including urine, blood, and pus.

Isolation and Identification of Clinical Isolates

Clinical isolates were obtained based on their morphological characteristics, cultural features, and biochemical profiles at Civil Hospital Karachi, Pakistan. The identification process followed standard microbiological procedures to ensure accurate classification of the bacterial strains.

Plant Collection and Authentication

The tall variety of Carica papaya Linn was cultivated and harvested from Darshan Channa (Memon Goth), Khokrapar Malir, Karachi, Pakistan. No pesticides were applied during the cultivation period. Leaves were collected from both male and female plants, specifically from the middle section of each plant, during the morning hours between 9:00 a.m. and 11:00 a.m. The ambient temperature during collection

was 32°C, with a relative humidity of 44%. Collected leaves were carefully packed in polyethylene bags for transportation. The plant specimens were taxonomically authenticated as the tall variety by Professor Dr. Shahnaz Dewar, Department of Botany, University of Karachi, Pakistan. Voucher specimen numbers 107 and 108 were deposited in the Department of Pharmacognosy, Faculty of Pharmacy, University of Karachi. The leaves were washed thoroughly three times with distilled water to remove surface dust. Using sterile surgical blades (Pin Tech Instruments, Punjab, Pakistan), leaf parts—lamina, petiole, and midrib—were separated, with only the lamina retained for further study. The lamina were air-dried at room temperature (24 ± 2°C) for two weeks, followed by shade-drying until fully dehydrated. Once dried, the material was ground into a coarse powder using a mechanical blender. The powders from male and female plants were stored separately in air-tight, labelled containers at ambient temperature to prevent moisture absorption [1].

Preparation of Ethanolic Extracts

Ethanolic extraction was carried out separately for male and female Carica papaya leaves. A total of 500 grams of dried leaf powder was soaked in 1000 mL of ethanol and placed in wide-mouth jars. The mixtures were left to macerate at room temperature for two weeks, with intermittent shaking (10–15 times daily for 10 minutes) to ensure thorough extraction. After the extraction period, the mixtures were filtered using Whatman No. 42 filter paper. The resulting filtrates were stored in air-tight containers at 4°C until further processing. Solvent removal was carried out under reduced pressure using a Büchi Rotavapor® R-200. The concentrated extracts were then freeze-dried to obtain the final crude ethanolic extracts [8].

Preparation of Papaya Leaf Ethanol Extract Test Solution

One gram of the ethanolic extract was accurately weighed and dissolved in dimethylsulfoxide (DMSO) to a final volume of 10 mL, yielding a stock solution with a concentration of 100 mg/mL (100%). Serial dilutions of the stock solution were then prepared to obtain working concentrations of 75 mg/mL 75%), 50 mg/mL (50%), and 25 mg/mL (25%) [9].

Collection of Antibiotic

The antibiotic Avelox Tablets 400mg Bayer Pharma (Pvt) ltd was procured for comparative analysis in antimicrobial susceptibility testing.

Susceptibility Testing

The sensitivity and resistance patterns of the microorganisms were evaluated following standardized procedures [10,8].

Preparation of Inoculum, Broth, and Media Plates

Mueller-Hinton medium (Oxoid Ltd., Basingstoke, Hampshire, England) was utilized for antimicrobial susceptibility testing of the clinical isolates. Colonies exhibiting identical morphological characteristics were selected from agar plates.

In accordance with the National Committee for Clinical Laboratory Standards (NCCLS) guidelines, Mueller-Hinton broth and agar media were prepared. Using a sterile wire loop, individual colonies were carefully transferred into tubes containing 4 to 5 mL of appropriate broth and incubated at 37°C for 8 to 24 hours.

Bacterial suspensions were then adjusted to match the turbidity of the 0.5 McFarland standard, ensuring a standardized inoculum concentration. A sterile cotton swab was dipped into the bacterial suspension and streaked evenly in three directions across the

surface of Mueller-Hinton agar plates to achieve a uniform bacterial lawn. The plates were then allowed to dry for 10 minutes before further testing.

Application of material in well

By using sterile cork borer, wells were made in media with a diameter of 6 to 8mm and applied 1ml of crude ethanolic extract and its dilutions with the help of 3mL sterile syringe under aseptic conditions. Moxifloxacin 40 µg/mL was used as positive control and ethyl acetate as negative control[13]. Wells were completely filled to ensure contact with agar. The wells were bored in such a manner that they were not less than 25 mm from each other and were 15 mm from the edge of the plate.

Incubation of plates

After that plates were incubated at 37^{o} C for 24 hours. The diameter of the zones of growth inhibition around each well was measured in mm by using Vernier caliper.

Minimum inhibitory concentration (MIC)

For MIC determination, micro-broth dilution technique was used. Ethanolic extract dilutions were prepared i.e. 80 mg/mL, 60 mg/mL , 40 mg/mL , 20 mg/mL , 10 mg/mL , and 5 mg/mL. 2ml each of Mueller–Hinton broth and extracts were mixed. Precisely, to each of the test tubes, 1ml of standardized inoculum having 3.3 x 10^{6} CFU/ml was added and incubated for 24 hours at temperature 35°C in aerobic condition. Broth and extracts containing tubes lacking inoculum served as positive control while as negative control, tubes containing broth and inoculum were used. To determine minimum inhibitory concentration, the tubes were analyzed after incubation period of 24 hours. The lowest concentration showed MIC with evidence of lacking of growth [11].

Minimum Bactericidal Concentration (MBC)

To determine MBC, Mueller-Hinton agar sterile plates were inoculated separately with sample test tubes that showed absence of growth. The test plates were again incubated for 24 hours at 35^{o}C in incubator and then analyzed. The highest dilution lacking bacterial growth was considered as MBC [1].

Results:

The antibacterial activity of ethanolic extracts from both female and male Carica papaya leaves was evaluated against four clinical bacterial isolates: Escherichia coli, Staphylococcus epidermidis, Staphylococcus aureus, and Klebsiella pneumoniae. The results, expressed as average diameters of the inhibition zones (in mm), are presented in Table 1(A) and 1(B).

Table -1 (A) Average diameter of clear zone of Inhibition (mm) from female tree leaves ethanolic extracts

CLINICAL ISOLATES	**Test**				**Control**	
	Average diameter of clear zone of Inhibition (mm)					
	Female tree leaves Ethanolic extract dilutions / mL				**DMSO -ve**	**Moxifloxacin +ve**
	25mg/mL	**50mg/mL**	**75mg/mL**	**100mg/mL**	**mL**	**mL**
Escherichia coli	8.4	11.8	15	18	NZ	26

Staphylococcus epidermidis	9.4	15.4	19.2	22.2	NZ	28
Staphylococcus aureus	8.8	13.9	17.2	22	NZ	27
Klebsiella pneumoniae	7.2	13.2	16.5	19	NZ	25

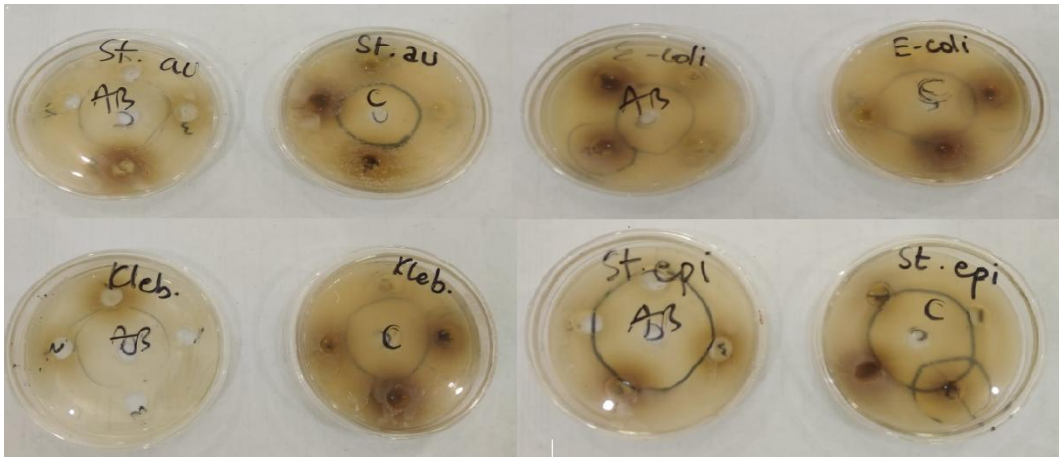
Table -1 (B**) Average diameter of clear zone of Inhibition (mm) from Male tree leaves ethanolic extracts**

CLINICAL ISOLATES	**Test**				**Control**	
	Average diameter of clear zone of Inhibition (mm)					
	Male tree leaves Ethanolic extract dilutions / mL				**DMSO -ve**	**Moxifloxacin +ve**
	25mg/mL	**50mg/mL**	**75mg/mL**	**100mg/mL**	**mL**	**mL**
Escherichia coli	6.4	10.2	13.6	16.8	NZ	26
Staphylococcus epidermidis	8.2	12.6	18	20.2	NZ	28
Staphylococcus aureus	8	12.2	17	21	NZ	27
Klebsiella pneumoniae	6.1	11	14.8	17	NZ	25

The ethanolic extracts from female papaya leaves showed a clear, concentration-dependent increase in antibacterial activity. At the highest concentration (100 mg/mL), the largest zone of inhibition was observed against Staphylococcus epidermidis (22.2 mm), followed by S. aureus (22 mm), K. pneumoniae (19 mm), and E. coli (18 mm). Moxifloxacin, as positive control, produced significantly larger zones of inhibition (25–28 mm), confirming its strong antibacterial efficacy.

Similarly, ethanolic extracts from male papaya leaves also exhibited dose-dependent antibacterial activity. The highest inhibition was again recorded against S. epidermidis (20.2 mm) at 100 mg/mL, followed by S. aureus (21 mm), K. pneumoniae (17 mm), and E. coli (16.8 mm). Compared to the female extracts, male extracts demonstrated slightly lower antibacterial activity across all concentrations for each pathogen.

AB: female tree leaves ethanolic extract C: male tree leaves ethanolic extract



Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC)

The MIC and MBC values of the ethanolic extracts from both female and male Carica papaya leaves were assessed against four clinical bacterial isolates, and the outcomes are summarized in Table 2(A) and 2(B).

Table -2(A) MIC and MBC of different dilutions of Ethanolic Extracts of Female Papaya leaves.

Bacterial Strains	MIC				MBC			
	25 mg/mL	50 mg/mL	75 mg/mL	100 mg/mL	25 mg/mL	50 mg/mL	75 mg/mL	100 mg/mL
Escherichia coli	ND	ND	ND	SD	ND	ND	ND	SD
Staphylococcus epidermidis	ND	ND	SD	D	ND	ND	SD	D
Staphylococcus aureus	ND	ND	SD	D	ND	ND	SD	D
Klebsiella pneumoniae	ND	ND	ND	SD	ND	ND	ND	SD

NOTE (MIC; Minimum Inhibitory Concentration, MBC; Minimum Bactericidal Concentration, ND; Not Detected, D; Detected, SD; Slightly Detected)

Table -2(B) MIC and MBC of different dilutions of Ethanolic Extracts of Male Papaya leaves.

Bacterial Strains	MIC				MBC			
	25 mg/mL	50 mg/mL	75 mg/mL	100 mg/mL	25 mg/mL	50 mg/mL	75 mg/mL	100 mg/mL
Escherichia coli	ND	ND	ND	ND	ND	ND	ND	ND
Staphylococcus epidermidis	ND	ND	ND	SD	ND	ND	SD	D
Staphylococcus aureus	ND	ND	ND	SD	ND	ND	SD	D
Klebsiella pneumoniae	ND	ND	ND	ND	ND	ND	ND	ND

NOTE (MIC; Minimum Inhibitory Concentration, MBC; Minimum Bactericidal Concentration, ND; Not Detected, D; Detected, SD; Slightly Detected.

The MIC and MBC tests revealed that the female leaf extract showed detectable antibacterial activity primarily at higher concentrations (≥75 mg/mL). For Staphylococcus epidermidis and Staphylococcus aureus, MIC is slightly detected at 75 mg/mL and fully detected at 100 mg/mL while MBC is slightly detected at 75 mg/mL and fully detected at 100 mg/mL . In case of Escherichia coli and Klebsiella pneumoniae, MIC & MBC were only at 100 mg/mL (SD), with no detection is observed at lower concentrations. These results suggest that the extract from female papaya leaves exhibited both inhibitory and bactericidal activity, particularly against Gram-positive bacteria (S. epidermidis and S. aureus), at 75–100 mg/mL. In contrast, Gram-negative strains (E. coli and K. pneumoniae) required higher concentrations and showed only slight inhibition or killing, reflecting their greater resistance. In comparison, the male leaf extract displayed weaker antibacterial effects. Against Staphylococcus epidermidis and Staphylococcus aureus, MIC was slightly detected only at 100 mg/Ml while MBC is slightly detected at 75 mg/mL and fully detected at

100 mg/mL, for Escherichia coli and Klebsiella pneumoniae: No MIC or MBC detected at any concentration tested.

Discussion:

The findings of this study demonstrate that female Carica papaya leaf extracts possess superior antibacterial activity compared to their male counterparts across all tested bacterial strains and concentrations. Notably, the efficacy of the female extracts was most pronounced at higher concentrations (75 mg/mL and 100 mg/mL), particularly against Staphylococcus epidermidis and Staphylococcus aureus. At these concentrations, the female extracts consistently produced larger zones of inhibition, suggesting a higher concentration or more potent combination of bioactive antimicrobial compounds in female papaya leaves. It has been reported that both male and female Carica papaya leaf extracts showed strong antibacterial activity, with the female extract slightly more effective against Pseudomonas aeruginosa [12]. Overall, the female Carica papaya leaf extracts exhibited superior antibacterial activity compared to male leaf extracts across all tested bacterial strains and concentrations. The difference was most notable at higher concentrations (75 mg/mL and 100 mg/mL), particularly against S. epidermidis and S. aureus, where the female extracts consistently produced larger inhibition zones. A Study indicated that ethanolic seed extract showed the highest antibacterial activity (14.3 ± 1.2 mm inhibition zone), while leaf extract had lower activity. Same results indicated **2022.** MIC values confirmed efficacy at 12.5 mg/ml for ethanol seed extract [13,14]. This suggests that female papaya leaves may contain higher concentrations or a more effective profile of bioactive antimicrobial compounds. These results indicate that male papaya leaf extracts were less potent, with limited inhibitory and bactericidal activity, and only against Gram-positive bacteria at high concentrations (75–100 mg/mL). Gram-negative bacteria were completely resistant to all tested concentrations. In contrast, the antibacterial activity of male papaya leaf extracts was markedly weaker. Their inhibitory effects were limited, showing activity only against Gram-positive bacteria and only at the highest tested concentrations. Furthermore, none of the Gram-negative bacterial strains exhibited susceptibility to any concentration of the male extracts, indicating a complete resistance. This differential response between Gram-positive and Gram-negative bacteria may be attributed to the structural differences in their cell walls, which can affect permeability to plant-derived antimicrobial compounds. Another study indicated that Ethanol extracts more potent than aqueous and are effective against C. bacillus, S. epidermidis [15]. Overall, the results suggest that gender plays a significant role in the phytochemical composition of Carica papaya leaves, with female plants potentially offering more effective antibacterial agents. Further phytochemical analysis is warranted to isolate and characterize the specific compounds responsible for this enhanced activity and to better understand the mechanisms underlying the observed antimicrobial effects.

The water extract of both male and female papaya leaves yielded no significant antibacterial activity against the test isolates used while the ethanol extract of both male and female leaves demonstrated high antibacterial activity against both Gram negative and Gram positive test isolatesused. Although both the male and female extracts demonstrated high antibacterial activities against the test isolates, the female extract was slightly more effective than the male extract with the highest activity (18mm zone of inhibition) demonstrated against Pseudomonas aeruginosa when compared with the male leaf extract which demonstrated (17 mm zone of inhibition) against Pseudomonas aeruginosa. The inhibition zones of the extracts were compared to that of the control and the activity of the extracts was as good as that of the antibiotic.The water extract of both male and female papaya leaves yielded no

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Conclusion:

In conclusion, Female papaya leaves exhibited stronger antimicrobial activity than male leaves, showing both MIC and MBC effects at lower concentrations (75 mg/mL) in some strains. Gram-positive bacteria (S. epidermidis and S. aureus) were more susceptible to both extracts than Gram-negative strains, likely due to structural differences in their cell envelopes. No antibacterial activity was detected at 25 mg/mL or 50 mg/mL for any strain, indicating that these lower concentrations are sub-therapeutic. These findings suggest that Female Carica papaya leaves are a more potent source of natural antibacterial compounds and warrant further phytochemical and pharmacological investigation.

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