

Original Article



Antimicrobial Effect of *Ficus carica* on Nosocomial Bacterial Infections

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Abstract

Background: The incidence of drug resistance against chemical antimicrobial drugs has directed the attention to the use of medicinal plants in the treatment of infections. This study aimed to evaluate the antimicrobial activity of *Ficus carica* extracts against pathogenic bacteria, especially nosocomial infections.

Methods: In this experimental study, aqueous and alcoholic extracts of *F. carica* were extracted. This study investigated inhibitory effects of plant extracts against pathogenic bacteria such as *Staphylococcus saprophyticus*, *Escherichia coli*, *Salmonella typhimurium*, and *Proteus mirabilis* as well as pathogenic nosocomial including *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter*, and *Pseudomonas aeruginosa* through disk diffusion methods, well diffusion method, and microdilution. Serial dilutions of the extracts were prepared in the range of 50 to 1000 mg/mL to determine the minimum inhibitory concentration.

Results: The aqueous extract of the plant showed higher inhibitory effects against microbial strains compared to the alcoholic extract. The two strains of *S. saprophyticus* and *S. aureus* indicated greater susceptibility than extracts (e.g., aqueous, methanol, and ethanol). Statistically, there was a significant difference in the minimum inhibitory concentration of aqueous extract growth compared to alcoholic extracts. The aqueous extract had a minimum inhibitory concentration of 133 mg/mL and a minimum bactericidal concentration of 200 mg/mL on gram-positive bacteria of *S. saprophyticus* and *S. aureus*, respectively.

Conclusion: The study found *F. carica* that extract had significant effects on microorganisms of two gram-positive bacteria including *S. saprophyticus* (62 mm in diameter) and *S. aureus* (60 mm in diameter), and the bacterium *P. aeruginosa* revealed the highest resistance against gram-negative bacteria. The extracts also indicated significant effects compared to the antibiotics as a control. Although further research is needed in this regard, *F. carica* extract can be suggested as a new antimicrobial agent in medical research.

Keywords: Medicinal plant extract, Pathogenic bacteria, Minimum inhibitory concentration, Digestive and skin disease

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Introduction

The *Ficus carica* tree is native to Iran, Asia Minor, and Syria and is currently grown in most Mediterranean countries (1). *F. carica* fruit has a high nutritional and medicinal value, and dried *F. carica* has higher concentrations of energy, minerals, and vitamins compared to fresh *F. carica* so that 100 g of dried *F. carica* provide 249 calories. Its dried fruit is a smart option to enjoy the properties of *F. carica* throughout the year, and this dried fruit contains vitamin C, which along with other minerals and vitamins enhances the body's immune system, and vitamins can act as natural antioxidants in the body. Its fruit contains large amounts of polyphenols, flavonoids, and anthocyanins (2) and has high antioxidant properties. Catechin is one of the most important flavonoid compounds measured

in *F. carica* fruit by the aluminum chloride colorimetric method. This compound has anti-inflammatory, anti-allergic, and tumor growth inhibitory effects. It also has a vascular protective, antithrombotic, and hematocrit effect that impacts prothrombin time, thromboplastin time, and red blood cell volume. It also has a protective effect on the gastrointestinal tract, removes gallstones, and has anti-hair loss properties. Moreover, it has antimicrobial, antifungal, and antiviral effects (3).

Anthocyanins, as flavonoid compounds, are involved in absorbing free radicals in the body. Catechin is a phenolic compound that is a natural antioxidant and a secondary metabolite of plant fruits that has been identified by the Folin-Ciocalteu method. Metabolites in *F. carica* include hydroxycinnamic acid (3-o-caffeic-quinic acid,



5-o-caffeic-quinic acid), glycosides flavonoids (Quercetin 3-rutinoside), and furanocoumarins (psoralen and bergapten). Further, organic acids including oxalic acid, citric acid, malic acid, shikimic acid, and fumaric acids have been identified in *F. carica* pulp and skin (4). Saponins are secondary metabolites distributed throughout the plant, acting as a chemical barrier or shield in the plant defense system against pathogens in plant tissues that are more vulnerable to fungal or bacterial attacks. Saponins are rich in medicinal properties and have other properties such as antioxidant, anti-cancer, anti-diabetic, and anti-fat properties (5).

Dried *F. carica* decoction treats inflammation of the respiratory tract, kidneys, pneumonia, pleurisy, measles, scarlet fever, smallpox, and skin diseases; moreover, it strengthens the immune system and is effective in preventing hypertension. *F. carica* phenolic compounds are nutrients that have anti-cancer, antioxidant, and analgesic properties and inhibit lipid peroxidation properties (6). It is also useful in the treatment of cardiovascular disease, cataracts, and asthma. *F. carica* fruit extract is useful for antioxidant enzymatic activities in preventing liver damage against hepatotoxicity of CCL4 protein and the use of antioxidant enzymes and plays a role in maintaining liver cells (7). It has antibacterial, antiviral, analgesic, anti-angiogenic, and anti-inflammatory activity, and previous pharmacological studies have demonstrated anti-fever, anti-diabetes, anti-platelet, hyperlipidemia, and anti-wart properties of *F. carica* (8).

Materials and Methods

Consumed Materials

Chemicals, laboratory culture media, and antibiotic discs were provided by Merck (Germany).

Bacterial Strains

In the collection of pathogenic bacteria, four bacteria including *Staphylococcus aureus* with resistance to MRSA (methicillin-resistant), *Pseudomonas aeruginosa* with resistance to XDR (susceptible to one or two antimicrobial groups), *Klebsiella pneumoniae* with resistance to KPC (*K. pneumoniae* carbapenemase), and *Acinetobacter* with resistance to KPC as resistant groups were prepared from Al-Zahra hospital in Isfahan. In addition, four bacteria of *Escherichia coli*, *Staphylococcus saprophyticus*, *Proteus mirabilis*, and *Salmonella typhimurium* as susceptible groups were prepared from Shahid Ashrafi University of Isfahan and then studied.

Preparation of Microbial Suspension

The standard half McFarland turbidity criterion was used to obtain uniform and homogeneous suspensions. The suspension prepared with a turbidity equivalent to half McFarland for bacteria was about 108 cells.

Preparation of Plant Extracts

The *F. carica* plant sample was first prepared from Isfahan

herbarium. After receiving the sample, the contaminated and unusable parts were removed, and then the fruits were washed and placed in the shade for drying. Then, they were powdered by a crushing mill. In this study, 96% ethanol, methanol, and water alcoholic solvents were used. First, the powdered fruit was dissolved in 30 g in 100 cc of sterile distilled water, 96% methanol, and 96% ethanol. Then, it was placed on a shaker away from light for 24 hours. The resulting extract was filtered using Whatman filter paper, and the extract was placed at room temperature to evaporate the solvent. Then, the pure extract was transferred to a sterilized petri dish and placed in an incubator at 37 °C for drying. At the end of work, the dried extracts in the petri dishes were shaved with a scalpel blade and poured into sterile tubes, then they were placed in the freezer (at temperature of -22°C) for storage until use. The second method was using a rotary apparatus: first, 30 g of the dried and powdered plant sample was immersed in 100 mL of the desired solvent for 48 hours and stored in a dark place. Then, the plant and solvent mixture were separated by a funnel and filter paper, and the filtered solution was placed in a rotary balloon and was brought to at least of volume in a rotary apparatus under a rotating vacuum. Then, it was separated in a test tube and collected in a dark container.

Preparation of Different Concentrations of Plant Extracts

Necessary amounts of plant extracts (i.e., aqueous, methanol, and ethanol) were weighed carefully (0.01 g) by digital scales, and 2% dimethyl sulfoxide solution was poured in appropriate amounts and completely dissolved using a Vortex device. Plant extracts were prepared for testing against human pathogenic bacteria in three concentrations of 330, 500, and 1000 mg/mL. A 0.22-micron syringe filter (made in the USA) was used to sterilize the diluted extracts.

Disk Diffusion Method

Using the disk diffusion method, the susceptibility of microorganisms to antimicrobials was determined according to the conventional Kirby-Bauer method. Then, 20 µL of the mentioned concentrations (330, 500, and 1000 mg) in three replications and 20 µL each time were placed on each disk. Further, antibiotic disks of ampicillin, sulfamethoxazole, ciprofloxacin, and gentamicin were used as a positive control, while paper disks containing 20µL of solvent were used as a negative control.

Well Diffusion Method

The well was created by using a sterile pasteurized pipette next to the flame and by completely observing sterile conditions at the desired number of concentrations, and 50µL of different concentrations of each filtered extract was poured separately into the wells using a 0.22-micron syringe. For the control, 2% DMSO was poured into the middle of the well. Then, the cultured plates were incubated at 37°C for 24 hours, and the diameter of the

growth inhibition zone was measured (the experiment was performed in three replications).

Microdilution Method

This method was performed on a 96-cell sterile plate. 100 μ L of bacterial suspension and 100 μ L of different dilutions (100 to 1000 mg) prepared from the plant extracts were added to each well. The first column wells containing bacterial suspension and culture medium were considered as negative control, while the second column wells containing bacterial suspension and culture medium along with 2% dimethyl sulfoxide were considered as solvent control.

In addition, the third column containing broth culture medium, pathogen suspension, and 100 μ L of the desired concentration of ampicillin antibiotic was considered as a positive control. In all cases, three replications were considered, then, the plates were incubated for 24 hours at 37°C, and finally, their absorption was read in an ELISA reader at 570 and 655 nm. After the mentioned period, the first well that did not grow for each bacterium was reported as the minimum growth inhibitory concentration (MIC) (9).

Results

Evaluation of Extraction Method With Rotary Apparatus and Manual Method

Due to the low quality of the compounds extracted by the rotary apparatus and the ineffectiveness of various aqueous, methanol, and ethanol extracts on antibiogram tests, the manual extraction method was performed, and phytochemical compounds could be extracted in this method. The manual method was found to have a higher quality than the extraction method with a rotary apparatus due to the significant effect of extracts. The results of disk diffusion tests showed that concentrations of 330 to 1000 mg/mL of aqueous, methanol, and ethanol extracts of the plant had an antimicrobial effect on all bacteria, but the highest inhibitory effect was related to the concentration of 1000 mg on aqueous extract. The highest susceptibility was found in *S. saprophyticus* with 62 mm, *S. aureus* with 60 mm, *E. coli* with 55 mm, and *Salmonella typhimurium* with 52 mm (Figure 1).

Tests obtained from well diffusion method showed that concentrations of 100 to 300 mg/mL of extracts in all gram-positive and gram-negative bacteria caused a growth inhibition zone and in resistant bacteria, the lowest concentration of aqueous extract could have the greatest inhibitory effect on *S. aureus* with 62 mm. Furthermore, other resistant bacteria (e.g., *K. pneumoniae*, *Acinetobacter*, and *S. aureus*) showed the highest susceptibility to 1000 mg/mL aqueous extract.

Among the four antibiotic disks of ampicillin, gentamicin, ciprofloxacin, and sulfamethoxazole, the effect of ampicillin disk with an inhibition zone diameter of 30 mm in most bacteria and gentamycin with a smaller inhibition zone diameter in weak gram-positive and gram-negative strains were identified. In addition, all four resistant strains (i.e., *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, and *Acinetobacter*) showed 100% resistance to four antibiotics. The negative control group, which contained 20 μ L of solvent, exhibited no growth inhibition effect on resistant bacteria, but it was effective on the group with susceptibility of between 1 and 5 mm.

Results of Minimum Bactericidal Concentration (MBC) and MIC Determination

Table 1 presents the MIC and MBC values of the aqueous extract of *F. carica* fruit after three replications. *S. aureus*, *S. saprophyticus*, and *E. coli* showed a total MIC value of 133 mg/mL, while *P. mirabilis* and *S. typhimurium* exhibited an MIC value of greater than 133 mg/mL, and concentrations higher than this value were required to kill all strains (Table 1).

Results of Determining MBC and MIC of Methanol Extract of *F. carica* Fruit

Table 2 presents the MBC and MIC of methanol extract of *F. carica* fruit after three replications. According to this table, the MIC of methanol extract is related to *S. aureus* and *S. saprophyticus* (200 mg/mL), while its highest inhibitory concentration is related to *P. aeruginosa* (1000 mg/mL). Methanol extract of *F. carica* fruit with the lowest concentration can kill *S. aureus* and *S. saprophyticus*, but a concentration of more than 200 mg/mL is required to kill *P. aeruginosa*.

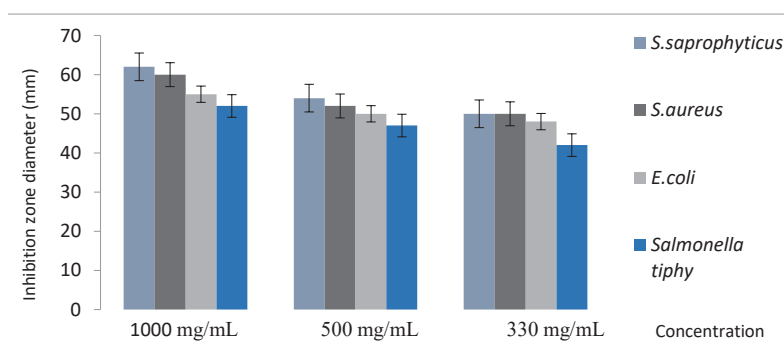


Figure 1. Evaluation of Aqueous Extract of *Ficus carica* at Concentrations of 330, 500, and 1000 mg/mL in Gram (+/-) Bacteria, Aqueous Extract of *Ficus carica* Fruit (mg/mL).

Table 1. Results of Antibacterial Activity of Aqueous Extract of *Ficus carica* Fruit Against Pathogenic Strains (mg/mL)

MBC	MIC	Strains
200	133	<i>S. aureus</i> MRSA
200	133	<i>S. saprophyticus</i>
250	200	<i>P. mirabilis</i>
200	133	<i>E. coli</i>
250	200	<i>S. typhimurium</i>
333	250	<i>K. pneumonia</i> KPC
333	250	<i>Acinetobacter</i> KPC
--	500	<i>P. aeruginosa</i> XDR

Abbreviations: MBC: Minimum bactericidal concentration; MIC: Minimum inhibitory concentration.

Table 2. Results of Antibacterial Activity of Aqueous Extract of *Ficus carica* Fruit Against Pathogenic Strains (mg/mL)

MBC	MIC	Strains
250	200	<i>S. aureus</i> MRSA
250	200	<i>S. saprophyticus</i>
333	250	<i>P. mirabilis</i>
333	250	<i>E. coli</i>
333	250	<i>S. typhimurium</i>
500	333	<i>K. pneumonia</i> KPC
500	333	<i>Acinetobacter</i> KPC
--	1000	<i>P. aeruginosa</i> XDR

Abbreviations: MBC: Minimum bactericidal concentration; MIC: Minimum inhibitory concentration.

In ethanol extract, the MIC and lethal concentrations decreased in gram-positive and gram-negative bacteria compared to aqueous and methanol extracts. Due to bacterial resistance and high growth in positive control (e.g., culture medium of nutrient broth, antibiotics, bacterial suspension), we observed the susceptibility of gram-positive and gram-negative bacteria to aqueous, methanol, and ethanol extracts, respectively. Moreover, among all bacteria, *P. aeruginosa* indicated a high resistance to ampicillin as a positive control, and no lethal concentration was recorded in any of the concentrations for this bacterium.

Discussion

Ficus carica extract also showed that gram-positive bacteria were more susceptible to gram-negative bacteria. Thus, it can be concluded that the effect of plant extract on gram-positive bacteria was greater. In all cases, the antibacterial effect increased by increasing the concentration of plant extracts. Aqueous, methanol, and ethanol extracts had the highest antimicrobial effect, respectively. *S. saprophyticus* was the most susceptible bacterium of gram-positive bacteria and *P. aeruginosa* was the most resistant bacterium among gram-negative bacteria.

Among the four antibiotic disks of ampicillin, gentamicin, ciprofloxacin, and sulfamethoxazole, the effect of ampicillin disk (with an inhibition zone diameter of 30 mm in most bacteria) and gentamicin (with a

smaller inhibition zone diameter) were found to be weak in gram-positive and gram-negative strains, respectively. Moreover, all four resistant strains (i.e., *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, and *Acinetobacter*) showed 100% resistance to four antibiotics. High level of vitamin C turns it to be a potent antioxidant.

The present study revealed that aqueous and methanol extracts at concentrations of 500 and 1000 mg/L had a significant effect on gram-positive and gram-negative bacteria, and they showed greater effects on gram-positive bacteria compared to gram-negative bacteria.

Examining the antimicrobial activity of *F. carica* methanol extract against oral bacteria, Jeong et al (10) proved the antimicrobial effect of *F. carica*, and they further found that *E. coli* and *S. aureus* were the most susceptible gram-positive and gram-negative cells. In the present study, susceptibility of *E. coli* bacteria to gram-negative and *S. aureus* to gram-positive was proven.

In an experiment conducted by Rashid et al (11) entitled "Antimicrobial activity of leaf extract in comparison with latex extract against selected bacteria and fungi", results demonstrated that latex extract of *F. carica* had a stronger effect than ethanol extract of leaf on most bacteria and fungi. Further, results indicated that latex had a lethal effect on several bacteria and was more active than the gentamicin antibiotic.

The diameter of inhibition zone was 15 mm in gram-positive bacteria of *S. aureus* and 13 mm in gram-negative bacteria of *P. aeruginosa*. This diameter was 11 mm in *K. pneumoniae*, 10 mm in *E. coli*, and 15 mm in *S. typhimurium*. A study entitled "Phytochemical analysis, antioxidants and antimicrobial activity of three samples of dried *F. carica* from the region of Mascara (Western Algeria)" was conducted by Benmaghnia et al (12). The results indicated that ethanol extract could inhibit growth of most strains, and the inhibition zone diameter was 10 mm in *S. aureus*, 0.8 mm in *P. aeruginosa*, 10 mm in *E. coli*, and 10 mm in *P. mirabilis*. Compared to the inhibition zone diameter, in the present study, we witnessed the superiority of the inhibition zone in ethanol extract.

Moreover, Hosainzadegan et al (13) conducted an investigation entitled "Antibacterial effects of cooked and raw *F. carica* alone and in combination with each other" and proved the antibacterial effect of *F. carica* in the form of methanol extract.

Based on the results of the research conducted by Pajohi Alamoti et al (14) on aqueous extract of sumac and pathogenic bacteria in different temperature conditions, the effect of aqueous extract on gram-positive bacteria (*S. aureus*) was reported to be greater than that of gram-negative bacteria (*E. coli* and *S. typhimurium*), which was consistent with the results of the present study.

Furthermore, Mirbagheri et al (15) compared antimicrobial effect of different components of Iranian oak against *E. coli* and found that the effect of methanol extracts on bacteria was concentration-dependent. Investigating the anti-microbial activity and interaction

of aqueous and ethanol extracts of *Cordia myxa* leaves on pathogenic microorganisms in vitro, Akhbaryoon et al (16) demonstrated that the highest resistance to aqueous and ethanol extracts of *C. myxa* was related to the gram-negative bacterium of *P. aeruginosa*. The results of this study were in line with the results of the present study.

Likewise, Lazreg-Aref et al (17) conducted an experiment entitled “Chemical composition and antibacterial activity of latex hexane extract of *F. carica* fruit”. The results of this study showed that *S. aureus* and *S. saprophyticus* were more susceptible to disk diffusion method than to other bacteria, which was consistent with the results of the present study in terms of bacterial susceptibility.

The research conducted by Al-Snafi (8) indicated that *F. carica* fruit contained alkaloids, tannins, glycosides, flavonoids, saponins, coumarins, terpenes, phenols, essential oils, carbohydrates, proteins, and minerals. Pharmacological studies also showed that *F. carica* had antiviral, antibacterial, antioxidant, anti-cancer, analgesic, anti-angiogenic, anti-diabetic, anti-inflammatory, anti-wart, and liver-protective properties.

A study conducted by Soni et al (18) entitled “Estimation of nutrients, phytochemical, antioxidant and antibacterial activity of dried *F. carica*” reported the presence of secondary metabolites of dried *F. carica* such as phenols, flavonoids, alkaloids, and saponins along with the antioxidant activity. They also asserted that the *F. carica* had an inhibitory effect on *P. mirabilis*. Another study conducted by Jagathambal et al (19) entitled “Phytochemical and antimicrobial activity of seven solvent extracts of dried *F. carica* against five human pathogens” indicated the presence of secondary metabolites in all extracts and the antibacterial effect of ethanol extract against *S. typhimurium*.

Gram-positive bacteria of *S. saprophyticus* and *S. aureus* exhibited the highest susceptibility to aqueous, methanol, and ethanol extracts, while *P. aeruginosa* exhibited the lowest susceptibility to all three aqueous, methanol, and ethanol extracts. The highest effect of controls (positive) was observed in the susceptible strains related to the antibiotics ampicillin and ciprofloxacin, and antibiotics were not found in the resistant strains. Further, the concentration of 1000 mg/mL was identified as the most effective concentration for gram-positive and gram-negative bacteria. Moreover, aqueous and methanol extracts showed a superior antibacterial effect in susceptible strains and resistant strains; further, all three types of extracts were superior to ampicillin, gentamicin, ciprofloxacin, and sulfamethoxazole.

Conclusion

Based on the results of antimicrobial properties of different plant extracts, it is recommended to examine their antimicrobial effect on laboratory animals. It is also recommended to examine the antioxidant properties of the plant in both in vitro and in vivo models. It is also suggested to examine the effect of plant fruit extracts on

cancer cell lines. Given the antibacterial effects of plant extracts, it is also recommended that the inhibitory effects of the extracts on other organisms such as fungi, viruses, and nematodes be investigated and that extraction be performed by different methods.

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Authors' contributions

Shayda Jabbari carried out the experiment and wrote the article, Maryam Sadat Mirbagheri Firoozabad supervise the project and wrote the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article

Ethical issues

This article does not contain any studies with human participants or animals performed by any of the authors

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