

Contents lists available at ScienceDirect Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb



Floral research http://dx.doi.org/10.1016/j.apjtb.2015.12.010

Phenolic and flavonoid contents, antioxidant and antimicrobial activities of leaf extracts from ten Algerian *Ficus carica* L. varieties



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ARTICLE INFO

Article history: Received 9 Nov 2015 Received in revised form 1 Dec 2015 Accepted 10 Dec 2015 Available online 31 Dec 2015

Keywords: Fig leaves Phenolics Flavonoids Antioxidant activity Antimicrobial activity

ABSTRACT

Objective: To determine the total phenolic and flavonoid contents, antioxidant and antimicrobial activities of methanolic leaf extracts of ten Algerian fig (*Ficus carica* L.) varieties (uniferous, biferous and caprifig tree).

Methods: Phenolics were extracted by Soxhlet method and analyzed by the Folin– Ciocalteu colorimetric method. Flavonoids were determined by aluminum trichloride assay and the antioxidant capacity was determined by the 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay. The antimicrobial activity was studied with the disc diffusion method and a macrodilution broth method was used to determine the minimal inhibitory concentrations and minimal lethal concentrations.

Results: The mean extract yield was $14.10\% \pm 0.66\%$ (n = 10). Leaf extract of biferous followed by uniferous varieties had the highest total phenolic contents [(52.296 ± 5.232) and (48.973 ± 2.015) mg gallic acid equivalent/g of dry plant extract respectively], flavonoids [(14.388 ± 0.333) and (14.136 ± 1.082) mg quercetin equivalent/g of dry plant extract] and antioxidant capacity [IC₅₀ (798.754 ± 108.590) and (825.004 ± 110.835) µg/mL]. Antioxidant capacity of fig leaves was significantly correlated with phenolic contents (r = 0.748). These extracts showed bactericidal activity and moderate antifungal activity, and the minimal inhibitory concentrations and minimal lethal concentrations were determined on *Bacillus cereus* and *Staphylococcus aureus*.

Conclusions: All tested extracts contain phenolic compounds and exhibited an antioxidant activity and an antimicrobial effect against Gram-positive and Gram-negative bacteria. Further researches on identification and purification of phenolic compounds are required.

1. Introduction

Phenolic compounds are common plant secondary metabolites which have not only physiological functions in plants but also positive effects for human health because they can act as antioxidants ^[1]. Antioxidants play important roles in preventing pathogenic processes related to cancer, cardiovascular disease, macular degeneration, cataracts and asthma, and can enhance immune function. Antioxidant defenses protect the body from the detrimental effects of free radicals generated as byproducts of normal metabolism [2].

In addition to antioxidative roles, phenolic compounds from different plants had been reported to have antimicrobial activity against different pathogenic microorganisms [3–5]. There is an increasing interest in medicinal plants as an alternative to synthetic drugs, particularly against microbial agents because of the growth of antibiotic resistance [6]. The search for new antimicrobial agents like phenolic compounds has therefore become indispensable.

Thousands of plants are well known in traditional medicine system for their medicinal and therapeutic potentials worldwide

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Peer review under responsibility of Hainan Medical University. The journal implements double-blind peer review practiced by specially invited international editorial board members.

alike fig [*Ficus carica (F. carica)*] which is a deciduous tree belonging to the Moraceae family. It is one of the earliest cultivated fruit trees and an important crop worldwide for both dry and fresh consumption [1,7,8]. Its fruit, root and leaves are used in the native system of medicine in different disorders such as gastrointestinal (colic, ulcers, indigestion, loss of appetite and diarrhea), respiratory (sore throats, coughs and bronchial problems), inflammatory, furuncles, cancer and cardiovascular disorders [9,10].

Infusions or decoctions of fig tree leaves have been traditionally employed in the treatment of tumors and diseases associated with inflammation, in the prevention of nutritional anemia and as anthelmintic [10,11]. Some biological activities of different parts from *F. carica*, namely, antioxidant, antimicrobial, acetyl cholinesterase inhibition, anticarcinogenic, anti-inflammatory, inhibition of low density lipoprotein oxidation in humans and antidiabetic have been reported [12–25].

Some phenolic compounds, with reported pharmacological properties have already been isolated from fig leaves, namely, furanocoumarins like psoralen and bergapten, flavonoids like quercetin 3-*O*-rutinoside and phenolic acids like ferulic acid, 3-*O*-caffeoylquinic acid and 5-*O*-caffeoylquinic acid [11].

The aim of the present study was to determine the total phenolic and flavonoid contents of leaf extracts obtained from ten Algerian *F. carica* varieties and to evaluate their biological activity, especially as antioxidant and antimicrobial agent. To our knowledge, this is the first report comparing phenolic composition and bioactivity of the Algerian fig leaves varieties.

2. Materials and methods

2.1. Standards and reagents

Folin–Ciocalteu, gallic acid, quercetin, butylhydroxytoluene (BHT), 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma–Aldrich (USA). Methanol, acetic and hydrochloric acids, isoamylic alcohol, ammonium, benzene, sodium carbonate, ferric trichloride, aluminum trichloride, dimethyl sulfoxide (DMSO) were obtained from Merck (Germany), Rectapur, Cheminova (France) and Fluka. Mueller-Hinton agar and broth and Sabouraud dextrose agar were obtained from Pasteur Institute (Algeria).

2.2. Plant material

Ten Algerian varieties of *F. carica* (uniferous: "Bidha", "Hamra", "Onk Elhamam", "Zarrouk", "Chatwi", "Boughandjo" and "Safra"; biferous: "Bakkor" and "Bither" and caprifig tree: "Dhokkar") leaves were collected in Lakhdaria, Province of Bouira (northeast of Algeria). The leaves were airdried at room temperature for 20 days and were powdered and stored for later analysis.

2.3. Extracts preparation

Thirty gram of powdered leaves samples were extracted with 300 mL pure methanol for 8 h using the Soxhlet apparatus. Afterwards, the resulting extracts were filtered and solvent was evaporated under reduced pressure at 35 $^{\circ}$ C using rotary

vacuum evaporator (BÜCHI). At last, the residues were kept in small sterile bottles under refrigerated conditions until used. The yield (%) of evaporated dried extracts was calculated as 100 DW_{ext}/DW_{samp} , where DW_{ext} was dry weight of extract after evaporation of solvent and DW_{samp} was the dry weight of sample.

2.4. Microbial strains

F. carica leaf extracts were tested against two strains of fungi: *Aspergillus brasiliensis* (ATCC 16404) (*A. brasiliensis*) and *Candida albicans* (ATCC 10231) (*C. albicans*). Of the nine tested bacteria, five were Gram-positive [*Bacillus cereus* (ATCC 10876) (*B. cereus*), *Bacillus subtilis* (ATCC 9372) (*B. subtilis*), *Staphylococcus aureus* (ATCC 6538) (*S. aureus*), *Enterococcus faecalis* (ATCC 29200) (*E. faecalis*) and *Micrococcus luteus* (ATCC 4698)] and four were Gram-negative [*Klebsiella pneumoniae* (ATCC 4352), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922) (*E. coli*) and *Salmonella* sp.]. These microorganisms were obtained from culture collection of Pasteur Institute (Algiers), Laboratory of Microbiology of SAIDAL (Bridge of Constantine, Algiers) and Algerian Drugs Laboratory (Tipaza, Algeria).

2.5. Phytochemical analysis

Phytochemical tests of the aqueous leaf extracts of fig (maceration of 5 g of leaf powder in 50 mL of distilled water for 30 min) were carried out qualitatively for the presence of an-thraquinones, coumarins, alkaloids, flavonoids, saponins, anthocyanin and tannins according to the standard methods [26].

2.6. Total phenolic contents

Total phenolic contents of each sample were measured by the Folin–Ciocalteu's method [27]. Total phenolic content was expressed as milligrams gallic acid equivalents per gram of dry plant extract (mg GAE/g DE) through the calibration curve of gallic acid that its linearity range was from 10 to 100 μ g/mL ($R^2 > 0.99$).

2.7. Total flavonoid contents

Total flavonoid content was determined using aluminum trichloride assay [28]. Total flavonoid content was expressed as milligrams quercetin equivalents per gram of dry plant extract (mg QE/g DE) through the calibration curve of quercetin that its linearity range was from 0.5 to 8 μ g/mL ($R^2 > 0.99$).

2.8. Antioxidant activity

Briefly, all extracts were dissolved in pure methanol at eight different concentrations (50–2800 μ g/mL). A total of 0.3 mL of extract was mixed with 2.7 mL of methanol solution containing DPPH radical (6 × 10⁻⁵ mol/L). The mixture was shaken for 20 s and the absorbance was measured at 517 nm (Schimadzu-UV-2401 PC) after 60 min incubation at room temperature and dark area. Pure methanol was used as blank solution and DPPH solution was used as a control. The inhibition percentage of the absorbance was calculated using the equation:

Inhibition (%) =
$$\left[\left(A_{control} - A_{sample} \right) / A_{control} \right] \times 100$$

where, $A_{control}$ was the absorbance of the solution without extract and A_{sample} was the absorbance of solution with extract in different concentrations [29]. The sample concentration providing IC₅₀ was calculated by plotting inhibition percentages against concentrations of the sample. BHT and gallic acid were used as standards.

2.9. Antimicrobial activity

2.9.1. Disc diffusion assay

F. carica leaf extracts were dissolved in DMSO and were sterilized by filtration on 0.45 µm Millipore filters. Disc diffusion method was employed for the determination of antimicrobial activity of the extracts. A total of 100 µL of suspensions containing 10⁷ CFU/mL of bacteria, in exponential growth phase, and 10⁶ CFU/mL of yeast were spread on Mueller-Hinton agar medium and Sabouraud dextrose agar respectively [30]. Filter paper disks (9 mm of diameter) were impregnated with 50 µL of each extract (7.5 mg/disc) and placed on the inoculated Petri dishes. Negative control was performed using DMSO solvent employed to dissolve the different extracts. Ciprofloxacin (100 µg/disc), oxacillin (500 µg/disc) and lamidaz (100 µg/disc) were individually used as positive controls for bacteria and fungi. Petri dishes were then incubated during 24 h at 37 °C for bacterial strains and 48 h at 30 °C for fungi. Antimicrobial activity was evaluated by measuring the inhibition zone (mm) against the studied microorganisms, including disc diameter.

2.9.2. Macrodilution assay

A macrodilution broth method was used to determine the minimal inhibitory concentrations (MIC) and minimal lethal concentrations (MLC) for *S. aureus* and *B. cereus* which were determined as highly sensitive to *F. carica* leaf extracts (inhibition diameter: 15 mm) in disc diffusion assay. Serial doubling dilution of each extract was prepared in DMSO with final concentrations ranging from 1.09 to 35.00 mg/mL. A total of 950 μ L of Mueller-Hinton broth was mixed with 50 μ L of bacterial suspension (10⁷ CFU/mL) and 1 000 μ L of each extract dilution. Mixture was incubated for 24 h at 37 °C [30].

To evaluate MLC, aliquots (10 μ L) of broth were taken from each negative tube, after MIC determination and cultured in Mueller-Hinton agar plates. Plates were then incubated for 24 h at 37 °C.

2.9.3. Statistical analysis

All measurements were performed in triplicate and the results were represented as mean \pm SEM. Statistical analyses were realized with the GraphPad Prism 6 statistics program. Data statistical analyses were achieved by using One-way ANOVA and Tukey-test. The level of significance was set at P < 0.05.

3. Results

3.1. Phytochemical analysis

The results of our preliminary phytochemical analysis revealed that the aqueous extract of dried powdered leaves tested contained flavonoids, alkaloids, coumarins and saponins.

3.2. Yield of extract, total phenolic and flavonoid contents

Yield of extract shown in Table 1 ranged between 12.52% for "Bakkor" variety and 19.80% for "Safra" variety. The methanolic extracts of "Bither", "Bidha" and "Chatwi" fig leaves presented the highest quantities of phenolic compounds [(58.704 ± 0.455), (53.519 ± 0.417) and (52.370 ± 0.353) mg GAE/g DE respectively] (Table 1). Indeed, the total phenolic content was significantly different among the ten varieties (P < 0.05) and the biferous followed by uniferous varieties had the highest total phenolic contents [means: (52.296 ± 5.232) and (48.973 ± 2.015) mg GAE/g DE respectively]. Whereas caprifig tree had the lowest total phenolics [(46.074 ± 0.134) mg GAE/g DE at mean].

In our study, the highest amounts of flavonoids were noted in "Chatwi" and "Safra" varieties with (16.211 ± 0.156) and (16.093 ± 0.166) mg QE/g DE correspondingly (Table 1). The lowest and similar values were recorded in "Dhokkar" and "Zarrouk" varieties. It seemed that flavonoid content was significantly different among the ten leaf extracts studied (P < 0.05) and biferous followed by uniferous varieties had the highest flavonoid amount [means: (14.388 ± 0.333) and (14.136 ± 1.082) mg QE/g DE].

Table 1

Yield, total phenolic contents and total flavonoids of fig leaf extracts.

Varieties	Yield of extracts (%)	Total phenolic contents (mg GAE/g DE)	Total flavonoids (mg QE/g DE)
Onk	14.18	49.741 ± 0.817^{a}	12.558 ± 0.116^{a}
Elhamam			
Hamra	15.91	42.889 ± 0.357^{b}	12.492 ± 0.093^{a}
Zarrouk	13.47	48.815 ± 0.515^{af}	11.700 ± 0.132^{a}
Boughandjo	16.64	47.407 ± 0.522^{ae}	14.455 ± 0.396^{b}
Safra	19.80	48.074 ± 0.464^{ae}	16.093 ± 0.166^{ce}
Bidha	13.71	$53.519 \pm 0.417^{\circ}$	$15.446 \pm 0.040^{\text{deg}}$
Chatwi	15.13	$52.370 \pm 0.353^{\rm ac}$	16.211 ± 0.156^{e}
Bither	14.48	58.704 ± 0.455^{d}	$13.980 \pm 0.060^{\text{fbe}}$
Bakkor	12.52	45.889 ± 0.849^{e}	$14.795 \pm 0.306^{\text{gb}}$
Dhokkar	13.94	$46.074 \pm 0.134^{\text{e}}$	11.667 ± 0.041^{a}

Data were represented as mean \pm SEM of three measurements. Different letters symbolized significant differences (P < 0.05) by mean of the nonparametric Tukey-test.

3.3. Antioxidant capacities

Leaf extracts of the ten Algerian fig varieties were investigated and control samples of gallic acid and BHT exhibited DPPH scavenging capacity, in a concentration-dependent way (Figures 1 and 2).

The results of antioxidant capacity were shown in Table 2. The lowest IC₅₀ values indicated the highest free radical scavenging activity of the extract. In general, the amount of antioxidant capacity (IC₅₀) of fig leaf extracts ranged between 659.97 and 1 119.59 µg/mL with an average of 849.21 µg/mL "Chatwi", "Onk Elhamam", "Bither", "Bidha" and "Zarrouk" were the varieties with stronger ability to scavenge free radical DPPH, which was related with the highest phenolic contents comparing to the other varieties. Antioxidant capacity of fig leaves was significantly correlated with phenolic contents (r = 0.748) but not with flavonoid values (r = 0.007).

In comparison, it seemed that the radical scavenging activities of the positive controls, gallic acid and BHT $[IC_{50} = (15.48 \pm 0.13) \text{ and } (82.77 \pm 0.43) \text{ µg/mL}, \text{ respectively}]$ were higher than that of the *F. carica* leaf extracts.

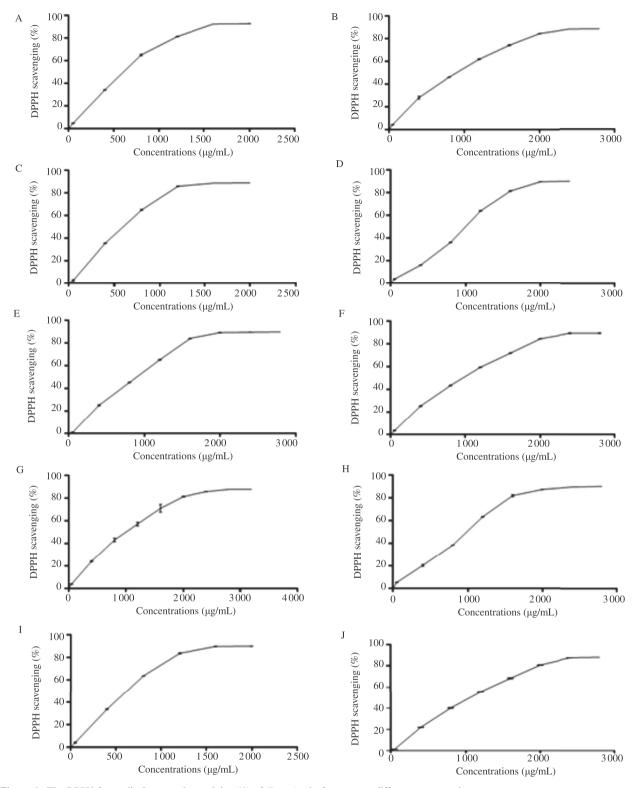


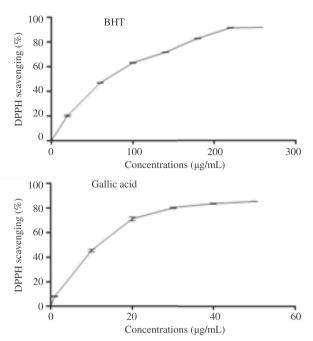
Figure 1. The DPPH free radical scavenging activity (%) of *F. carica* leaf extracts at different concentrations. A: Onk Elhamam; B: Safra; C: Chatwi; D: Zarrouk; E: Dhokkar; F: Boughandjo; G: Hamra; H: Bither; I: Bidha; J: Bakkor; Each value was represented as mean \pm SEM of three measurements.

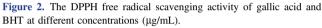
3.4. Antimicrobial activity

3.4.1. Disc diffusion assay

Most extracts showed bactericidal activity against different species of Gram-positive and Gram-negative bacteria and a moderate antifungal activity (Figure 3). *S. aureus* and *B. cereus* bacteria were more sensitive to *F. carica* extracts.

No inhibition was observed with the solvent control (DMSO) which was used as solvent to solubilize the dry extracts. Bacterial and fungal growth was inhibited by the antibiotics and





Each value was represented as mean \pm SEM of three measurements.

Table 2

Free radical scavenging capacities of fig leaf extracts, gallic acid and BHT.

Varieties	IC ₅₀ (µg/mL)
Onk Elhamam	$665.19 \pm 4.38^{\text{ecg}}$
Hamra	1094.32 ± 8.00^{a}
Zarrouk	$681.77 \pm 5.00^{\text{dbceg}}$
Boughandjo	1037.13 ± 5.92^{a}
Safra	$983.56 \pm 6.15^{\rm f}$
Bidha	672.55 ± 2.73^{bcdeg}
Chatwi	$659.97 \pm 0.92^{\circ}$
Bither	$665.76 \pm 3.36^{\rm gc}$
Bakkor	1119.59 ± 12.24^{i}
Dhokkar	$931.74 \pm 5.16^{\rm h}$
Gallic acid	15.48 ± 0.13^{j}
BHT	82.77 ± 0.43^{k}

The IC₅₀ values were obtained by linear regression analysis. Different letters symbolized significant differences (P < 0.05) by mean of the Tukey-test. Data were represented as mean ± SEM of three measurements.

used as control. Ciprofloxacin inhibition zones varied from (30.67 ± 0.67) mm for *E. faecalis* to (48.00 ± 0.58) mm for *Salmonella* sp., oxacillin inhibition zones ranged between (17.67 ± 0.67) mm for *B. cereus* and (58.67 ± 0.33) mm for *B. subtilis* and lamidaz inhibition zones were (20.67 ± 0.67) mm for *C. albicans* and (32.33 ± 1.45) mm for *A. brasiliensis*.

3.4.2. Macrodilution assay

Evaluation of MIC and MLC of the ten *F. carica* leaf extracts showed a variability of inhibition among the bacterial strains tested (Table 3). *B. cereus* showed more sensibility to these extracts when compared with *S. aureus*. The leaf extracts of "Dhokkar" variety were proved to be more active with MIC and MLC values ranging from 2.19 to 8.75 mg/mL and 4.38–17.50 mg/mL, respectively (Table 3).

Table 3

Antibacterial activity (MIC and MLC) of *F. carica* leaf extracts for *S. aureus* and *B. cereus*. mg/mL.

Extracts		S. aureus	B. cereus
Bidha	MIC	8.75	4.48
	MLC	17.50	8.75
Dhokkar	MIC	8.75	2.19
	MLC	17.50	4.38
Onk Elhamam	MIC	17.50	4.38
	MLC	35.00	4.38
Zarrouk	MIC	17.50	4.48
	MLC	35.00	4.48
Hamra	MIC	17.50	4.48
	MLC	17.50	8.75
Boughandjo	MIC	17.50	8.75
	MLC	35.00	35.00
Safra	MIC	17.50	8.75
	MLC	17.50	8.75
Bither	MIC	8.75	4.48
	MLC	17.50	17.50
Bakkor	MIC	17.50	4.48
	MLC	35.00	17.50
Chatwi	MIC	17.50	8.75
	MLC	35.00	17.50

Experiments were performed in duplicate. MIC and MLC were determined by a macrodilution method (mg/mL, w/v).

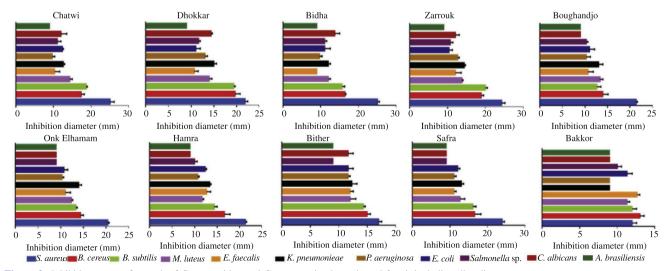


Figure 3. Inhibition zones of growth of Gram-positive and Gram-negative bacteria and fungi, including disc diameter. Data were represented as mean \pm SEM of three measurements. Significant differences (P < 0.05) were observed between tested microorganisms among the same variety. *M. luteus: Micrococcus luteus; K. pneumoniae: Klebsiella pneumoniae; P. aeruginosa: Pseudomonas aeruginosa.*

4. Discussion

F. carica leaves may constitute an excellent source of bioactive compounds, specifically, phenolic compounds. Phenolic contents in our study were highest than the sum of the determined phenolic compounds registered by Oliveira *et al.* [18] on "Branca Tradicional" and "Pingo de Mel" fig leaves and by Konyaltoğlu *et al.* [31]. On the other hand, stem was the rich fig part on phenolic compounds [(133.00 ± 3.50) mg GAE/g DM] [32]. In fact, the total phenolic content is significantly different among the three vegetal materials, following the order: leaves > peels > pulps [18,33]. This fact is not surprising since these compounds, especially flavonoids, act as UV filters, protecting some cell structures, like chloroplasts, from harmful effects of UV radiation [34]. In the review by Saoudi and El Feki, fig stem was shown to have a high amount of flavonoids [(43.25 ± 2.00) mg QE/g DE] [32].

The qualitative composition of fig leaves extracts revealed three hydroxycinnamic acids (3- and 5-*O*-caffeoylquinic acids and ferulic acid), one flavonoid glycoside (quercetin 3-*O*-rutinoside) and two furanocoumarins (psoralen and bergapten) [11,18]. In addition, Teixeira *et al.* identified chlorogenic acid in fig leaves [35].

Antioxidants have recently become a topic of increasing interest to health and food science researchers and medical experts [36]. The antioxidant potential of *F. carica* pulps, peels and leaves was checked [13,18]. All materials exhibited activity against DPPH and nitric oxide radicals. However, only the leaves presented capacity to scavenge superoxide radical. Leaves were always the most effective part, which seems to be related with phenolic compounds [18]. Similar to our results, a strong correlation between the phenolic content and the antioxidant capacity of figs has been previously reported by different authors [1,18,31,37].

The effect of phenolic compounds on preventing radical scavenging was studied and it is generally assumed the ability of these compounds to act as hydrogen donors [12,38]. Antioxidant capacities of our studied varieties were lower than those of Oliveira *et al.* on "Branca Tradicional" and "Pingo de Mel" fig varieties [18]. Flavonoids, carotenoids and triterpenes have antioxidant activity by scavenging reactive oxygen species which prevent potential damage to cellular components such as DNA, proteins and lipids [39].

Fig extracts and latex showed antimicrobial activity against a wide range of bacteria including antibiotic-resistant species and fungal species [17,30]. Our results showed that the Gram-positive bacteria were more sensitive to inhibition by fig leaf extracts [(15.4 \pm 0.6) mm at mean, n = 50] than Gram-negative bacteria [(11.3 \pm 0.2) mm at mean, n = 40]. This phenomenon was previously reported [40,41]. It is not known exactly why Gramnegative bacteria should be less susceptible, but it may be related to the outer membrane which contains peptidoglycan and lipopolysaccharide, endows the bacterial surface with strong hydrophilicity and acts as strong permeability barrier [42]. Hydro-alcoholic *F. carica* leaf extract and its derived fractions display moderate antimicrobial potential against *S. aureus*, *E. coli* and *Pseudomonas*, in the range of 0%–13% [13].

Our results of antibacterial activity of fig leaf extracts against *S. aureus* were lower than those obtained by Lee and Cha (MIC: 2.5–20 mg/mL and MLC: 5–20 mg/mL), with the same part of plant against clinical isolates of methicillin-resistant *S. aureus* [17]. Whereas, Olufemi and Olusegun registered a higher MIC

(25 mg/mL) with *F. carica* leaf aqueous extracts and a lower MIC (6.25 mg/mL) with ethanolic extracts against *S. aureus* [41].

At last of this work, fig leaves of different tested varieties appeared as a good source of health-promoting polyphenols and flavonoids and had beneficial effects like antioxidant and antimicrobial activities against Gram-positive and Gram-negative bacteria. To increase the antioxidant and the antimicrobial effects of leaf extracts from fig tree, it seems important to identify and purify their phenolic compounds in further studies.

Conflict of interest statement

We declare that we have no conflict of interest.

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