



FRUIT EXTRACTS OF ALGERIAN *FICUS CARICA* L.: POTENT *IN VITRO* ANTI-INFLAMMATORY ACTIVITY AND TARGETED ANTIMICROBIAL EFFECTS

EXTRACTOS DE FRUTOS DE *FICUS CARICA* L. DE ARGELIA: POTENTE ACTIVIDAD ANTIINFLAMATORIA *IN VITRO* Y EFECTOS ANTIMICROBIANOS DIRIGIDOS

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SUMMARY

Background and aims: This study investigated the antimicrobial and antiinflammatory properties of extracts from four Algerian *Ficus carica* L. varieties, including figs and breba figs (*Bakor*).

M&M: Methanolic and aqueous (decoction and infusion) extracts were evaluated for antimicrobial activity against six bacterial pathogens and *Candida albicans*, and for *in vitro* anti-inflammatory activity using protein denaturation and erythrocyte membrane stabilization assays. Statistical analyses were performed using nonlinear regression and two-way ANOVA ($p < 0.05$).

Results: Only aqueous infusion extracts showed antimicrobial activity, particularly against *Staphylococcus aureus*, *Enterococcus faecalis*, and *Escherichia coli*. Most extracts, especially aqueous and methanolic preparations from Lahmar varieties, exhibited stronger inhibition of protein denaturation than diclofenac. Several extracts also stabilized erythrocyte membranes, and HPLC analysis suggested associations with phenolic compounds.

Conclusions: These findings support traditional uses and identify aqueous fig infusions, particularly from Lahmar varieties, as promising preparations with anti-inflammatory and selective antimicrobial effects.

KEY WORDS

Algeria, antimicrobial activity, anti-inflammatory activity, *Ficus carica*, erythrocyte membrane stabilization.

RESUMEN

Introducción y objetivos: Este estudio investigó las propiedades antimicrobianas y antiinflamatorias de extractos de frutos de cuatro variedades argelinas de *Ficus carica* L., incluyendo higos y brevas (*Bakor*).

M&M: Se evaluaron extractos metanólicos y acuosos (decocción e infusión) para determinar su actividad antimicrobiana frente a seis bacterias patógenas y *Candida albicans*, así como su actividad antiinflamatoria *in vitro* mediante ensayos de inhibición de la desnaturalización proteica y estabilización de la membrana eritrocitaria. Los análisis estadísticos se realizaron mediante regresión no lineal y ANOVA de dos vías ($p < 0,05$).

Resultados: Solo los extractos obtenidos por infusión acuosa mostraron actividad antimicrobiana, particularmente frente a *Staphylococcus aureus*, *Enterococcus faecalis* y *Escherichia coli*. La mayoría de los extractos, especialmente las preparaciones acuosas y metanólicas de las variedades Lahmar, exhibieron una inhibición de la desnaturalización proteica superior a la del diclofenac. Además, varios extractos mostraron actividad estabilizadora de la membrana eritrocitaria, y el análisis por HPLC sugirió una asociación entre estas actividades biológicas y la presencia de compuestos fenólicos.

Conclusiones: Estos hallazgos respaldan los usos tradicionales e identifican las infusiones acuosas de higo, particularmente de las variedades Lahmar, como preparaciones prometedoras con efectos antiinflamatorios y antimicrobianos selectivos.

PALABRAS CLAVE

Actividad antiinflamatoria, actividad antimicrobiana, Argelia, estabilización de la membrana eritrocitaria, *Ficus carica*.

INTRODUCTION

The common fig tree (*Ficus carica* L.) holds a prominent place in Algerian arboricultural and ethnobotanical heritage, with a national orchard estimated at several million trees (Ferradji *et al.*, 2011). Its importance extends beyond fruit production, as its organs, particularly the fruits, have been used for centuries in traditional medicine to treat a variety of ailments, such as respiratory, digestive, inflammatory, and skin disorders (Lansky & Paavilainen, 2011; Irudayaraj *et al.*, 2016). These empirical uses strongly suggest the presence of active compounds with antimicrobial and anti-inflammatory properties. The emergence of antibiotic resistance and the side effects associated with synthetic non-steroidal anti-inflammatory drugs make the search for new therapeutic molecules from natural sources crucial. Medicinal plants, as complex chemical libraries, represent an invaluable reservoir for the discovery of such compounds. *F. carica*, in particular, has been the subject of preliminary reports mentioning various biological activities, including hepatoprotective, antispasmodic, and antioxidant effects (Guarrera, 2005; Irudayaraj *et al.*, 2016).

Recent advances have significantly expanded our understanding of *Ficus carica* bioactive compounds. Kebal *et al.* (2022) demonstrated that fig fruit extracts exhibit dose-dependent anti-inflammatory effects *in vivo*, correlating strongly with total phenolic and flavonoid content. A comprehensive 2024 review by Fazel *et al.* confirmed that *F. carica* possesses diverse therapeutic properties including anti-inflammatory, antimicrobial, and antioxidant activities, attributed to its rich polyphenolic profile. Using HPLC and GC-MS, Lackner *et al.* (2025) identified key phenolic compounds —gallic acid, catechin, rutin, and psoralen-related molecules— in fig leaf extracts and established their antimicrobial efficacy against various pathogens. These contemporary findings underscore the continued relevance of *F. carica* as a source of bioactive molecules and provide a mechanistic framework for the present investigation. The therapeutic potential of *Ficus carica* has been further substantiated by recent multi-model investigations. Hasnain *et al.* (2026) reported significant anti-inflammatory activity

of fig leaf extracts using a combination of *in vitro*, *in silico*, and *in vivo* approaches. These findings further support the potential of *F. carica* as a promising source of bioactive compounds with anti-inflammatory properties. However, a systematic evaluation of its antimicrobial and anti-inflammatory potential, specifically for local Algerian varieties, remains insufficient. The present study aims to scientifically explore this therapeutic potential using four fig varieties harvested from two distinct bioclimatic regions of Algeria. It pursues three main objectives: (i) to evaluate the antimicrobial activity of methanolic and aqueous extracts against a panel of Gram-positive and Gram-negative pathogenic bacteria and one yeast, (ii) to determine their *in vitro* anti-inflammatory activity via two relevant biochemical models: inhibition of thermal protein (albumin) denaturation and erythrocyte membrane stabilization, and (iii) to establish a preliminary correlation between these biological activities and the phenolic composition of the extracts, analyzed by high-performance liquid chromatography (HPLC). Despite increasing interest in *Ficus carica*, most studies have focused on leaves or non-Algerian cultivars, with limited data on fruit extracts. Comparative studies integrating antimicrobial, anti-inflammatory, and phytochemical profiling of different fruit types (fig vs. breba) from distinct Algerian bioclimatic regions remain scarce, and few investigations combine traditional extraction methods (infusion and decoction) with chromatographic characterization and robust statistical analysis under standardized conditions. Therefore, the present study addresses these gaps by providing a comprehensive evaluation of Algerian fig fruit extracts.

MATERIALS AND METHODS

Origin of Plant Material and Preparation of Extracts

As part of the evaluation of the therapeutic potential of Algerian medicinal plants, this study focused on the fruits of the common fig tree (*Ficus carica* L.). Four local varieties, including two Breba figs (caprifigs, *Bakor*) and two figs, were sampled during the 2017 season (May to September) in two distinct ecoregions. The arid

region of Bechar (Lahmar locality), characterized by a continental desert climate (Rezzoug *et al.*, 2016), provided the varieties *Var. 1* (breba fig) and *Var. 2* (fig). The semi-arid region of Mascara (El Bordj locality), subject to a Mediterranean climate (ANDI, 2013), provided the varieties *Var. 3* (breba fig) and *Var. 4* (fig). After drying in an oven (40 °C, 48 h) and grinding, the fruit powder was used to prepare two types of extracts, aiming to simulate traditional extraction methods (aqueous) and obtain a broad phytochemical profile (methanolic):

Methanolic extracts: Ultrasound-assisted extraction was performed using an ultrasonic bath (40 kHz, 250 W) for 30 min at room temperature after macerating 20 g of powdered material in 200 mL of methanol. The extract was then filtered, centrifuged, and concentrated under reduced pressure according to the protocol of Mahmoudi *et al.* (2013).

Aqueous extracts: in accordance with traditional practices (Kraft & Hobbs, 2004), extracts by decoction (15 min of boiling) and by infusion (15 min in boiled water) were prepared from 50 g of powder in 500 mL of distilled water. The twelve extracts obtained (4 methanolic, 4 aqueous decoctions, and 4 aqueous infusions) were dried, their yields calculated (Sembiring *et al.*, 2018), and stored at 4 °C for subsequent analyses.

Quantitative Phytochemical Profile

The content of major secondary metabolites in the extracts was determined by spectrophotometry. All assays were performed in triplicate, and results are expressed as milligrams of standard equivalent per gram of dry matter (mg/g DM).

Total Phenolic Compounds: determined by the Folin-Ciocalteu method at 765 nm, using gallic acid as a standard (El-Haci *et al.*, 2012).

Total Flavonoids: quantified by the aluminum chloride (AlCl₃) colorimetric test at 430 nm, with quercetin as a reference (Hebi & Eddouks, 2015).

Total Anthocyanins: evaluated by the differential pH method (pH 1.0 and 4.5), with readings at wavelengths 510 and 700 nm, and results expressed as cyanidin-3-glucoside equivalent (Ercisli *et al.*, 2012).

Condensed Tannins: estimated by the reaction with vanillin in an acidic medium ($\lambda = 550$ nm),

using catechin as a standard (Julkunen-Tiitto, 1985).

Antimicrobial Activity Assays

Microbial Strains: Antimicrobial activity was evaluated against a panel of pathogenic microorganisms obtained from international culture collections and provided by the Algerian Center for Quality Control and Packaging and the microbiology laboratory of Bechar Hospital. The tested strains included Gram-positive bacteria: *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 25923; Gram-negative bacteria: *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium*, *Klebsiella pneumoniae* ATCC 700603, and *Escherichia coli* ATCC 25922; as well as the yeast *Candida albicans* ATCC 10231.

Preparation of Inoculum: Microbial strains were initially cultured in nutrient broth and incubated at 37 °C for 18 h. The cultures were then adjusted by suspension in sterile physiological saline solution (0.9 % NaCl) using a vortex mixer. Serial dilutions were performed to standardize the inoculum. The final suspension was adjusted to 0.5 McFarland standard, corresponding to an optical density of 0.08–0.10 at 625 nm and a final concentration of approximately 10⁶ CFU/mL (Daoudi *et al.*, 2016).

Disk Diffusion Assay: The antimicrobial activity of methanolic and aqueous extracts of *Ficus carica* fruits was assessed using the agar disk diffusion method (Murray *et al.*, 2016). This qualitative technique is widely used as a preliminary screening tool to evaluate the *in vitro* antimicrobial potential of natural products and to compare their activity with standard antibiotics (Andrews, 2001; El Amri *et al.*, 2014).

Sterile Petri dishes containing Mueller–Hinton agar were inoculated with the standardized microbial suspensions. Sterile filter paper disks (6 mm diameter, Whatman No. 1), previously sterilized at 180 °C for 30 min, were impregnated with 25 µL of each extract and placed on the inoculated agar surface. Negative control disks were loaded with distilled water or dimethyl

sulfoxide (DMSO), while ampicillin (10 µg/mL) and tetracycline (30 µg/mL) were used as positive controls.

Plates were incubated at 37 °C for 24 h for bacterial strains and at 27 °C for 48 h for *Candida albicans*. After incubation, the diameters of inhibition zones were measured in millimeters. All experiments were performed in triplicate under identical conditions.

Minimum Inhibitory Concentration (MIC) Determination

Minimum inhibitory concentrations (MICs) were determined using the broth microdilution method in sterile 96-well microplates. Serial dilutions of the extracts (0.78–50 mg/mL) were prepared in Mueller–Hinton broth. The bacterial inoculum was adjusted to 0.5 McFarland standard (~10⁸ CFU/mL) and further diluted to obtain a final concentration of approximately 10⁶ CFU/mL in each well. The microplates were incubated at 37 °C for 24 h, and microbial growth was assessed visually. The MIC was defined as the lowest concentration of extract that completely inhibited visible microbial growth. (Celiktaş *et al.*, 2007; Falleh *et al.*, 2008; Liao *et al.*, 2010).

Evaluation of In Vitro Anti-inflammatory Activity

The anti-inflammatory activity was explored through two complementary biochemical tests, using sodium diclofenac as a positive control. The extracts were tested at concentrations ranging from 100 to 500 µg/mL.

Inhibition of Albumin Denaturation: the protective effect of the extracts against thermal denaturation (70°C) of human albumin was measured at 660 nm (Chandra *et al.*, 2012; Alhakmani *et al.*, 2013). The percentage of inhibition and the 50 % inhibitory concentration (IC₅₀) were calculated.

Erythrocyte Membrane Stabilization: the anti-hemolytic activity was evaluated on a 10 % suspension of human red blood cells, subjected to a heat shock (56°C) in the presence of the extracts. The absorbance of the released hemoglobin was read at 560 nm, and the percentage inhibition of hemolysis was determined (Bagad *et al.*, 2011; Chandra *et al.*, 2012).

Qualitative Analysis by High-Performance Liquid Chromatography (HPLC)

Methanolic extracts were selected for HPLC analysis based on their higher total phenolic content and stronger anti-inflammatory activity (lower IC₅₀ values) in order to identify their main constituents. Separations were performed using a YL9100 chromatograph equipped with a C18 column (Agilent, 150 × 4.6 mm, 5 µm). The mobile phase consisted of acidified water containing 1 % acetic acid (A) and methanol (B), applied under a linear gradient from 5 % to 95 % B over 55 min at a flow rate of 1 mL/min. Detection was performed at 254 and 280 nm. Peak identification was based on comparison of retention times with those of 33 authentic standards of phenolic compounds, coumarins, and alkaloids; however, no spectral confirmation (e.g., MS or diode-array detection) was performed, and therefore compound identification should be considered tentative.

Ethical Considerations

Human blood used for the erythrocyte membrane stabilization assay was obtained from healthy volunteers after informed consent. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Anti-Cancer Center of Algiers (Approval No.: 020202021).

Statistical Analyses

The results of phytochemical assays and biological tests are presented as mean ± standard deviation of three independent replicates (n=3). Differences between group means were analyzed by two-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test (significance threshold *p* < 0.05). For antimicrobial activity, comparisons between active extracts and positive controls (antibiotics) were performed using one-sample *t*-tests, as only the extract data had variance while control values were fixed references. IC₅₀ values were estimated using nonlinear regression (four-parameter logistic model), which better describes sigmoidal dose–response relationships. All statistical analyses were performed using R software (version 4.0.0) with the «*agricolae*» package (Mendiburu, 2020; R Core Team, 2020).

RESULTS

Extraction Yields and Quantitative Phytochemical Profile

The first stage of this work evaluated extraction efficiency and the phytochemical composition of different fig preparations. Extraction yields varied according to both solvent and variety; however, two-way ANOVA revealed that these differences were not statistically significant ($p > 0.05$). Among the tested extracts, aqueous decoction showed the highest yield, reaching 11.27 % for breba fig from El Bordj (*Dec. Var.3*). Methanolic and infusion extracts exhibited yields ranging from 4.89 % to 9.45 %, indicating that extraction technique and solvent polarity influence the recovery of soluble compounds (Table 1).

Phytochemical analysis revealed that methanolic extracts were generally richer in bioactive compounds (Table 2). The highest total polyphenol content was recorded in *MeOH Var.1* (10.40 ± 0.48 mg GAE/g), while the highest flavonoid content was observed in *MeOH Var.2* (1.69 ± 0.15 mg QE/g). Aqueous decoctions (Table 3) and infusions (Table 4) showed lower phytochemical contents compared to methanolic extracts. Statistical analysis showed a significant effect of extraction method on total flavonoid content ($F(2,6) = 8.30$, $p = 0.0187$), whereas varietal differences were not significant ($p > 0.05$). Complete statistical parameters, including ANOVA results and *post-hoc* Tukey test outcomes, are presented in Table 5.

Antimicrobial Activity

The antimicrobial screening using the agar disk diffusion method revealed a selective and

Table 1. Extraction Yield (%) of *Ficus carica* Preparations by Variety and Extraction Method.

References= Values represent percentage yield (w/w) based on dry plant material. Two-way ANOVA revealed no statistically significant differences in extraction yields among varieties or extraction methods ($p > 0.05$).

Variety (Type & Origin)	Methanolic Extract	Yield (%)	Aqueous Decoction	Yield (%)	Aqueous Infusion	Yield (%)
Breba fig Lahmar	<i>MeOH Var.1</i>	6.4	<i>Dec. Var.1</i>	7.57	<i>Inf. Var.1</i>	4.89
Fig Lahmar	<i>MeOH Var.2</i>	8.1	<i>Dec. Var.2</i>	8.69	<i>Inf. Var.2</i>	9.45
Breba fig El Bordj	<i>MeOH Var.3</i>	5.9	<i>Dec. Var.3</i>	11.27	<i>Inf. Var.3</i>	8.65
Fig El Bordj	<i>MeOH Var.4</i>	7.4	<i>Dec. Var.4</i>	7.16	<i>Inf. Var.4</i>	5.55

Table 2. Phytochemical Composition of Methanolic Extracts from Four Fig Varieties.

Abbreviations: TFT: Total Flavonoids (mg QE/g: mg quercetin equivalent/g); TPT: Total Polyphenols (mg GAE/g: mg gallic acid equivalent/g); TAT: Total Anthocyanins (mg C3G/g: mg cyanidin-3-glucoside equivalent/g); TTC: Total Condensed Tannins (mg CE/g: mg catechin equivalent/g). References= Values are mean $\pm$ SD ($n = 3$) expressed in mg equivalent per gram of dry matter (mg/g DM).

Variety (Type & Origin)	Extract	TFT (mg QE/g)	TPT (mg GAE/g)	TAT (mg C3G/g)	TTC (mg CE/g)
Breba fig Lahmar	<i>MeOH Var.1</i>	1.15 ± 0.28	10.40 ± 0.48	0.26 ± 0.02	0.195 ± 0.04
Fig Lahmar	<i>MeOH Var.2</i>	1.69 ± 0.15	3.251 ± 0.322	0.411 ± 0.01	0.24 ± 0.05
Breba fig El Bordj	<i>MeOH Var.3</i>	0.923 ± 0.09	1.789 ± 0.30	0.17 ± 0.03	0.125 ± 0.06
Fig El Bordj	<i>MeOH Var.4</i>	0.433 ± 0.06	4.770 ± 0.11	0.55 ± 0.09	0.186 ± 0.01

Table 3. Phytochemical Composition of Aqueous Decoction Extracts from Four Fig Varieties. References= Values are mean $\pm$ SD (n = 3) expressed in mg equivalent per gram of dry matter (mg/g DM). For abbreviations, see Table 2A legend.

Variety (Type & Origin)	Extract	TFT (mg QE/g)	TPT (mg GAE/g)	TAT (mg C3G/g)	TTC (mg CE/g)
Breba fig Lahmar	<i>Dec. Var.1</i>	0.81 $\pm$ 0.09	2.26 $\pm$ 0.13	0.148 $\pm$ 0.05	0.17 $\pm$ 0.04
Fig Lahmar	<i>Dec. Var.2</i>	0.471 $\pm$ 0.11	3.11 $\pm$ 0.20	0.156 $\pm$ 0.03	0.21 $\pm$ 0.01
Breba fig El Bordj	<i>Dec. Var.3</i>	0.635 $\pm$ 0.15	1.445 $\pm$ 0.07	0.173 $\pm$ 0.01	0.155 $\pm$ 0.04
Fig El Bordj	<i>Dec. Var.4</i>	0.41 $\pm$ 0.04	1.855 $\pm$ 0.173	0.29 $\pm$ 0.01	0.09 $\pm$ 0.03

Table 4. Phytochemical Composition of Aqueous Infusion Extracts from Four Fig Varieties. References= Values are mean $\pm$ SD (n = 3) expressed in mg equivalent per gram of dry matter (mg/g DM). For abbreviations, see Table 2A legend.

Variety (Type & Origin)	Extract	TFT (mg QE/g)	TPT (mg GAE/g)	TAT (mg C3G/g)	TTC (mg CE/g)
Breba fig Lahmar	<i>Inf. Var.1</i>	0.157 $\pm$ 0.032	1.06 $\pm$ 0.04	0.223 $\pm$ 0.05	0.125 $\pm$ 0.05
Fig Lahmar	<i>Inf. Var.2</i>	0.296 $\pm$ 0.027	1.41 $\pm$ 0.07	0.211 $\pm$ 0.03	0.137 $\pm$ 0.03
Breba fig El Bordj	<i>Inf. Var.3</i>	0.205 $\pm$ 0.07	0.992 $\pm$ 0.04	0.109 $\pm$ 0.01	0.104 $\pm$ 0.01
Fig El Bordj	<i>Inf. Var.4</i>	0.133 $\pm$ 0.077	1.27 $\pm$ 0.03	0.152 $\pm$ 0.01	0.118 $\pm$ 0.01

generally weak antimicrobial profile. Methanolic extracts (Table 6) and aqueous decoctions (Table 7) showed no detectable inhibition zones against all tested microorganisms at the concentrations used. In contrast, aqueous infusion extracts (Table 8) exhibited limited antibacterial activity against selected strains. Specifically, *Inf. Var.1* (Breba fig Lahmar) inhibited *Enterococcus faecalis* (8.5 $\pm$ 1.0 mm) and *Staphylococcus aureus* (14.0 $\pm$ 0.0 mm), while *Inf. Var.2* (Fig Lahmar) showed activity only against *Escherichia coli* (10.5 $\pm$ 1.0 mm). No antifungal activity was observed against *Candida albicans*. When compared to standard antibiotics, inhibition zones ranged from 11 to 16 mm, indicating that the observed activity of the extracts was weak to moderate in comparison to reference drugs. Statistical comparisons with positive controls showed that *Inf. Var.2* exhibited significantly lower activity

than tetracycline against *E. coli* ($p < 0.01$). *Inf. Var.1* showed no significant difference compared to tetracycline against *S. aureus* ($p = 0.12$). The comparison between *Inf. Var.1* and ampicillin for *S. aureus* could not be statistically assessed due to zero variance in replicate measurements. Overall, most extracts and microorganisms showed no measurable inhibition, confirming the limited antimicrobial potential of non-infusion extracts under the tested conditions. The MIC values for the aqueous infusion extracts are presented in Table 9.

In Vitro Anti-inflammatory Activity

The anti-inflammatory activity was evaluated through two relevant biochemical models.

Inhibition of Protein Denaturation: the anti-inflammatory potential assessed via inhibition of protein denaturation demonstrated that all fig

Table 5. Statistical Analysis of Phytochemical Composition: Two-way ANOVA and *Post-hoc* Tukey Test. References= *Post-hoc* Tukey Test for TFT (Grouped by Extract Type).

Parameter	Factor	df	F-value	p-value	Significance
TFT	Variety	3	—	> 0.05	NS
	Extraction Method	2	8.30	0.0187	*
	Variety × Method	6	—	> 0.05	NS
TPT	Variety	3	—	> 0.05	NS
	Extraction Method	2	—	> 0.05	NS
	Variety × Method	6	—	> 0.05	NS
TAT	Variety	3	—	> 0.05	NS
	Extraction Method	2	—	> 0.05	NS
	Variety × Method	6	—	> 0.05	NS
TTC	Variety	3	—	> 0.05	NS
	Extraction Method	2	—	> 0.05	NS
	Variety × Method	6	—	> 0.05	NS

Table 5 (continued). References= *Values with different superscript letters are significantly different ($p < 0.05$). NS: not significant; * $p < 0.05$.

Extract Type	Mean TFT (mg QE/g) ± SD	Grouping*
Methanolic	1.049 ± 0.26	a
Decoction	0.582 ± 0.20	ab
Infusion	0.198 ± 0.07	b

extracts exhibited significantly higher activity than diclofenac sodium ($p < 0.05$) (Fig. 1A-C; Table 10; Fig. S1-S3). IC_{50} values of the extracts were consistently lower than that of the reference drug (7.26 mg/mL). The most active samples were Lahmar varieties, particularly *Inf. Var.2*: $IC_{50} = 1.92$ mg/mL and *Dec. Var.2*: $IC_{50} = 1.96$ mg/mL. At 500 µg/mL, these extracts inhibited albumin denaturation by more than 14 %, compared with 5.8 % for diclofenac, confirming strong relative activity under *in vitro* conditions (Fig. 1B, C).

Erythrocyte Membrane Stabilization: the membrane stabilization assay, used as a model of lysosomal membrane protection, showed more variable results (Fig. 2A-C; Table 11; Fig. S4-S5). The strongest activity was observed for *MeOH Var.4* (Fig. El Bordj), *Inf. Var.4* (Fig. El Bordj) and Diclofenac (reference). All exhibited IC_{50} values of approximately 1.1 mg/mL, indicating comparable potency. In contrast, *MeOH Var.3* and *Dec. Var.3* showed weak activity ($IC_{50} > 30$ mg/mL), suggesting strong dependence of activity on both extraction method and fruit origin.

Characterization of Bioactive Compounds by HPLC

To correlate the biological activities with their underlying chemical composition, methanolic extracts were analyzed by HPLC. HPLC profiling of methanolic extracts revealed that the phytochemical composition was strongly influenced by the interaction between fruit type and geographical origin. The Fig Lahmar (*Var.2*)

Table 6. Antimicrobial Activity of *F. carica* Methanolic Extracts Using the Disk Diffusion Method. References= Data are presented as mean $\pm$ SD (n = 3). (–): No inhibition zone detected. **TC:** Tetracycline (30 μ g); **AP:** Ampicillin (10 μ g). **Variety key:** *MeOH Var.1:* Breba fig Lahmar; *MeOH Var.2:* Fig Lahmar; *MeOH Var.3:* Breba fig El Bordj; *MeOH Var.4:* Fig El Bordj. No inhibition zones were observed for any extract. Statistical comparison with positive controls was not possible.

Microbial Strains	<i>MeOH Var.1</i>	<i>MeOH Var.2</i>	<i>MeOH Var.3</i>	<i>MeOH Var.4</i>	TC (30 μ g)	AP (10 μ g)
<i>Enterococcus faecalis</i>	–	–	–	–	–	–
<i>Staphylococcus aureus</i>	–	–	–	–	11 $\pm$ 2	16 $\pm$ 1
<i>Escherichia coli</i>	–	–	–	–	15 $\pm$ 1	–
<i>Pseudomonas aeruginosa</i>	–	–	–	–	–	–
<i>Klebsiella pneumoniae</i>	–	–	–	–	–	12 $\pm$ 1
<i>Salmonella typhimurium</i>	–	–	–	–	–	13 $\pm$ 2
<i>Candida albicans</i>	–	–	–	–	–	–

Table 7. Antimicrobial Activity of *F. carica* Aqueous Decoctions Using the Disk Diffusion Method. References= Data are presented as mean $\pm$ SD (n = 3). (–): No inhibition zone detected. **TC:** Tetracycline (30 μ g); **AP:** Ampicillin (10 μ g). **Variety key:** *Dec. Var.1:* Breba fig Lahmar; *Dec. Var.2:* Fig Lahmar; *Dec. Var.3:* Breba fig El Bordj; *Dec. Var.4:* Fig El Bordj. No inhibition zones were observed for any extract. Statistical comparison with positive controls was not possible.

Microbial Strains	<i>Dec. Var.1</i>	<i>Dec. Var.2</i>	<i>Dec. Var.3</i>	<i>Dec. Var.4</i>	TC (30 μ g)	AP (10 μ g)
<i>Enterococcus faecalis</i>	–	–	–	–	–	–
<i>Staphylococcus aureus</i>	–	–	–	–	11 $\pm$ 2	16 $\pm$ 1
<i>Escherichia coli</i>	–	–	–	–	15 $\pm$ 1	–
<i>Pseudomonas aeruginosa</i>	–	–	–	–	–	–
<i>Klebsiella pneumoniae</i>	–	–	–	–	–	12 $\pm$ 1
<i>Salmonella typhimurium</i>	–	–	–	–	–	13 $\pm$ 2
<i>Candida albicans</i>	–	–	–	–	–	–

displayed the most complex profile, characterized by the co-occurrence of gallic acid, catechin, and rutin, compounds known for their synergistic antioxidant and anti-inflammatory properties. In contrast, Fig El Bordj (*Var.4*) uniquely contained berberine, a bioactive alkaloid with well-documented pharmacological relevance.

Caprifig (breba) samples (*Var.1* and *Var.3*) shared a conserved profile marked by the presence of psoralen, a furanocoumarin with reported antimicrobial activity, as well as syringic acid and kaempferol. Additionally, *Var.3* contained detectable levels of quercetin, further contributing to its phytochemical diversity (Figs. 3-6).

Table 8. Antimicrobial Activity of *F. carica* Aqueous Infusions Using the Disk Diffusion Method.

References= Data are presented as mean $\pm$ SD (n = 3). (–): No inhibition zone detected. Different superscript letters indicate significant differences compared to the positive control (one-sample *t*-test, $p < 0.05$). **Statistical notes:** ^aa: $p < 0.001$ vs. tetracycline (*E. faecalis*); ^bb: $p < 0.01$ vs. tetracycline (*E. coli*); ^{NS}NS: not significant vs. tetracycline (*S. aureus*, $p = 0.12$); ^{NP}NP: not performed due to zero variance. **TC:** Tetracycline (30 μ g); **AP:** Ampicillin (10 μ g). **Variety key:** *Inf. Var. 1:* Breba fig Lahmar; *Inf. Var. 2:* Fig Lahmar; *Inf. Var. 3:* Breba fig El Bordj; *Inf. Var. 4:* Fig El Bordj.

Microbial Strains	<i>Inf. Var. 1</i>	<i>Inf. Var. 2</i>	<i>Inf. Var. 3</i>	<i>Inf. Var. 4</i>	TC (30 μ g)	AP (10 μ g)
<i>Enterococcus faecalis</i>	8.5 $\pm$ 1.0 ^a	–	–	–	0 $\pm$ 0	–
<i>Staphylococcus aureus</i>	14.0 $\pm$ 0.0 ^{ANS,NP}	–	–	–	11 $\pm$ 2	16 $\pm$ 1
<i>Escherichia coli</i>	–	10.5 $\pm$ 1.0 ^b	–	–	15 $\pm$ 1	–
<i>Pseudomonas aeruginosa</i>	–	–	–	–	–	–
<i>Klebsiella pneumoniae</i>	–	–	–	–	–	12 $\pm$ 1
<i>Salmonella typhimurium</i>	–	–	–	–	–	13 $\pm$ 2
<i>Candida albicans</i>	–	–	–	–	–	–

Table 9. Minimum Inhibitory Concentration (MIC) of *F. carica* Aqueous Infusions.

References= Values are expressed in mg/mL. (–): No activity detected. Negative controls showed no activity. **Variety key:** *Inf. Var. 1:* Breba fig Lahmar; *Inf. Var. 2:* Fig Lahmar; *Inf. Var. 3:* Breba fig El Bordj; *Inf. Var. 4:* Fig El Bordj.

Microbial Strains	<i>Inf. Var. 1</i>	<i>Inf. Var. 2</i>	<i>Inf. Var. 3</i>	<i>Inf. Var. 4</i>
<i>Enterococcus faecalis</i>	6.25	–	–	–
<i>Staphylococcus aureus</i>	3.125	–	–	–
<i>Escherichia coli</i>	–	6.25	–	–
<i>Pseudomonas aeruginosa</i>	–	–	–	–
<i>Klebsiella pneumoniae</i>	–	–	–	–
<i>Salmonella typhimurium</i>	–	–	–	–
<i>Candida albicans</i>	–	–	–	–

DISCUSSION

The results suggest a promising bioactive potential, as polyphenols and flavonoids are frequently implicated in antimicrobial and anti-inflammatory activities. The dose-dependent activity during the protein denaturation inhibition assay suggests a potential role of the phenolic compounds present in stabilizing protein structure in the face of thermal stress. The significant

differences observed in the erythrocyte membrane stabilization assay ($p < 0.05$) could reflect specific compositions of membranotropic compounds (such as certain flavonoids or saponins) that vary according to variety and extract type. The observed antimicrobial activity, although moderate and selective, is significant. The exclusive inhibition by aqueous extracts obtained by infusion, particularly against *Staphylococcus aureus*, *Enterococcus faecalis*, and *Escherichia coli*, underscores the

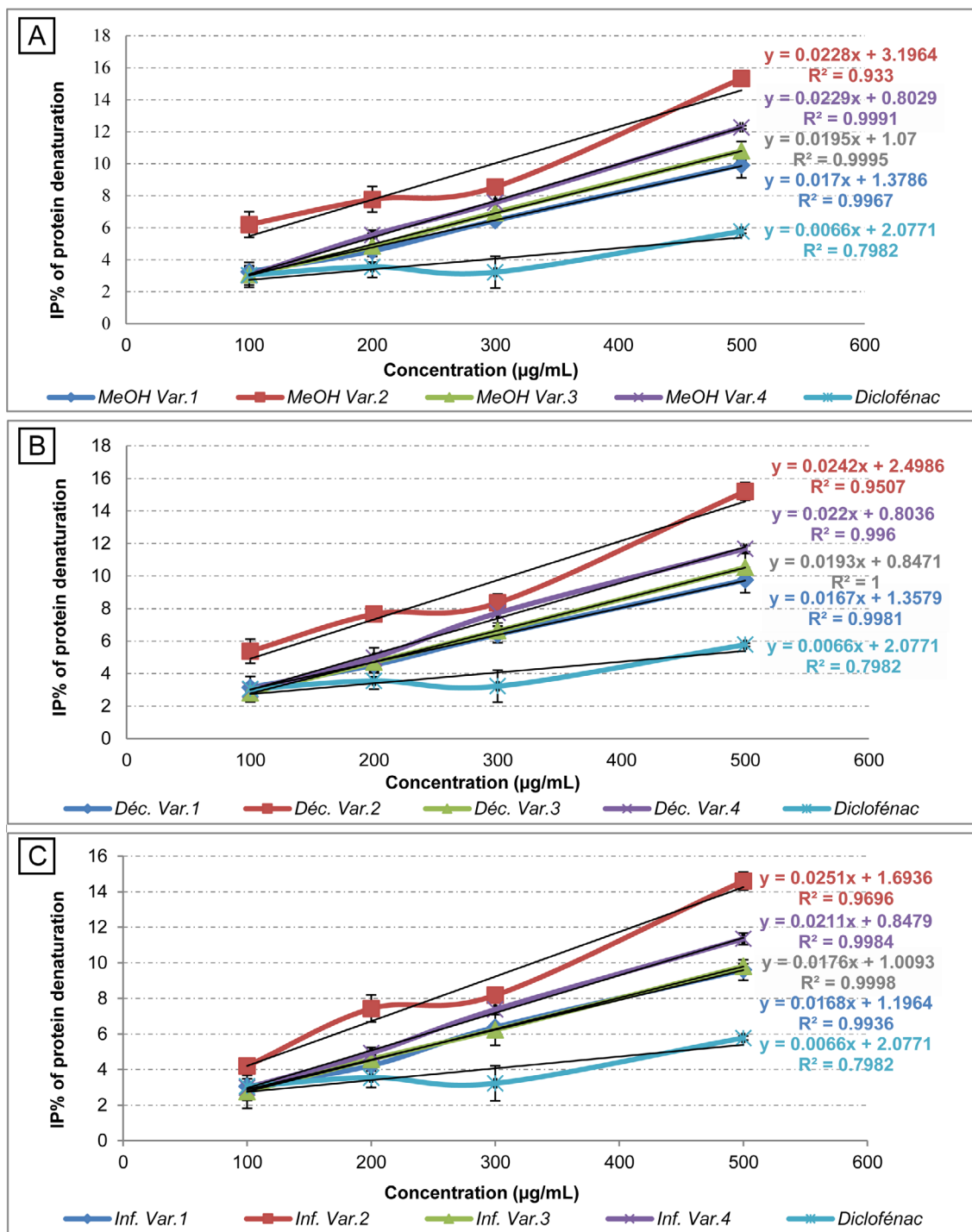


Fig. 1. Inhibition of human albumin denaturation by *F. carica* fruit extracts prepared using different extraction methods. **A:** Methanolic extracts: MeOH Var.1, Breba fig Lahmar; MeOH Var.2, Fig Lahmar; MeOH Var.3, Breba fig El Bordj; MeOH Var.4, Fig El Bordj. **B:** Decoctions: Dec. Var.1, Breba fig Lahmar; Dec. Var.2, Fig Lahmar; Dec. Var.3, Breba fig El Bordj; Dec. Var.4, Fig El Bordj. **C:** Infusions: Inf. Var.1, Breba fig Lahmar; Inf. Var.2, Fig Lahmar; Inf. Var.3, Breba fig El Bordj; Inf. Var.4, Fig El Bordj.

Table 10. IC₅₀ Values of *F. carica* Extracts in the Protein Denaturation Inhibition Assay. References= **One-way ANOVA:** Factor (Variety): $F(4, 8) = 2061.76$, $p < 0.001$. Uppercase letters (A–D) indicate significant differences at $p < 0.05$. Values sharing the same letter within each column are not significantly different ($p > 0.05$).

Variety (Type & Origin)	Methanolic Extract	IC ₅₀ (mg/mL)	Decoction Extract	IC ₅₀ (mg/mL)	Infusion Extract	IC ₅₀ (mg/mL)
Breba fig Lahmar	MeOH Var.1	2.860 ^{AA}	Dec. Var.1	2.912 ^{AA}	Inf. Var.1	2.904 ^{AA}
Fig Lahmar	MeOH Var.2	2.052 ^{AA}	Dec. Var.2	1.962 ^{AB}	Inf. Var.2	1.924 ^{AB}
Breba fig El Bordj	MeOH Var.3	2.509 ^{AA}	Dec. Var.3	2.546 ^{AB}	Inf. Var.3	2.783 ^{AA}
Fig El Bordj	MeOH Var.4	2.148 ^{AA}	Dec. Var.4	2.236 ^{AB}	Inf. Var.4	2.329 ^{AB}
Reference	Diclofenac sodium	7.261^{AB}	Diclofenac sodium	7.261^{AC}	Diclofenac sodium	7.261^{AC}

importance of the extraction method. This result suggests that the antibacterial principles in fig fruits are mainly water-soluble. The absence of antimicrobial activity in methanolic extracts (Table 6) and aqueous decoctions (Table 7) suggests that the bioactive compounds responsible for the observed effects are extracted most efficiently by aqueous infusion. This may be due to thermal degradation or differential solubility of phenolic compounds under the other extraction conditions. Specifically, the higher temperature and prolonged exposure during decoction could degrade thermolabile antimicrobial compounds, while methanolic extraction may fail to solubilize certain polar bioactive molecules that are readily extracted by hot water infusion.

The selective activity of aqueous extracts in our study is consistent with findings from Aloriby *et al.* (2025), who evaluated *Ficus carica* leaf extracts prepared by maceration using methanol, acetone, and distilled water against multidrug-resistant pathogens. Although their study reported minimal efficacy of *F. carica* extracts compared to *Olea europaea*, they emphasized that extraction solvent and method critically determine antimicrobial outcomes, supporting our observation that only specific extraction conditions (aqueous infusion) yielded activity (Aloriby *et al.*, 2025). These specific chemical fingerprints, resulting from

combined genetic and environmental factors, provide a robust explanatory framework for the differences in antimicrobial activity measured *in vitro*.

This study provides *in vitro* evidence supporting the traditional use of the fig tree (*Ficus carica* L.) in treating infections and inflammatory disorders, while identifying specific activity profiles linked to extract type and variety origin. It complements literature data that also attributes antimicrobial properties to other parts of the plant, such as leaves (Rashid *et al.*, 2014), and confirms that *F. carica* possesses antibacterial action among its many pharmacological properties (Baby & Justin Raj, 2011; Mawa *et al.*, 2013). The absence of activity of methanolic extracts and decoctions at the tested concentrations indicates that the active compounds might be thermosensitive or that their optimal extraction requires specific conditions. The evaluation of anti-inflammatory activity provided particularly striking results. The superior ability of many extracts, especially those from Lahmar varieties, to inhibit the thermal denaturation of albumin compared to sodium diclofenac is a strong indicator of therapeutic potential. This model, which simulates an aspect of acute inflammation (Alhakmani *et al.*, 2013), is often correlated with the presence of phenolic compounds.

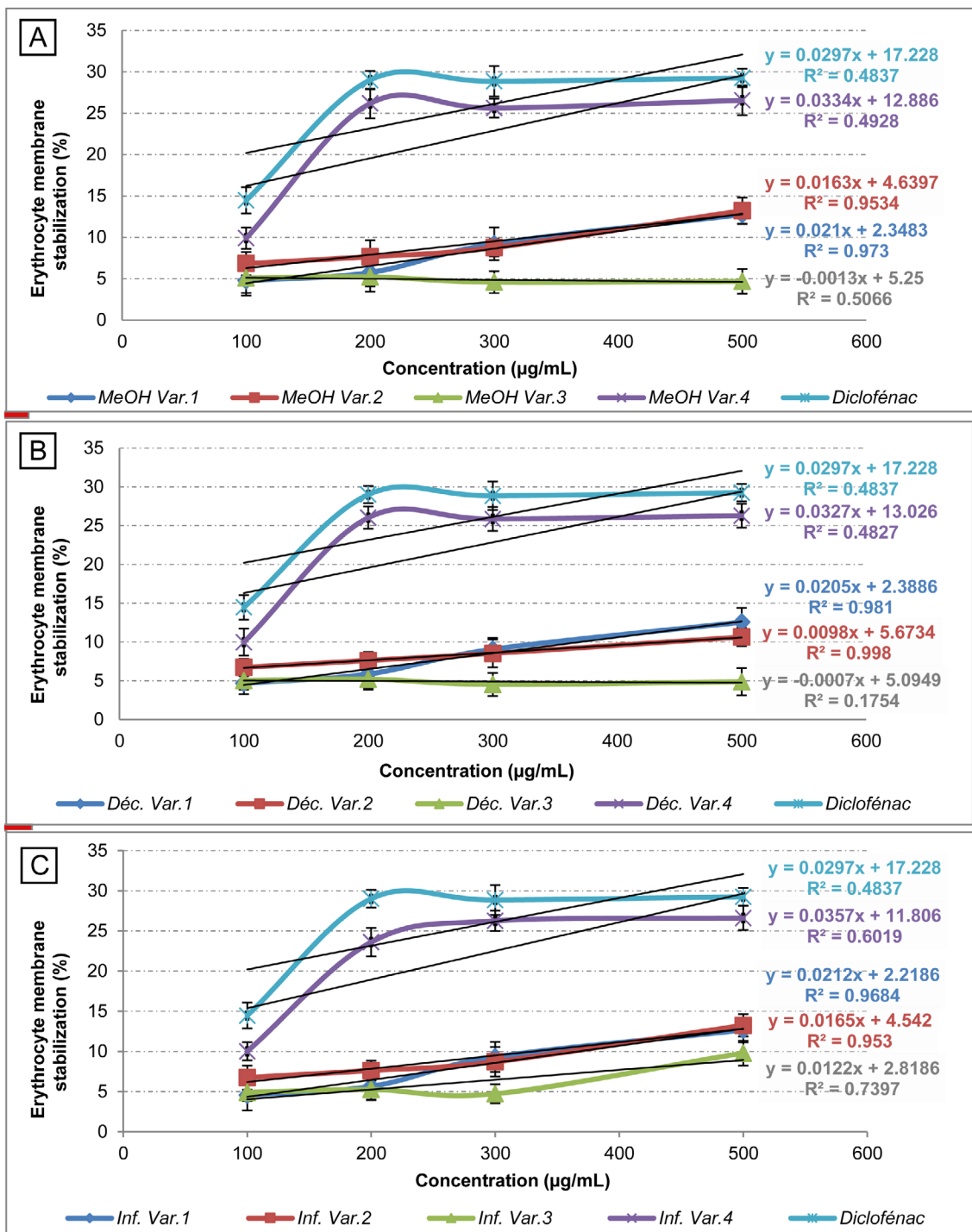


Fig. 2. Inhibition of erythrocyte membrane stabilization by *F. carica* fruit extracts prepared using different extraction methods. **A:** Methanolic extracts: MeOH Var.1, Breba fig Lahmar; MeOH Var.2, Fig Lahmar; MeOH Var.3, Breba fig El Bordj; MeOH Var.4, Fig El Bordj. **B:** Decoctions: Déc. Var.1, Breba fig Lahmar; Déc. Var.2, Fig Lahmar; Déc. Var.3, Breba fig El Bordj; Déc. Var.4, Fig El Bordj. **C:** Infusions: Inf. Var.1, Breba fig Lahmar; Inf. Var.2, Fig Lahmar; Inf. Var.3, Breba fig El Bordj; Inf. Var.4, Fig El Bordj.

Table 11. IC₅₀ Values of *F. carica* Extracts in the Erythrocyte Membrane Stabilization Assay. References= **One-way ANOVA results:** Factor (Variety): F(4, 8) = 3.486, p = 0.0626 (not significant at p < 0.05). Factor (Extract Type): F(2, 8) = 1.0797, p = 0.3845 (not significant). Uppercase letters (A–D) indicate significant differences at p < 0.05. Values sharing the same letter within each column are not significantly different (p > 0.05).

Variety (Type & Origin)	Methanolic Extract	IC ₅₀ (mg/mL)	Decoction Extract	IC ₅₀ (mg/mL)	Infusion Extract	IC ₅₀ (mg/mL)
Breba fig Lahmar	MeOH Var.1	2.269 ^{AB}	Dec. Var.1	2.322 ^{AA}	Inf. Var.1	2.253 ^{AA}
Fig Lahmar	MeOH Var.2	2.782 ^{AA}	Dec. Var.2	4.523 ^{AC}	Inf. Var.2	2.755 ^{AB}
Breba fig El Bordj	MeOH Var.3	34.423 ^{AC}	Dec. Var.3	64.150 ^{AD}	Inf. Var.3	3.867 ^{AB}
Fig El Bordj	MeOH Var.4	1.111 ^{AA}	Dec. Var.4	1.130 ^{AB}	Inf. Var.4	1.069 ^{AC}
Reference	Diclofenac sodium	1.103 ^{AA}	Diclofenac sodium	1.103 ^{AB}	Diclofenac sodium	1.103 ^{AC}

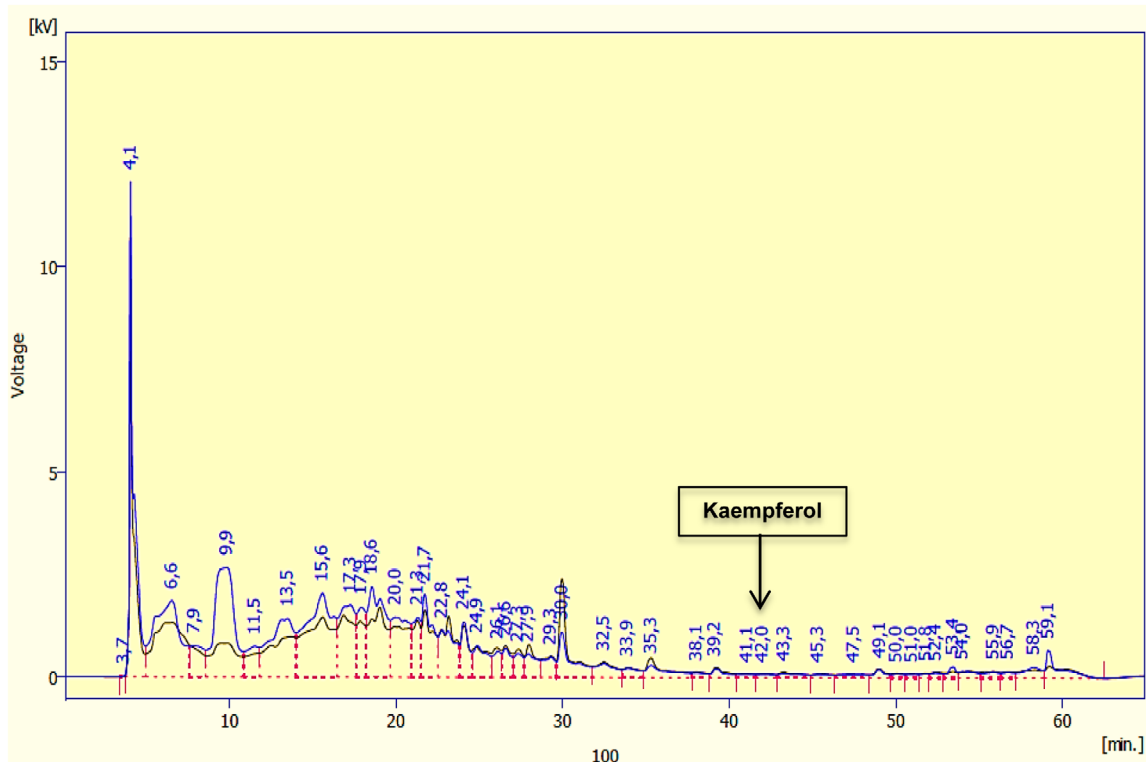


Fig. 3. Chromatogram of methanolic extract of Breba fig Lahmar (MeOH Var.1).

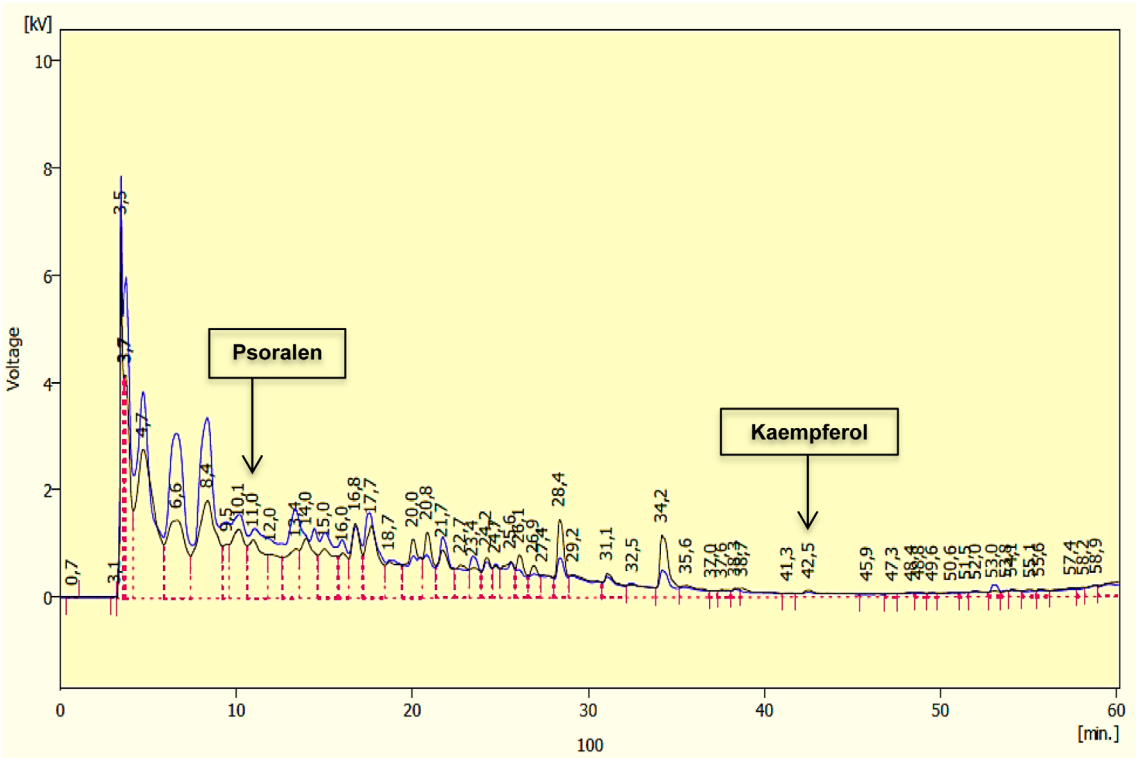


Fig. 4. Chromatogram of methanolic extract of Fig Lahmar (MeOH Var.2).

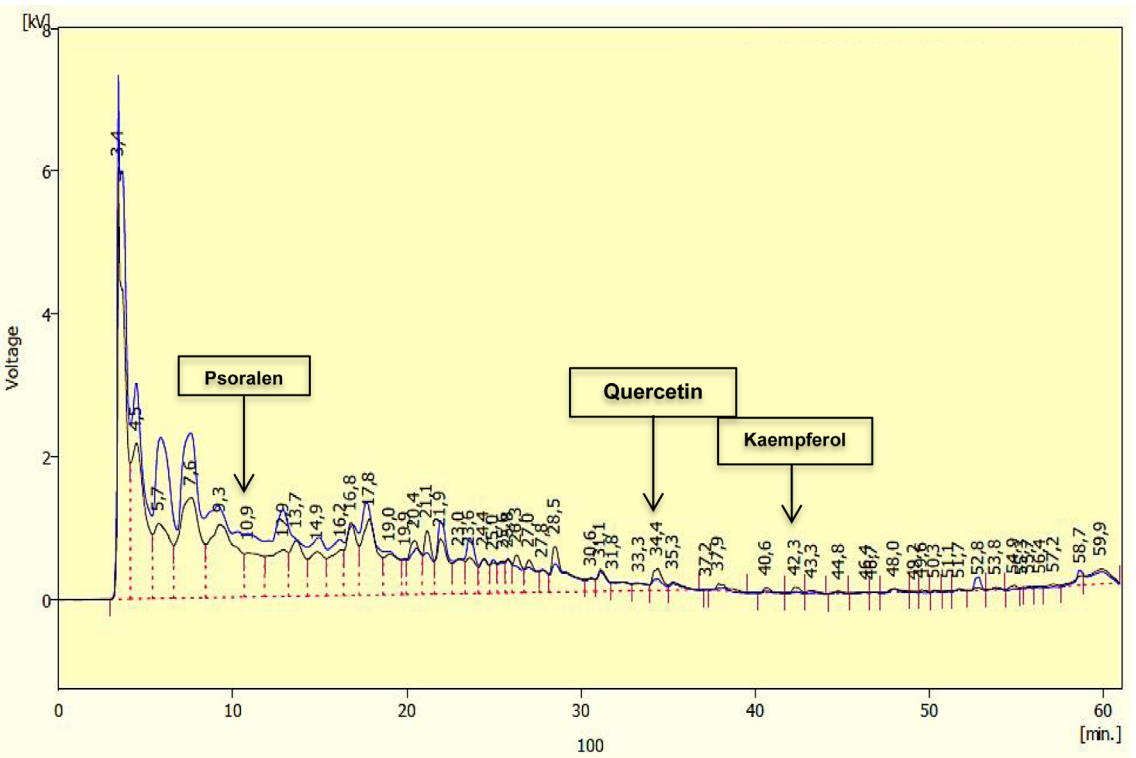


Fig. 5. Chromatogram of methanolic extract of Breba fig El Bordj (MeOH Var.3).

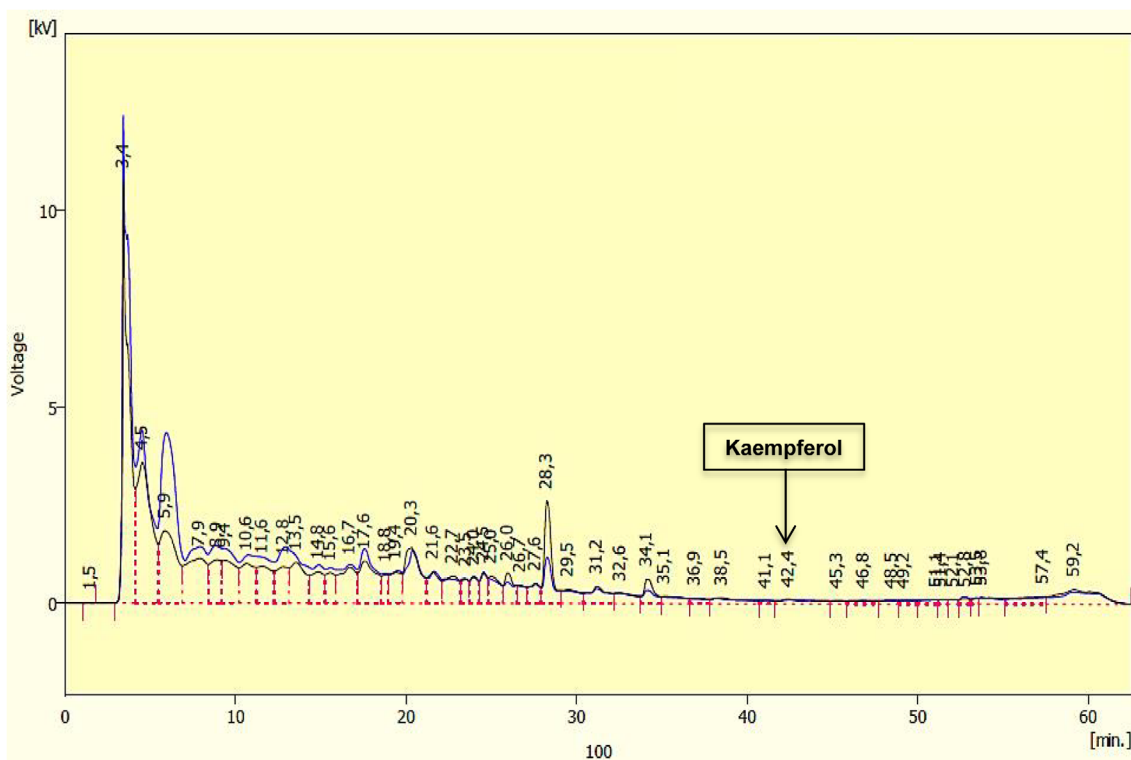


Fig. 6. Chromatogram of methanolic extract of Fig El Bordj (MeOH Var.4).

Our finding that several extracts exhibited lower IC₅₀ values (1.92–2.86 mg/mL) than diclofenac (7.26 mg/mL) is remarkable and aligns with the work of Kebal *et al.* (2022), who reported that aqueous and ethanolic fig fruit extracts (250–500 mg/kg) produced significant, dose-dependent inhibition of carrageenan-induced paw edema in mice, with histological confirmation of reduced inflammatory infiltration. The superior activity of our extracts may be attributed to the high phenolic content, consistent with the positive correlation between total phenolics and anti-inflammatory efficacy reported by Kebal *et al.* (2022). Hasnain *et al.* (2026) reported specific quantitative data, including 55 ± 0.03 % inhibition of heat-induced hemolysis, 28 ± 0.01 % inhibition of proteinase activity, and 51.2 ± 0.05 % inhibition of bovine serum albumin denaturation, alongside substantial levels of total flavonoids (123 mg rutin equivalents/g) and phenolic content (333 mg gallic acid equivalent/g). Additionally, Yuan *et al.* (2025) identified 38 prenylated flavonoids from fig fruits, including 10 novel compounds, and demonstrated

their inhibitory effects on the NF-κB and STAT3 inflammatory pathways, providing a molecular mechanism for the anti-inflammatory activity observed in traditional fig preparations. A recent review by Yeasmin *et al.* (2025) comprehensively summarized the anti-inflammatory, antidiabetic, and anticancer properties of fig fruit, attributing these effects to steroids and polyphenolic phytochemicals that collectively exhibit significant bioactivity. Furthermore, Vardanyan *et al.* (2025) used LC-Q-Orbitrap HRMS to identify over 140 distinct phytochemicals in fig leaf extracts, primarily flavonoids and phenolic compounds, and demonstrated significant reduction of nitric oxide production and lipid peroxidation in microglial cell models, reinforcing the anti-inflammatory potential of *F. carica* at the cellular level.

The significant activity in the erythrocyte membrane stabilization test, a mechanism analogous to that of some steroidal anti-inflammatory drugs, reinforces this hypothesis. Indeed, the literature attributes notable anti-inflammatory properties to flavonoids and tannins, two groups of

compounds abundant in our extracts, often linked to their ability to inhibit various key enzymes in the inflammatory process (Sudharshan *et al.*, 2010). The membrane-stabilizing activity we observed is consistent with the comprehensive review by Fazel *et al.* (2024), who identified *F. carica* as possessing significant anti-inflammatory and anti-arthritic properties mediated through modulation of signaling proteins. Vardanyan *et al.* (2025) provided cellular-level evidence supporting our observations, demonstrating that fig leaf ethanolic extract significantly reduced nitric oxide production and lipid peroxidation in BV-2 microglial cell lines while enhancing antioxidant enzyme activity (SOD and catalase). These findings indicate that the anti-inflammatory effects of *F. carica* extend beyond protein denaturation inhibition to include modulation of inflammatory mediators at the cellular level, offering a mechanistic explanation for the potent activity observed in our extracts (Vardanyan *et al.*, 2025).

The phytochemical profile established by HPLC allows for preliminary correlations between composition and activity. The simultaneous presence of gallic acid, catechin, epicatechin, and rutin in the most active extracts (notably *MeOH Var.1* and *Var.2* from Lahmar) is an important clue. These molecules, frequently reported in studies on figs (Veberic *et al.*, 2008; Oliveira *et al.*, 2009; Viuda-Martos *et al.*, 2015a; Viuda-Martos *et al.*, 2015b), are recognized for their anti-inflammatory properties. The selective antimicrobial activity of aqueous infusions observed in our study aligns with the phytochemical profiling by Lackner *et al.* (2025), who identified gallic acid (5.66 µg/mL), catechin (6.78 µg/mL), and rutin (8.60 µg/mL) as major compounds in *F. carica* extracts using HPLC-DAD. The presence of these same compounds in our HPLC analysis supports their potential contribution to the observed antibacterial effects against *S. aureus* and *E. faecalis*. The phenolic composition of Algerian *Ficus carica* varieties is consistent with regional phytochemical profiles. Siga *et al.* (2025) investigated four Algerian edible plants, including *F. carica* from the Laghouat region, and reported the presence of chlorogenic acid (10.18 mg/g) and rutin (4.88 mg/g) as major phenolic compounds in fig extracts using HPLC-DAD analysis (Siga *et al.*, 2025). Notably, this study identified epicatechin, catechin, and pyrocatechol in other Algerian

plants, compounds that are structurally related to those detected in our extracts. The geographical proximity of the Laghouat region to our collection sites in Algeria reinforces the relevance of these findings and supports the presence of region-specific phenolic profiles in Algerian fig varieties.

Furthermore, Yuan *et al.* (2025) demonstrated that prenylated flavonoids from fig fruits exhibit structure-activity relationships where the prenyl type and substitution position critically influence biological activity, suggesting that the specific anti-inflammatory potency of our Lahmar variety extracts may be attributable to particular prenylated flavonoid isomers (Yuan *et al.*, 2025). This phenolic diversity is consistent with profiles reported for other Mediterranean varieties. For example, the analysis by Electrospray Ionization Quadrupole Time-of-Flight Tandem Mass Spectrometry coupled with Ultra-Performance Liquid Chromatography (UPLC-ESI-Q-TOF-MS/MS) of leaves of Tunisian varieties of *F. carica* also identified common compounds like rutin and psoralen, as well as specific molecules such as prenylated genistein derivatives and various furanocoumarins (Belguith-Hadriche *et al.*, 2017). The detection of specific compounds like berberine in the *MeOH Var.4* extract from El Bordj, an alkaloid with extensive pharmacological properties, also opens interesting perspectives.

Despite the promising results, several limitations must be acknowledged. First, the anti-inflammatory activity was assessed using only two *in vitro* models, which represent simplified and indirect mechanisms of inflammation that cannot be directly extrapolated to *in vivo* conditions. Second, compound identification by HPLC was based solely on retention times without spectral confirmation (e.g., MS or DAD), limiting the reliability of phytochemical assignments. Third, the antimicrobial activity observed was moderate and limited to specific strains, suggesting a narrow spectrum of action. Fourth, the MIC values obtained (3.125–6.25 mg/mL) are considerably higher than those of conventional antibiotics (µg/mL range), indicating modest antimicrobial potency. However, it is worth noting that Padang *et al.* (2025) reported MIC values for *Ficus carica* ethanol extract against drug-resistant *Staphylococcus aureus* MRSA and *Klebsiella pneumoniae* ESBL in the range of 80–100 % extract concentration, with inhibition zones

of only 3.30 mm at 100 % concentration, indicating that the modest antimicrobial potency we observed is consistent with other reports on fig fruit extracts against resistant strains (Padang *et al.*, 2025).

This suggests that while fig extracts may not rival conventional antibiotics, their value lies in their anti-inflammatory properties and potential as adjunctive therapies. Future studies should address these limitations by employing LC-MS/MS for definitive compound confirmation and extending the evaluation to cell-based inflammatory models (e.g., LPS-stimulated macrophages). Additionally, recent genomic advances by Ren *et al.* (2025) identified key genes (*FcANS*, *FcCHS10*) involved in anthocyanin and flavonoid biosynthesis in fig, along with *FcMS* for psoralen production. Investigating whether varietal differences in these genetic markers explain the superior anti-inflammatory activity of Lahmar varieties observed here represents a promising direction for future research.

CONCLUSION

This study provides preliminary scientific support for the traditional use of Algerian figs in the management of inflammation and infections. The results reveal remarkable *in vitro* anti-inflammatory activity, with several extracts showing higher activity than diclofenac under specific *in vitro* models of protein and cell membrane protection. In parallel, a selective antimicrobial activity was observed, specific to aqueous infusions, indicating preferential extraction of water-soluble antibacterial principles by this traditional method. HPLC analysis tentatively correlated these effects with the presence of specific phenolic compounds (gallic acid, catechin, rutin). This work paves the way for future structural identification and mechanistic investigations of the active principles responsible for these promising properties.

AUTHOR CONTRIBUTIONS

MM and MM conceptualised the project. MM led data collection, data analysis and write-up of manuscript. MM and AE assisted with data collection and data analysis. MM and AE reviewed

and gave input on data analysis and write-up of the manuscript. All authors reviewed and commented on the manuscript and approved the final manuscript.

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