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**Research Article**

# *In vitro* and *in silico* evaluation of *Capparis spinosa* L. essential oil

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**Abstract**

This study explores the antibacterial and antioxidant properties of *Capparis spinosa* essential oils from seven Algerian populations, using *in vitro* and molecular modeling approaches, specifically targeting bacterial biofilm formation. EOs demonstrated highly variable antimicrobial activity, with the greatest sensitivity observed in *Staphylococcus aureus* (inhibition zone up to 44.3 mm) and Bacillus cereus (up to 37.3 mm). The antioxidant activity was significant ($IC_{50}$ 0.85 mg/mL) and confirmed by HPTLC. *In silico* molecular docking targeted bacterial biofilm, revealing a high binding affinity of -6.9 kcal/mol for the α-Duprezianene. Furthermore, Molecular modeling studies, including SwissADME and OSIRIS Property Explorer, predicted favorable pharmacokinetic (ADME) profiles and low toxicity risks for the active compounds. These results support the traditional use of *C. spinosa* and its potential as a source for novel, safe, and effective anti-biofilm agents.

**Keywords:** Biological activities, *Capparis spinosa*, Essential oil, Molecular docking

## Introduction

Essential oils (EOs) are volatile compounds produced by the secondary metabolism of aromatic plants used for millennia for their benefits (Shankar *et al.,* 2021). They have a variety of pharmacological effects, such as: antioxidant, anticancer, antibacterial, anti-inflammatory and neuroprotective properties, proved by recent scientific research (Bacchetti *et al.,* 2022; Rout *et al.,* 2022; Özcan & Uslu, 2023; Santana De Oliveira *et al.,* 2023), which make them interesting for medicinal applications in addition of their agrochemical, food and cosmetic applications (Bunse *et al.,* 2022; Sousa *et al.,* 2022). *C. spinosa*, Capparaceae, common throughout Algeria, has been among the most used plants since antiquity. The Caper bush grows naturally on skeletal, rocky, dry and stony soils (Manikandaselvi *et al.,* 2016). Different parts of the plant are used in traditional medicine to treat various human diseases such as itching mosquito bites, hives asthma and digestive problems (Kalantari *et al.,* 2018; Zhang & Ma, 2018). The local population in the Algerian Sahara uses the bark of the roots, to treat rheumatism, headaches, spleen, and liver diseases, ulcers, and even dromedary scabies (Benseghir-Boukhari & Seridi, 2007). Continuing our previous study (Halima *et al.,* 2017) where *C. spinosa* essential oils from seven stations (Figure 1) were analyzed. On the other hand, molecular modeling, and more specifically docking, has become an indispensable tool for predicting interactions between bioactive compounds and their protein targets. In the context of bacterial infections, biofilms represent a major therapeutic challenge due to their increased resistance to antibiotics. Proteins involved in biofilm formation, such as LasR (quorum sensing regulator), AgrA (virulence regulator in *Staphylococcus aureus*), and DNA gyrase (a key enzyme in bacterial replication), are promising targets for the development of novel antibacterial agents. This study uses *in silico* approaches to evaluate the affinity of the main compounds of *C. spinosa* EOs towards these proteins, in order to elucidate their potential mechanisms of action and guide future applications in pharmacology.

## Materials and methods

The *in vitro* and *in silico* antibacterial properties of EOs from seven Algerian populations of *Capparis spinosa* (Figure 1) in addition to their antioxidant activity with two methods free radical scavenging activity DPPH and HPTLC methods.

### *Antibacterial activity*

The disk diffusion method (EUCAST, 2025) was used to detect the antibacterial activity of *C. spinosa* essential oils. Nine gram-positive and negative bacteria species, obtained from Pasteur Institute of M'Sila and the laboratory of microbiology from Setif University Hospital: *Bacillus cereus* ATCC 11778, *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* MRSA ATCC 43300, *Enterococcus faecalis* ATCC 51299, *Escherichia coli* ATCC 25922, *Salmonella enterica* ATCC 43972, *Klebsiella pneumoniae* ATCC 700603, *Proteus mirabilis* ATCC 35659, and *Psudomonas aeruginosa* ATCC 27853. Sterile disks of 6 mm diameter were impregnated with 10 µL of the diluted essential oil (1/2, 1/5 and 1/10 v/v DMSO). Each experiment is performed in triplicate and the average is calculated.

### *Docking analysis and protein preparation*

#### *The target choice*

According to the literature, extracts of *C. spinosa* acts on the formation of biofilms, the mechanism of quorum

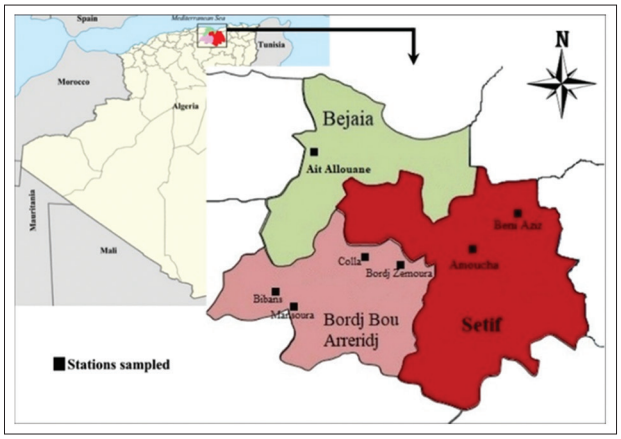



**Figure 1:** *Capparis spinosa* sampled stations

sensing and DNA gyrase in bacteria (Issac Abraham *et al.,* 2011; Di Lodovico *et al.,* 2022; Hassan *et al.,* 2023). Three vital proteins with diverse roles were the subject of the *in silico* study (Table 1). For the study of molecular docking as well as for pharmacotoxicity, the main compounds (Table 1) were selected and their 3D structures were used.

### *In silico antibacterial study*

Molecular docking of the phytocompounds as well as the natural ligands was done against the selected targets proteins with PDB IDs: 2UV0, 4G4K and 1KZN to determine their binding affinities. The 3d structures of the phytocompounds and ligands were obtained in SDF format files from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and Molview (https://molview.org/?cid=5478883) then converted to PDB format by Open Babel tools version 2.4.1. The proteins energies optimization was realized using Chem3D v 16.0.1.4 software. The 3d structures of the target proteins were obtained in PDB format from the Protein Data Bank (https://www.rcsb.org/). Autodock Vina in PyRx 0.8 was used to generate the best predicted binding modes and corresponding binding energies. The interactions were visualized in 3D and 2D forms using BIOVIA Discovery Studio visualizer 2024 v.24.1.0.23298 software. Bonds between the ligands and interacting residues are depicted with a distance range of Å.

### *Pharmacokinetics and toxicity prediction*

Lipinski's method was employed to assess the drug-like properties of phytocompounds, which sets limits on four specific physicochemical parameters (Lipinski, 2004). These are the characteristics of an orally active drug: the octanol-water partition coefficient (milogP) and the number of hydrogen bond donors (n-OH and n-NH) should not exceed 5, and the number of hydrogen bond acceptors (n-ONs) should be less than 10. The molecular weight (MW) should be below 500 D, and no more than one violation should occur (Adjissi *et al.,* 2022). Molinspiration Cheminformatics free web services (https://www.molinspiration.com) and SwissADME free online tools (http://www.swissadme.ch/) were used to predict physicochemical and pharmacokinetic parameters, while OSIRIS Property Explorer online tools (https://www.organic-chemistry.org/prog/peo/) were used to predict toxicity risks.

**Table 1:** Targeted bacterial proteins in molecular docking

| Protein | PDB code | Natural ligand/CID |
|---|---|---|
| LasR-OC12 HSL Complex | 3IX3 | N-3-Oxo-Dodecanoyl-L-Homoserine Lactone/3246941 |
| *S. aureus* AgrA LytTR Domain | 4G4K | Glycerin/753 |
| *E. coli* DNA Gyrase | 1KZN | Clorobiocin/54706138 |

### *Free radical scavenging activity DPPH method*

The evaluation of antioxidant activity of *C. spinosa* EO samples was performed using the Table 2 radical 2,2-diphenyl-1- picrylhydrazyl (DPPH) method, following the protocol described by Dung *et al.* (2008). 100 µL of each of the methanolic solutions of the tested oils at different concentrations are added to 2.9 mL of DPPH methanolic solution (0.004%). Then, the mixture was left in the dark for 30 min at laboratory temperature and the absorbance was measured with a spectrophotometer (SECOMAM - Prim'Light) at 517 nm. BHT was used as a reference molecule. The antioxidant activity is estimated in percentage of inhibition, according to the following formula:

$$I\ (inhinition)\ (\%) = \left( \frac{\text{Absorbance of the control} - \text{Absorbance of the sample}}{\text{Absorbance of the control}} \right) x100$$

$IC_{50}$ was calculated graphically and all tests were performed in triplicate.

### *HPTLC*

This method has many advantages for separating compounds from complex extracts with lower costs, it is used to screen the biological activity of natural compounds in biological tests on plant material (Meier & Spriano, 2010; Do *et al.,* 2021). Material included a CAMAG HPTLC system (Muttenz, Switzerland) equipped with an Automatic TLC Sampler (ATS 4), an Automatic Developing Chamber (ADC2) with humidity control, and a TLC Visualizer, Vision CATS software and a Chromatogram Immersion Device III and TLC Plate Heater III for derivatisation. The samples were prepared by dissolving 1 mg of each fraction in 1 mL of methanol. 20 µL of the preparation was applied to the crude extracts on 8 mm bands, from the lower edge of the plate. The mobile phase was a mixture of ethyl acetate, dichloromethane, formic acid, acetic acid, and water (100:25:10:10:11). Plates were developed over a distance of 70 mm from the lower edge using a twin trough glass chamber saturated for 20 min with mobile phase under controlled humidity (RH: 33%). After development, plates were dried under a stream of cool air for 10 min.

### *Antioxidant derivatisation using DPPH*

After migration, the plate was dipped into a solution of DPPH (0.6 mM), in methanol for 5 seconds, and kept for 2 minutes in the dark. After taking a picture under white light, the plate was heated for 2 minutes at 110 °C, and a new photo was taken in the same condition. Antioxidant compounds appear as a white spot against a purple background.

### *Statistical analysis*

Data on antimicrobial and antioxidant activities are expressed as mean±standard deviation. Statistical significance is analyzed by three-way ANOVA tests using CoStat (v 6.4). Differences at $P<0.05$ were considered significant. A desirability test is used for assessing the effect of variables, which can predict the effect of each factor of the design. The scales range from zero to one (from most undesirable values to most desirable values).

## Results

### *Antibacterial activity*

The antibacterial activity of essential oils from *C. spinosa* populations was evaluated, by the disk diffusion method, on nine ATTC strains. The results are expressed by the diameter of the inhibition zones (Table 3).

**Table 2:** The main compounds used as ligands

| Compound | Pubchem CID |
|---|---|
| α-pinene | 6654 |
| β-phellandrene | 11142 |
| n-Nonanal | 31289 |
| Isopulegyl acetate | 94579 |
| α-Duprezianene | 91749682 |
| Hexadecanoic acid | 985 |
| 1-Docosene | 74138 |
| Nonacosane | 12409 |

EOs from *C. spinosa* populations showed effective effects against all bacteria tested at ½ dilutions except *E. coli* which was the most resistant at all dilutions tested. The EOs from Ait Allouane and Colla exerted a significant antimicrobial activity on five strains, particularly *S. aureus* and *B. cereus*, followed by the EOs of Bibans and Bordj Zemoura population which inhibited at least three strains significantly. On the other hand, *C. spinosa* oils are almost inactive against *K. pneumoniae*, *P. mirabilis* and *E. faecalis*. Statistical analysis by ANOVA showed that the factors (populations, doses and bacteria) and their interactions are highly significant at $P<0.001$) (Table 4).

The best inhibitory power was observed at ½ dilutions, with an average inhibition diameter of 15.76 mm (Table 5). While the effects of dilutions (1/5 and 1/10) are not significant with low inhibition diameters.

Colla population EO presents the strongest activity against bacterial strains, with an average inhibition diameter of 19.84 mm; followed by the oil of Ait-Allouane population with a diameter of 19.15 mm, while the oils from the Amoucha population are the least active against the bacteria tested, with an average diameter of 17.65 mm (Table 6).

*C. spinosa* oil showed significant activity on *B. cereus*, *S. aureus*, *S. enterica*, *E. faecalis* and *P. aeruginosa* (Table 7). The action is very significant on *K. pneumoniae*, *S. aureus* MRSA, *P. mirabilis*, and moderately significant on *E. coli*.

### *Desirability test*

*C. spinosa* EO has values equal to the prediction value, which is 0.26017 (Figure 2). The doses of oil used (1/2 and 1/5) have activity against the bacteria tested, with values greater than the predicted value. While the D3 (dilution 1/10) has a value equal to the value of the prediction. The

**Table 3:** Inhibition zones of *C. spinosa* essential oils

| | Dilutions | *E. coli* | *S. aureus* | *K. pneumoniae* | *B. cereus* | *S. aureus MRSA* | *P. aeruginosa* | *S. enterica* | *P. mirabilis* | *E. faecalis* |
|---|---|---|---|---|---|---|---|---|---|---|
| Bibans | 1/2 | 0 | 11.2±0.9 | 17.5±0.5 | 2 4±1.73 | 10.5±0.5 | 35.2±1.1 | 23±2.6 | 8.5±0.5 | 14±0 |
| | 1/5 | 0 | 8.67±0.8 | 10.4±0.4 | 12.7±0.6 | 8.5±0.5 | 0 | 9±0 | 8±0 | 11.3±1.2 |
| | 1/10 | 0 | 7.17±0.3 | 7.5±0.5 | 10.5±0.5 | 7.33±0.3 | 0 | 8.67±0.6 | 7.33±0.6 | 9.33±0,6 |
| Bordj-Zemoura | 1/2 | 0 | 35.5±0.5 | 10.7±0.3 | 24.3±0.6 | 14.2±0.8 | 17.2±1.3 | 14.3±0.6 | 9.5±0.5 | 14.3±0.6 |
| | 1/5 | 0 | 18.7±3.8 | 9.75±0.3 | 13.3±0.6 | 9.5±0 | 12.8±1.1 | 13.8±0.8 | 8.5±0.9 | 12.7±0.6 |
| | 1/10 | 0 | 9±0.5 | 8.25±0.3 | 7.16±6.2 | 8.66±0.3 | 0 | 10.7±0.3 | 7±0 | 8.67±0.6 |
| Colla | 1/2 | 11.3±1.1 | 44.3±1.6 | 12.5±0.7 | 34.8±0.8 | 15.2±0.3 | 32.3±0.6 | 22.5±3.5 | 9±0 | 14±1.7 |
| | 1/5 | 0 | 11±0.5 | 8.5±0 | 12.7±0.6 | 10.7±0.3 | 12.5±1.5 | 12.2±0.3 | 7.3±0.6 | 12.3±1.5 |
| | 1/10 | 0 | 10.2±0.6 | 0 | 9.33±0.6 | 9.83±0.3 | 12.7±0.3 | 11±0.9 | 0 | 8.5±0.5 |
| Beni-Aziz | 1/2 | 10.2±0.3 | 12.7±1.3 | 12±0.5 | 34±1 | 10.2±0.6 | 16.7±1.5 | 10.5±1.3 | 10±0.5 | 14.3±0.6 |
| | 1/5 | 0 | 12.2±0.3 | 0 | 15±0 | 8.5±0.5 | 7.83±0.8 | 8.16±0.3 | 10.5±1 | 13.3±0.6 |
| | 1/10 | 0 | 11±0.5 | 0 | 13.3±1.5 | 7.2±0.3 | 0 | 7.66±0.3 | 7±0 | 8.66±0.6 |
| Amoucha | 1/2 | 0 | 13.6±0.3 | 11.8±1.3 | 36.3±1.2 | 9.83±0.3 | 14±0 | 10.3±0.6 | 9.33±0.6 | 12.3±0.6 |
| | 1/5 | 0 | 7.33±0.3 | 9.25±0.3 | 14.3±1.2 | 7.83±0.3 | 10.3±0.6 | 8.33±0.6 | 8.5±0.5 | 11.7±0.6 |
| | 1/10 | 0 | 0 | 0 | 10.3±0.6 | 7.16±0.3 | 7.16±0.3 | 7.5±0.5 | 8.16±0.8 | 10.5±0.5 |
| Mansoura | 1/2 | 9.5±1 | 21.3±1.5 | 11.5±0.5 | 29±1.73 | 10±0.5 | 14.3±1.2 | 12.2±0.8 | 10.5±0.5 | 14.5±0.5 |
| | 1/5 | 0 | 11±0.5 | 0 | 14±1 | 8.5±0.5 | 8.5±0.5 | 11.2±0.8 | 8.16±0.8 | 11.6±0.6 |
| | 1/10 | 0 | 7.5±0.05 | 0 | 10.3±0.6 | 7.16±0.3 | 0 | 9±0.5 | 8±0 | 9.16±0.8 |
| Ait-Allouane | 1/2 | 0 | 32.3±2.1 | 10.2±0.3 | 37.3±2.5 | 13.8±0.3 | 21.8±2.8 | 24.8±2.3 | 8.83±0.3 | 15±0 |
| | 1/5 | 0 | 12.7±0.8 | 0 | 20.7±1.5 | 9.66±0.3 | 8.16±0.8 | 14.7±0.6 | 7.83±0.3 | 12.8±0.3 |
| | 1/10 | 0 | 7.16±0.3 | 0 | 13±1.7 | 8.66±0.3 | 7.16±0.3 | 10.8±0.3 | 7.66±0.6 | 8.66±0.6 |
| Gentamicin | | 29±0.5 | 33.3±0.6 | 30.8±0.8 | 33±1 | 30.5±0.5 | 29.8±0.8 | 35.3±0.6 | 30.3±0.6 | 25.3±0.6 |
| Cefotaxime | | 21±1 | 27.5±0.5 | 30.3±0.7 | 33±1 | 27.8±0.8 | 31±1 | 30.7±0.6 | 30±1 | 39.3±1.2 |

**Table 4:** Interaction factors of *C. spinosa* essential oils

| Main effects | Degree of freedom | MS | F | P | |
|---|---|---|---|---|---|
| Intercept | | | | | |
| Stations | 6 | 85.2 | 108.6 | 0.00 | *** |
| Dilutions | 4 | 24545.7 | 31269.0 | 0.00 | *** |
| Bacteria | 8 | 1466.7 | 1868.5 | 0.00 | *** |
| Interaction | | | | | |
| Stations*Dilutions | 24 | 79.0 | 100.6 | 0.00 | *** |
| Stations*Bacteria | 48 | 46.2 | 58.8 | 0.00 | *** |
| Dilutions*Bacteria | 32 | 313.6 | 399.5 | 0.00 | *** |
| Stations*Dilutions *Bacteria | 192 | 35.1 | 44.7 | 0.00 | *** |

**Table 5:** Effect of oil dilutions and antibiotics on tested bacteria

| Rank | Mean Name | Mean | n |
|---|---|---|---|
| 1 | Gentamicin | 30.50$^{a}$ | 189 |
| 2 | Cefotaxime | 30.40$^{a}$ | 189 |
| 3 | 1/2 | 15.76$^{b}$ | 189 |
| 4 | 1/5 | 8.99$^{c}$ | 189 |
| 5 | 1/10 | 6.83$^{d}$ | 189 |

Means within the same column followed by different superscript letters are significantly different ($p<0.05$) according to Tukey's *post-hoc* test

**Table 6:** *C. spinosa* essential oils efficacy

| Rank | Name | Mean | n |
|---|---|---|---|
| 1 | Colla | 19.84$^{a}$ | 135 |
| 2 | Ait-Allouane | 19.15$^{b}$ | 135 |
| 3 | Bordj-zemoura | 18.81$^{c}$ | 135 |
| 4 | Bibans | 18.18$^{d}$ | 135 |
| 5 | Beni-Aziz | 17.97$^{de}$ | 135 |
| 6 | Mansoura | 17.87$^{e}$ | 135 |
| 7 | Amoucha | 17.65$^{f}$ | 135 |

**Table 7:** Sensitivity of bacteria to essential oils of *C. spinosa*

| Rank | Bacteria | Mean | n | S* |
|---|---|---|---|---|
| 1 | *B. cereus* | 24.52$^{a}$ | 105 | +++ |
| 2 | *S. aureus* | 20.63$^{b}$ | 105 | +++ |
| 3 | *S. enterica* | 20.26$^{c}$ | 105 | +++ |
| 4 | *E. faecalis* | 20.01$^{d}$ | 105 | +++ |
| 5 | *P. aeruginosa* | 18.98$^{e}$ | 105 | ++ |
| 6 | *S. aureus* MRSA | 17.51$^{f}$ | 105 | ++ |
| 7 | *P. mirabilis* | 17.46$^{f}$ | 105 | ++ |
| 8 | *K. pneumoniae* | 16.42$^{g}$ | 105 | ++ |
| 9 | *E. coli* | 10.88$^{h}$ | 105 | + |

S*: (+) sensitive; (++) very sensitive; (+++) extremely sensitive. Means within the same column followed by different superscript letters are significantly different ($p<0.05$) according to Tukey's *post-hoc* test

desirability test shows that the bacterial species tested have values higher than the predicted value, except *E. coli*, which has a value less than 0.26017.

### *Antioxidant activity*

The antioxidant activity of *C. sponosa* EOs is evaluated *in vitro* by the DPPH radical test. BHT was used as a reference. The EO has significant antioxidant dose dependent activity (Figure 3). The highest antioxidant activity is obtained by Colla population with $IC_{50}$= 0.85±0.01mg/mL (Table 8).

*C. spinosa* oils with their tested dilutions are capable of reducing the Table 9 free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) to yellow-colored diphenylpicrylhydrazine (DPPH-H) (Table 9).

**Table 8:** $IC_{50}$ values of *C. spinosa* essential oils

| Stations | $IC_{50}$ (mg/mL) |
|---|---|
| Bibans | 0.39±0.08 |
| Bordj Zemoura | 2.61±0.05 |
| Colla | 0.85±0.01 |
| Beni Aziz | 1.87±0.04 |
| Amoucha | 1.21±0.02 |
| Mansoura | 1.14±0.01 |
| Ait Allouane | 2.11±0.05 |
| BHT | 2.35±0.05 |

**Table 9:** Effect of oil dilutions on the percentage of antioxidant activity

| Rank | Name | Mean | n |
|---|---|---|---|
| 1 | D1 | 94.78$^{a}$ | 21 |
| 2 | D2 | 92.72$^{ab}$ | 21 |
| 3 | D3 | 88.09$^{b}$ | 21 |
| 4 | D4 | 81.73$^{c}$ | 21 |
| 5 | D5 | 66.04$^{d}$ | 21 |
| 6 | BHT | 85.95$^{e}$ | 168 |
| 7 | D6 | 47.33$^{f}$ | 21 |
| 8 | D7 | 32.46$^{g}$ | 21 |
| 9 | D8 | 20.30$^{h}$ | 21 |

### *Desirability test*

*C. spinosa* populations EOs have values equal to or greater than the prediction value, which is 0.52 (Figure 4). The dilutions of the oils (1/1 and 1/16) have significant antioxidant activity with values higher than the predicted value, while the BHT used as a positive control has a value lower than the predicted value. The antioxidant capacity of the EO of the populations studied was determined then compared to the activity of the reference BHT anti-radical compounds. The results obtained, expressed by the $IC_{50}$ (Inhibitory concentration of 50% of the free radical). This value is inversely proportional to the antioxidant capacity. In fact, the lower the $IC_{50}$ value, the higher the antioxidant activity.

### *Antioxidant activity by HPTLC*

The antioxidant power test carried out by HPTLC (Figure 5a) was positive, so this test analytically confirms the antioxidant power to the extent that a discoloration of the spots from purple to white of the antioxidant compounds was observed (Figure 5b).

### *Molecular docking results*

The docking results show that all compounds integrated the active sites of target proteins (Figure 6) with binding energies ranging from -3.2 to -6.9 kcal/mol (Table 10). The sesquiterpene α-Duprezianene showed the best binding energies with all three targets, notably with 3ix3 and 4g4k (-6.9 and 6.5 kcal/mol respectively), even better than that of the natural ligand (Clorobiocin).

### *Toxicity prediction*

The main compounds were of these EOs were evaluated for their eventual toxicity. In general,

**Table 10:** Phytocompounds scoring results

| Ligand / Protein | α-pinene | β-phellandrene | n-Nonanal | Isopulegyl acetate | α-Duprezianene | Hexadecanoic acid | 1-Docosene | Nonacosane | Natural ligands |
|---|---|---|---|---|---|---|---|---|---|
| Binding energies (kcal/mol) | | | | | | | | | |
| 4g4k | -5.0 | -5.6 | -4.5 | -5.8 | -6.5 | -5.4 | -5.3 | -4.9 | 3.8 |
| 1kzn | -4.6 | -4.9 | -3.7 | -5.1 | -5.6 | -4.8 | -3.2 | -3.7 | -8.0 |
| 3ix3 | -6.6 | -6.8 | -5.3 | -6.6 | -6.9 | -4.4 | -3.7 | -3.9 | -5.1 |

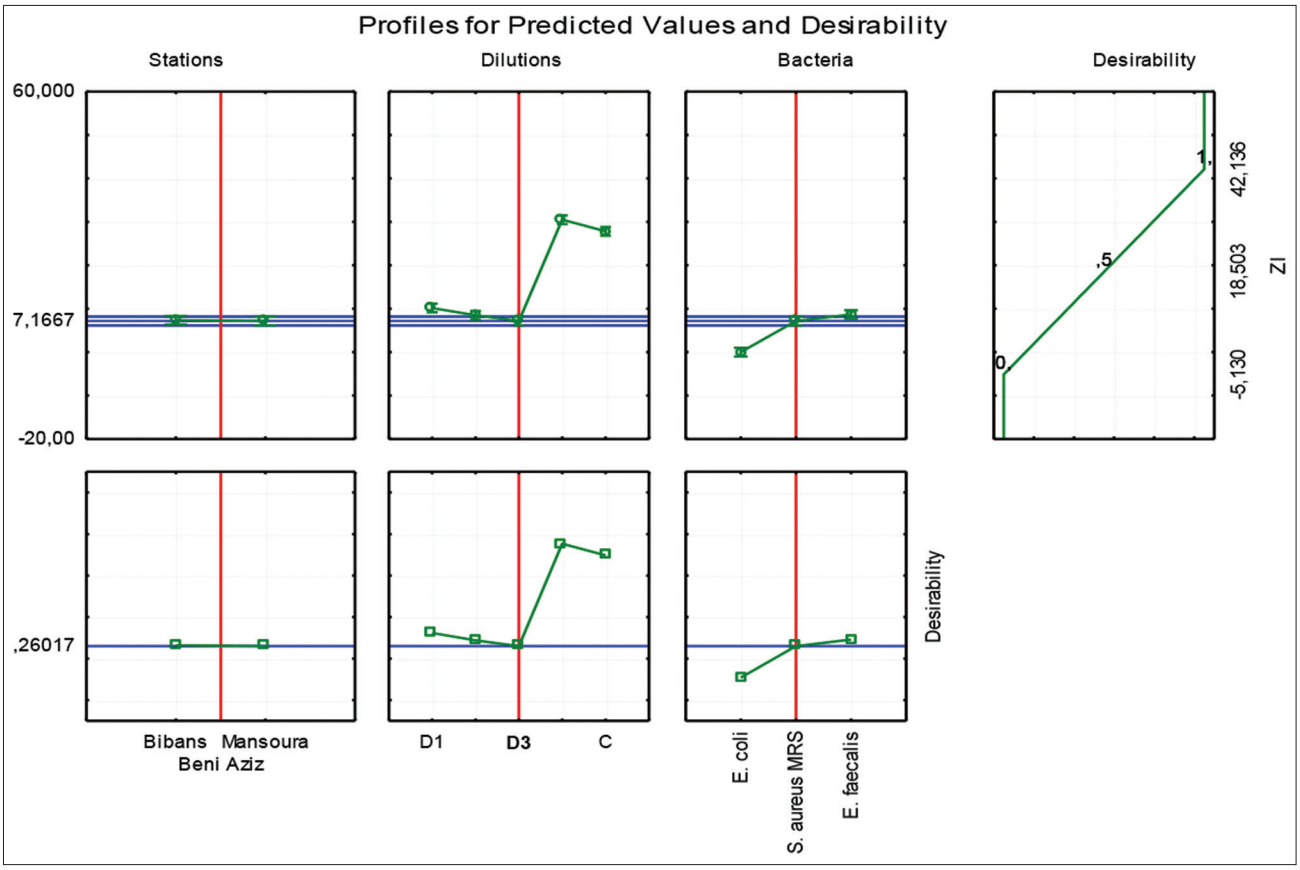



**Figure 2:** Desirability profile of *C. spinosa* essential oils

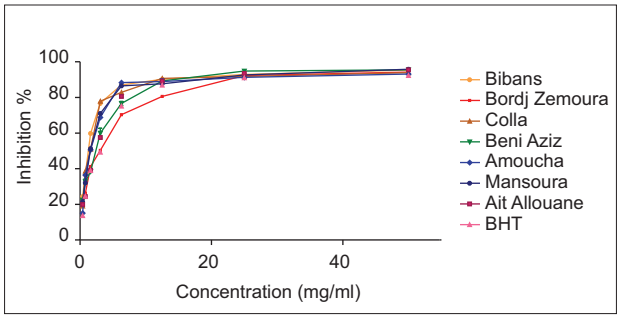



**Figure 3:** Antioxidant activity curves by the DPPH test

α-pinene, β-phellandrene, n-Nonanal Isopulegyl, acetate and α-Duprezianene have good physicochemical and pharmacokinetic featers (Table 11). All compounds meet the limit (miLogP<5), indicating moderately good lipid solubility, hexadecanoic acid, 1-Docosene, and nonacosane are highly lipophilic (miLogP>7), which may limit their aqueous solubility and oral absorption. Low values of polar surface area (TPSA) suggest good membrane permeability, except for hexadecanoic acid (37.3 g/mol), which may have reduced absorption. For MW, all compounds except Hexadecanoic acid, 1-Docosene and Nonacosane meet Lipinski's rules, this favors bioavailability. Hexadecanoic acid and α-Duprezianene are high-risk compounds because they inhibit CYP1A2, CYP2C19, and CYP2C9. Isopulegyl acetate and docosene are moderate-risk compounds because they inhibit CYP2C9 alone. β-Phellandrene, n-nonanal, α-pinene, and nonacosane are compounds with no risk of interaction. β-Phellandrene, n-Nonanal, and Isopulegyl acetate are soluble in water, while exadecanoic acid, 1-Docosene, and nonacosane are poorly soluble because lipophilic compounds (high miLogP) have reduced aqueous solubility. Low MW compounds and TPSAs (α-pinene, β-phellandrene, n-Nonanal and Isopulegyl acetate) cross the blood-brain barrier better. Highly lipophilic compounds such as n-Nonanal, 1-Docosene, Hexadecanoic acid penetrate the skin better. The n-Nonanal and Hexadecanoic acid (tumorigenic, CYP inhibitor, excessive lipophilicity) are risky compounds.

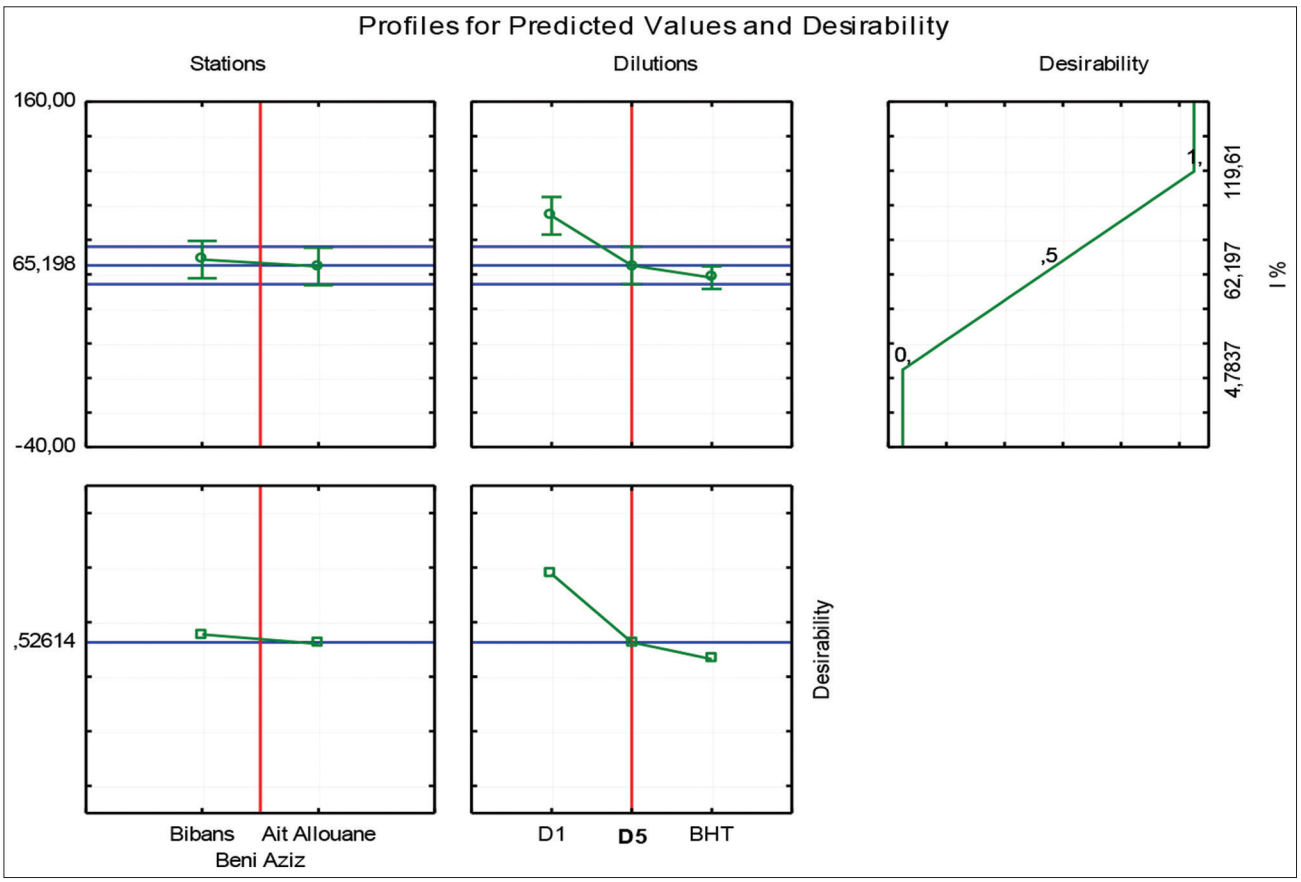



**Figure 4:** Desirability profile of *C. spinosa* essential oils

**Table 11:** Calculated physicochemical and pharmacokinetic parameters of the docked phytocompounds

| Compound | α-pinene | β-phellandrene | n-Nonanal | Isopulegyl acetate | α-Duprezianene | Hexadecanoic acid | 1-Docosene | Nonacosane |
|---|---|---|---|---|---|---|---|---|
| Physicochemical and pharmacokinetic parameters (Molinspiration Cheminformatics) | | | | | | | | |
| miLogP<5 | 3.54 | 3.58 | 4.10 | 3.35 | 3.73 | 7.06 | 9.44 | 10.11 |
| TPSA (oA)<500 | 0.00 | 0.00 | 17.07 | 26.30 | 0.00 | 37.30 | 0.00 | 0.00 |
| MW<500 (g/mol) | 136.24 | 136.24 | 142.24 | 196.29 | 190.33 | 256.43 | 308.59 | 408.80 |
| MV | 151.81 | 157.32 | 165.79 | 208.06 | 207.91 | 291.42 | 376.16 | 499.40 |
| nON<10 | 0 | 0 | 1 | 2 | 0 | 2 | 0 | 0 |
| nOHNH<5 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Lipinski's violation | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| Solubility and pharmacokinetics properties (SwissADME) | | | | | | | | |
| Water solubility | M to S | S | S | S | M to S | P to M | P to I | I |
| BBB permeant | Yes | Yes | Yes | Yes | Low | Yes | No | Low |
| Gastrointestinal absorption | Low | Low | High | High | No | High | Low | No |
| Log $K_p$: Skin permeation: cm/s | -3.95 | -4.69 | 4.85 | -4.99 | -4.11 | -2.77 | 0.48 | 2.08 |
| Cytochromes inhibitors | | | | | | | | |
| CYP1A2 | No | No | No | No | No | Yes | Yes | No |
| CYP2C19 | No | No | No | No | Yes | No | No | No |
| CYP2C9 | Yes | No | No | Yes | Yes | Yes | No | No |
| CYP2D6 | No | No | No | No | No | No | No | No |
| CYP3A4 | No | No | No | No | No | No | No | No |
| Toxicity risks (OSIRIS Property Explorer) | | | | | | | | |
| Mutagenic | No | No | Yes | No | No | No | No | No |
| Tumorigenic | No | No | No | No | No | Yes | No | No |
| Irritant | Yes | No | Yes | MR | No | Yes | Yes | No |
| Reproductive effective | No | No | Yes | No | No | No | No | No |

miLogP-Partition coefficient between n-octanol and water, TPSA-Topological polar surface area, MW-Molecular weight, MV-Molecular volume, nON-Number of hydrogen bond acceptors, nOHNH-Number of hydrogen bond donors, No-no indication found, S-Soluble, MS-Moderate to soluble, PM-poor to moderate, VS- very soluble, PI-Poorly to Insoluble, I-insoluble, MR-medium risk

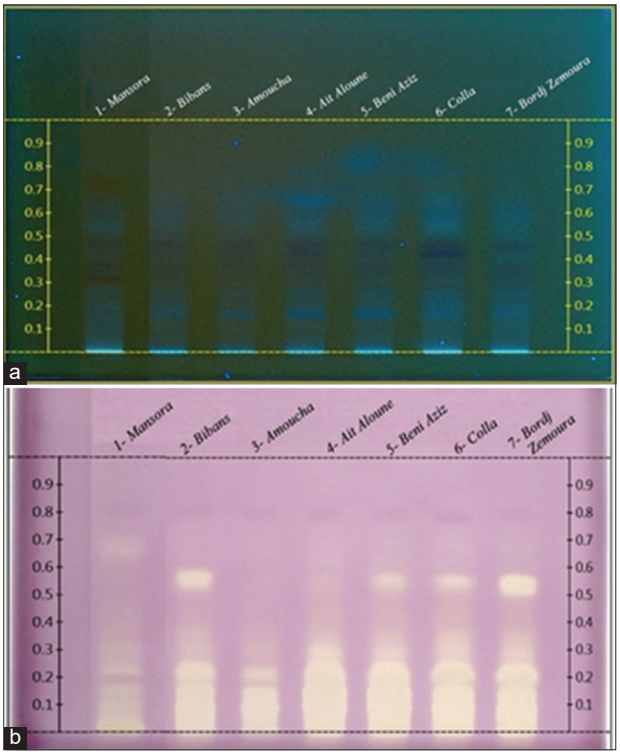



**Figure 5:** a) Plate visualized before derivatization under UV 366 nm and b) HPTLC analysis with DPPH derivatization of *C. spinosa* EO (under white light heating to 110 °C)

## Discussion

The results show a notable variation depending on the origin of the EOs, with certain populations presenting particularly high inhibition diameters for strains such as *S. aureus* and *B. cereus*. This variation is entirely plausible, because the chemical composition of EOs depends strongly on geographical, climatic (Raal *et al.,* 2024) and edaphic factors (Vaičiulytė *et al.,* 2022). Individuals of the same botanical species, with the same genome and phenotype differing in chemical composition and thus in biological activities (Benomari *et al.,* 2023). Furthermore, the antibacterial efficacy depends on the relative profile of major and minor compounds in the oil of each population.Several studies confirmed the antimicrobial potential of *C. spinosa* extracts. Furthermore, *Capparis* species are known to contain phenolic and terpene metabolites that may contribute to antibacterial activity (Uysal *et al.,* 2024). The methanolic extract of *C. spinosa* had high activity against *S. aureus*, *K. pneumonia* and *E. coli* (Al-Azawi *et al.,* 2018), *S. aureus*, *E. coli*, *S. enterica* and *P. aeruginosa* (Rajhi *et al.,* 2019), *S. aureus*, *B. cereus*, *E. coli* and *S. typhimurium* (Shahrour *et al.,* 2024). However, the oils from our populations are ineffective against *E. coli*, the same observations were reported by Adwan and Omar (2021) using the aqueous and ethanolic extract. Due to their double membrane, Gram-negative bacteria constitute a hydrophobic barrier limiting the diffusion of EOs therefore reducing their effectiveness which has been reported in several previous studies (Benachour *et al.,* 2019; Patterson *et al.,* 2019; Uysal *et al.,* 2024; Fratini *et al.,* 2025). *C. spinosa* extracts were reported to have remarkable antioxidant properties, although there is no research carried out on the antioxidant activity of this species EO, obtained by hydro-distillation. The methanolic extracts of *C. spinosa* (Tlili *et al.,* 2015; Allaith, 2016; Rajhi *et al.,* 2019; Elshibani *et al.,* 2020), the aqueous extracts (Tagnaout *et al.,* 2016; El Finou *et al.,* 2024). petroleum ether extract, chloroform extract and n-butyl alcohol extract (Yu *et al.,* 2017). However, the ethyl acetate extract of fruits and leaves showed low antioxidant activities (Fadili *et al.,* 2017). *In silico* approaches are revolutionizing drug design by providing predictive and cost-effective solutions for potential drugs (Islam *et al.,* 2025). The main compounds of *C. spinosa* EO integrated the active sites of target proteins especially α-Duprezianene with the best binding energies with the three targets, notably with LasR and AgrA proteins suggesting its potential action on blocking the process of bacterial biofilm formation.The van-der-Waals (vdW) and alkyl interactions are mainly responsible for the bonds with proteins. vdW bonds contribute to the overall stabilization of the ligand-receptor complex, while P-Sigma bonds are often important for binding specificity. For natural ligands, significant energies are expressed by classical hydrogen bonds, which are strong interactions and often crucial for specific binding and biological activity, in addition to carbon-hydrogen bonds. Occupational safety and safety performance have become a prominent area of research in the last three decades (Saleem & Malik, 2022). Since synthetic fragrances could be unsafe for human applications, some questions concerning the safety of synthetic compounds have encouraged more detailed studies of plant resources (Kalemba & Kunicka, 2003). For this EO, the main compounds were evaluated for their eventual toxicity. In general, α-pinene, β-phellandrene, n-Nonanal Isopulegyl, acetate and α-Duprezianene have good physicochemical and pharmacokinetic featers (Table 10). Skin permeation and skin concentration of the compounds should be considered after topical administration, as well as their blood concentration to evaluate efficacy and safety; the evaluation of the amount of drugs permeated through skin is important for topically applied drugs (Oshizaka *et al.,* 2012). All compounds meet the limit (miLogP<5), indicating moderately good lipid solubility, hexadecanoic acid, 1-Docosene, and nonacosane are highly lipophilic (miLogP>7), which may limit their aqueous solubility and oral absorption. Low values of polar surface area (TPSA) suggest good membrane permeability, except for hexadecanoic acid (37.3 g/mol), which may have reduced absorption. For MW, all compounds except meet Lipinski's rules, this favors bioavailability. The cytochromes P450 comprise a family of enzymes that are responsible for around three-quarters of all drug metabolism reactions that occur in human populations (Waring, 2020). Therefore, disruption of these interactions can lead to altered paths of metabolism and the production of toxic metabolites (Kandel & Lampe, 2014). Hexadecanoic acid and α-Duprezianene are high-risk compounds because they inhibit CYP1A2, CYP2C19, and CYP2C9, with a risk of liver toxicity and thrombosis. Isopulegyl acetate and docosene are moderate-risk compounds because they inhibit CYP2C9 alone. β-Phellandrene, n-nonanal, α-pinene, and nonacosane are compounds with no risk of interaction because they do not significantly inhibit CYPs, making their use safe in

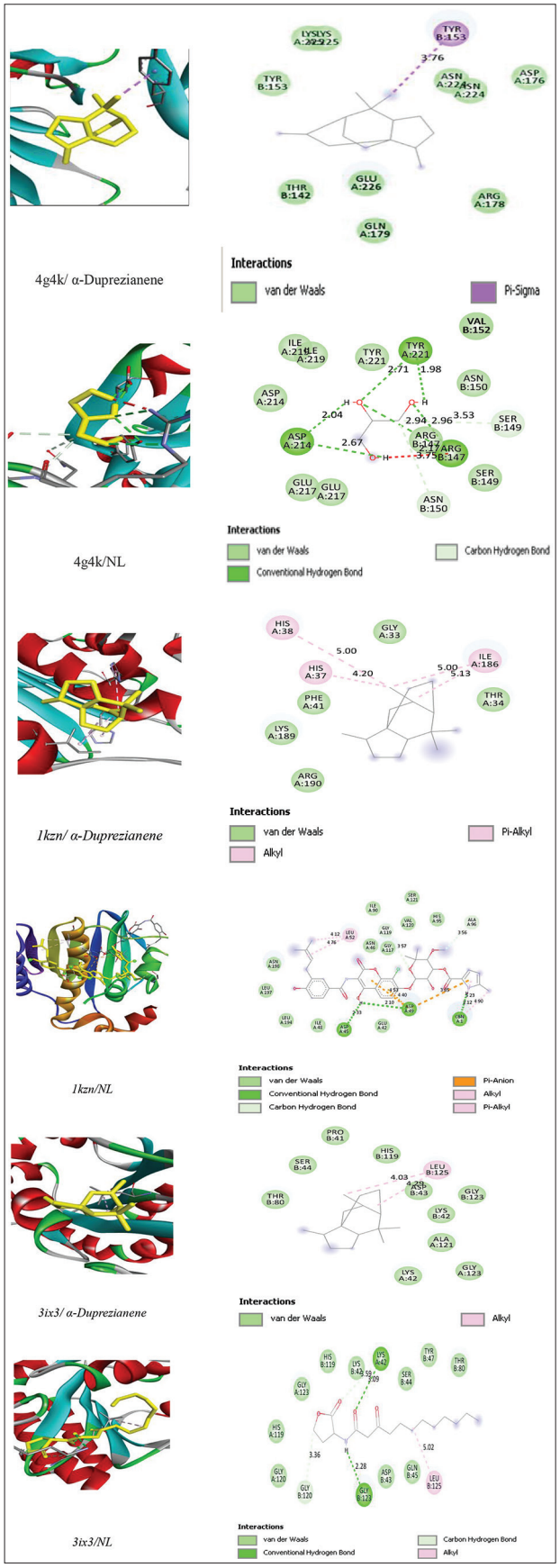



**Figure 6:** Interaction and bond distances of ligands (in yellow) inside the active site pocket as shown by molecular surface maps; NL: natural ligand, on the right: the 3d structure and on the left, the 2d structure

therapeutic formulations. β-Phellandrene, n-Nonanal, and Isopulegyl acetate are soluble in water, while exadecanoic acid, 1-Docosene, and nonacosane are poorly soluble because lipophilic compounds (high miLogP) have reduced aqueous solubility. Low MW compounds and TPSAs (α-pinene, β-phellandrene, n-Nonanal and Isopulegyl acetate) cross the blood-brain barrier better. Highly lipophilic compounds such as n-Nonanal, 1-Docosene, Hexadecanoic acid penetrate the skin better. The n-Nonanal and Hexadecanoic acid (tumorigenic, CYP inhibitor, excessive lipophilicity) are risky compounds.

## Conclusions

*Capparis spinosa* EOs exhibit noTable antibacterial activities, particularly against Gram-positive bacteria. Variations in efficacy between populations reflect chemical diversity influenced by geographical origin. Furthermore, the significant antioxidant activity, confirmed by DPPH and HPTLC, gives these oils a double therapeutic interest. Integration of docking results suggests a dual mechanism of action: direct inhibition on the cell wall and interference with intercellular communication mechanisms and biofilm formation processes. These results would reinforce the interest of *C. spinosa* in the design of new anti-infectious strategies, particularly in the fight against chronic infections associated with biofilms and confirm its potential as a natural source of antimicrobial agents, with promising prospects in pharmacology, food safety and cosmetics. This dual activity, combined with its natural origin and its important place in traditional pharmacopoeia, justifies further research, in particular by the evaluation of the effect on the formation and disruption of bacterial biofilms.

### Author contributions

Ounoughi Abdelkader and Benachour Halima: collecting plant samples and experimentation. Gilles Figuiredo: chromatographic analysis. Ramdani Messaoud, Lograda Takia, Ounoughi Abdelkader, Benachour Halima and Elkolli Meriem: treatment of results. Elkolli Meriem: writing of the original draft, review and editing. All authors approved the final manuscript.

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