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In vitro Assessment of Antibacterial Activity and Potential Genotoxic Effect of Fruit Extracts of *Capparis spinosa* L. Plant

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ABSTRACT

This research was carried out to assess the minimum inhibitory concentration (MIC) and the genotoxic potential of ethanolic and aqueous (cold and hot) fruit extracts of *Capparis spinosa* L. (*C. spinosa*) plant against different types of bacterial strains. The antimicrobial effect of these extracts against the tested bacteria was investigated using broth microdilution method. The potential genotoxic effect was evaluated by ERIC-PCR technique. Results of the current study revealed that the MIC values of ethanolic fruit extract against the tested bacterial had a range of 12.5 mg/ml to 25 mg/ml. However, aqueous fruit extracts had an MIC with a range of 50 mg/ml to 100 mg/mL. The potential genotoxic activity of cold aqueous extract was determined according to the changes in ERIC-PCR profile of *E. coli* strain treated with extract in comparison to that untreated (negative control). Results of this study suggest the genotoxic effect of aqueous fruit extract on *E. coli*. Further research is required to assess and identify the biological molecules and their mechanisms in the context of the genotoxicity. In vivo genotoxicity assessment or with the presence of liver extract is recommended to evaluate the safety of using fruits for therapeutic purposes and a valuable nutrient source.

Keywords: *Capparis spinose*, antimicrobial activity, potential genotoxic effect, ethanolic fruit extract, aqueous fruit extract.

1. INTRODUCTION

Capparis spinosa plant is commonly known as a caper, plant belonging to genus *Capparis* of the family Capparidaceae. It is a perennial spiny bush that has fleshy leaves and big-white to pinkish-white flowers. This plant has a deep tap roots, woody stems; evergreen leaves, orbicular to elliptic, base rounded and apex mucronate, alternate. It hasa complete flower, showy, with four sepals, and four white to pinkish-white-colored petals, several long violet-colored stamens, with a single stigma. The small bud(caper)that grows to become a flower, which results in a fruit caperberry development with a delicate fruity flavor[1].

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The bush of *C. spinosa* is native to the Mediterranean region, it is a drought tolerant plant, mainly distributed in arid and semi-arid regions of the tropical and subtropical world [1,2]. The fruit is considered as a rich source of high-value nutrients. The *C. spinosa* plant is used in indigenous medicine to prohibit and/or relieve several of health issues such as kidney problems, obesity, hepatitis and diabetes. A wide range of pharmacological activities of various *C. spinosa* plant's parts have been described. These activities including antibacterial, cytotoxic, antiviral, anthelminthic, antifungal, antioxidant, anti-inflammatory, antiarthritic, chondroprotective, cardiovascular, respiratory, antidiabetic, antiallergic and antihistaminic, hypolipidemic, antipyretic, anticarcinogenic, hepatoprotective, immunomodulatory, diuretic, hypoglycemic and antihepatotoxic[1,2].

Antibacterial effect of fruit extracts of *C. spinosa* plant on different bacterial species has been studied previously[3-6]. Genotoxicity of buds aqueous extract and leaf aqueous extract of *C. spinosa* plant has previously been studied[7,8]. However, the genotoxic potential of fruit extract has not been previously evaluated. The current study was carried out to determine the minimum inhibitory concentration (MIC) of ethanolic and aqueous fruit (cold and hot) extracts of *C. spinosa* growing wild in Palestine, against different types of bacteria. In addition, to assess the genotoxic potential of cold aqueous fruit extract on *Escherichia coli* (*E. coli*) ATCC 25922 strain using enterobacterial repetitive intergenic consensus (ERIC)-PCR technique

2. RESULTS

2.1. Antimicrobial activity of C. spinosa fruit extracts

Results of the present study revealed that the ethanolic, aqueous fruit (cold and hot) extracts of *C. spinosa* were active against the studied bacterial strains. Ethanolic fruit extract exhibited higher antibacterial activity against both Gram-positive and Gram-negative bacteria than aqueous fruit (cold and hot) extracts. The studied bacteria were sensitive to ethanolic fruit extract concentrations ranging from 12.5 to 25 mg/ml. However, these tested bacteria were susceptible to the aqueous fruit (cold and hot) extracts concentrations ranging from 50 mg/mL to 100 mg/mL. The MIC profile of ethanolic, aqueous fruit (cold and hot) extracts of *C. spinosa* plant against different tested bacterial strains is presented in Table 1.

Table 1: MIC profile of ethanolic and aqueous fruit (cold and hot) extracts of *C. spinosa* plant against different types of bacterial species.

Bacterial strain	Fruit Extracts MIC±SD[a] (mg/ml)		
	Ethanolic	Cold water	Hot water
***S. aureus*(ATCC 6538P)**	12.5±0.0	50±0.0	50±0.0
MRSA (clinical isolate)	25±0.0	100±0.0	100±0.0
***E. coli* (ATCC 25922)**	12.5±0.0	50±0.0	50±0.0
***K. pneumoniae* (ATCC 13883)**	25±0.0	100±0.0	100±0.0
***B.subtillus* (ATCC 6633)**	1.25±0.0	100±0.0	100±0.0
***S. epidermidis* (ATCC12228)**	12.5±0.0	50±0.0	50±0.0

SD[a]: Standard deviation.

2.2. Evaluation of the genotoxic potential of C. spinosa aqueous fruit extract

The alterations in the extracted genomic DNA from both treated and untreated *E. coli* strain with different concentrations of cold aqueous fruit extract of *C. spinosa* plant were assessed and compared at the same time intervals using ERIC-PCR technique. In the current study, the ERIC-PCR profile revealed that the bands with an amplicon fragment size of approximately 300-bp length and 450-bp length were less intense or invisible in *E. coli* strain treated with dose 32.25 µg/ml of cold aqueous fruit extract of *C. spinosa* plant for 2h (Figure 1, lane 3), when these bands compared with the same bands that was produced in the negative control (Figure 1, lane C1). However, the ERIC-PCR profile also showed that the bands with an amplicon fragment size of about 1000-bp length and 450-bp length were more intense in *E. coli* strain treated with doses 62.5 µg/ml and31.25 µg/ml for 5h of cold aqueous fruit extract of *C. spinosa* plant(Figure 1, lanes 5 and6), in comparison with the same bands emerged in the negative control (Figure 1, lane C2).In addition, the

results of ERIC-PCR exhibited that the band which had an amplicon fragment size of approximately 650-bp length was higher intense in *E. coli* strain treated with dose 32.25 µg/ml of cold aqueous fruit extract for 5h (Figure 1, lane 6), when that band compared with the same band appeared in the negative control (Figure 1, lane C2).In this study, the ERIC-PCR profile showed that bands with an amplicon fragment size of about 1000-bp length and 650-bp length were less intense in *E. coli* strain treated with a dose 125 µg/ml of aqueous fruit extract of *C. spinosa* for 24 h (Figure 2, lane 7), when these bands compared with the same bands that appeared in the untreated control (Figure 2, lane C3). In addition, the band with an amplicon fragment size of about 650-bp length had less intensity in *E. coli* strain treated with a dose31.25 µg/ml of aqueous fruit extract of *C. spinosa* for 24 h (Figure 1, lane 7),when that band compared with the same band revealed in the negative control (Figure 1, lane C3). However, the band with a fragment size 450-bp length had a higher intense in *E. coli* strain treated with a dose 32.25 µg/ml of aqueous fruit extract of *C. spinosa* for 24 h (Figure 1, lane 9), in comparison with the same band seen in the negative control (Figure 1, lane C3).

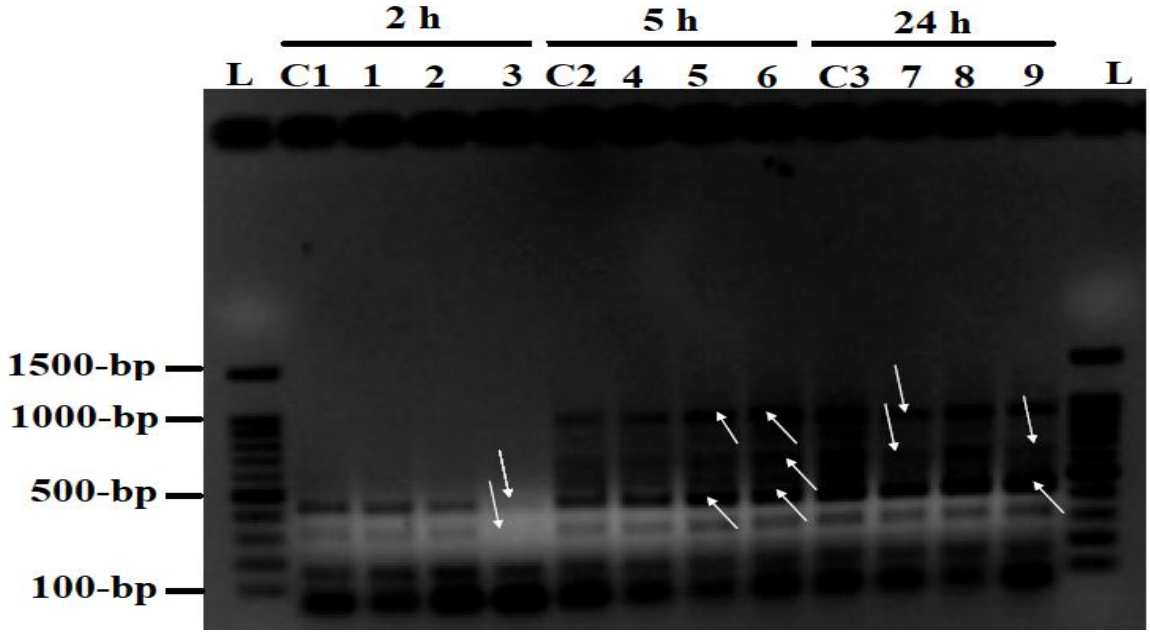

Figure 1: ERIC-PCR profile of *E. coli* strain treated with different concentrations of *C. spinosa* cold aqueous fruit extract at different time intervals and untreated (negative control). Lanes 1, 4 and 7 treated with 125 µg/ml; Lanes 2, 5 and 8 treated with 62.5 µg/ml; Lanes 3, 6 and 9 treated with 31.25 µg/ml of plant extract; Lanes C1, C2 and C3 are untreated (negative controls); Lanes L are 100-bp ladder).

3. DISCUSSION

Nowadays, researchers are seriously and continuously working on discovering and producing and synthesizing new drugs that act against bacterial infections. However, the bacterial strains are continuously opposing a challenge of this work by producing new strains that are resistant to the new produced drugs. In general, plants are considered a natural source that is rich with different by-products that harbor a potential antimicrobial activity against a broad range of pathogens[9,10]. In this study, ethanol and aqueous

(cold and hot) fruit extracts of *C. spinosa* plant were used to evaluate their antimicrobial properties against different bacterial pathogens by broth microdilution method. These pathogens included *S. aureus* (ATCC 6538P), MRSA (clinical isolate), *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 13883) and *B. subtillus* (ATCC 6633).The results confirmed that ethanolic and aqueous (cold and hot) fruit extracts exhibited antibacterial activity against these studied microorganisms. Antimicrobial activity of fruit *C. spinosa* plant has been reported previously using different types of extracts[3-6].The antimicrobial activity is depending on the type of extracts. It has been reported previously that, flavonoid molecules are considered one of the major class of phenolic group, which have antimicrobial properties by inhibition of nucleic acid synthesis, cytoplasm membrane function and energy metabolism[11].

Nutraceutical molecules that are derived from different natural sources such as medicinal plants. Most of them have various medicinal properties and are declared to provide protection against many pathogens and various diseases if taken regularly. At the same time, studies which showed the safety evaluation and toxic activity of nutraceuticals have been very limited, so the safety of using of many of nutraceuticals cannot be assured[12]. In this study, the potential genotoxic effect of cold aqueous fruit extract of *C. spinosa* plant against *E. coli* strain was evaluated using ERIC-PCR technique. Reviewing the scientific literature showed that this is the first report studied the genetoxicity of aqueous fruit extract of *C. spinosa* plant on bacteria using PCR technique. Results of the current study showed that aqueous fruit extract of *C. spinosa*, altered ERIC-PCR profiles of *E. coli* strain treated with the aqueous fruit extract, in comparison with untreated *E. coli* strain (negative control). These results highly suggest the potential genotoxic effect of aqueous fruit extract from *C. spinosa* plant on *E. coli*. Results of this study are in agreement with results that have been published recently[8], which showed the potential genotoxic activity of the aqueous leaf extract of *C. spinosa* plant against *E. coli* using two molecular fingerprinting based techniques. However, our results are in contrast to that published previously[13,14], which exhibited that using *C. spinosa* is safe and there is insignificant scientific evidence regarding any adverse or toxic effects. On the other hand, other recent study showed that *C. spinosa* extracts had no potential toxicity effect at low doses but showed some toxicity at high doses. This is because that the crude extracts might have potential toxicity effect at higher concentrations[15]. Results of the this report are in contrast to findings of a study published previously[7], which revealed that aqueous extract of *C. spinosa* buds is non-genotoxic and the study showed the potential antimutagenic effect of the aqueous extract of *C. spinosa* buds against chromosomal aberrations in *A. cepa* root meristem cells induced by Ethyl Methane sulfonate. These variations in results of potential genotoxicity effect could be due to differences in plant part, test system and method used to evaluate potential genotoxicity effect. In a literature review, it was exhibited that plant extracts could be mutagenic and antimutagenic at the same time depending on the test system used to evaluate potential genotoxic effect. This demonstrates that it requires a category of tests or assays before any significant conclusion that can be given about the potential genotoxic effect[16].

4. MATERIALS AND METHODS

4.1. Plant collection

The caperberries were collected from a natural habitat in Tulkarm province, West Bank-Palestine, during July, 2020. The plant was identified by the plant taxonomist Dr. Ghadeer Omar, Department of Biology and Biotechnology, An-Najah National University, Palestine. The collected caperberries were washed thoroughly with water to get rid of soil and dust particles, and then were left in a shadow area away from light to minimize or reduce the possible loss of active ingredients. The air dried caperberries were finely powdered using an electric grinder to make them ready for extract preparation.

4.2. Plant extract preparation

4.2.1. Ethanolic fruit extract preparation

The ethanolic fruit extract was prepared according to method described previously with slight modifications[8]. Briefly, approximately 20 g of dried fruit powder was mixed in 200 mL of 70% ethanol; the mixture was incubated on orbital shaker at room temperature for 24h. After that, the mixture was filtered using three layers of medical gauze to get rid of large insoluble particles. Then, the obtained filtrate was centrifuged at 5,000 rpm for 10 min at 4°C to get rid of the small and fine particles. To possess a dried powder, the supernatant was left in incubator at 40°C. Finally, the obtained ethanolic fruit extract powder was stored in a refrigerator at 4°C. Before starting the experiments, a final concentration of 200 mg/mL of the ethanolic fruit extract powder was prepared in 10% Dimethyl Sulfoxide (DMSO) to be ready for assays.

4.2.2. Cold aqueous fruit extract preparation

The cold aqueous fruit extract was prepared according to method described previously with some modifications[8]. Briefly, approximately 20 g of dried fruit powder was mixed in 200 mL of cold (room temperature) sterile distilled water. Then, other following steps were as well as described in ethanolic fruit extract preparation. Before starting the experiments, a final concentration of 200 mg/mL of the cold aqueous fruit extract powder was prepared in sterile distilled water to be ready for assays.

4.2.3. Hot aqueous fruit extract preparation

The hot aqueous fruit extract was prepared as well as the same of the cold aqueous fruit extract preparation, except that the powder of dried fruits was added to a boiling water for 2 min.

4.3. Determination of MIC

MIC of plant extracts was determined by the broth microdilution method in sterile 96- wells microtiter plates according to the CLSI instructions[17]. The extracts were two fold-serially diluted in Mueller Hinton broth in the wells of plates. After that, to each well a 10^5 CFU/mL of a bacterial inoculum size was added. In this study, each plate was included different control wells, such as wells with Mueller Hinton broth only, DMSO and Mueller Hinton broth with microorganism inoculum, and plant extracts and Mueller Hinton broth without microorganism inoculum. Each experiment for each plant extract was conducted in duplicate. The covered plates were then incubated at 37°C for 24 h. The lowest concentration of the plant extract that completely inhibited bacterial growth was identified as the MIC value for that extract**.** The MIC values for the extracts were determined by visual inspection. The bacterial species included in this study were **Staphylococcus** *aureus* (*S. aureus* ATCC 6538P), Methicillin-resistant **S. aureus** (MRSA, clinical isolate), **Escherichia coli** (*E. coli* ATCC 25922), **Klebsiella pneumoniae** (*K. pneumoniae* ATCC 13883) and **Bacillus subtilis** (*B. subtillus* ATCC 6633).

4.4. Evaluation of the genotoxic potential of C. spinosa cold aqueous fruit extract

Few colonies from a 24 h old *E. coli* ATCC 25922 strain growth culture plated on Nutrient agar medium were sub-cultured under sterile conditions into a bottle containing 10-mL of nutrient broth, then the bacterial growth culture incubated at 37°C for 45 min with continuous shaking. After that, aseptically, 2 mL *E. coli* culture was added to each of four sterile bottles, each of which containing 25 mL broth medium. These bottles were incubated at 37°C for 1 hour with continuous shaking. The final concentration of cold aqueous fruit extract was 125 µg/mL in first bottle, 62.5 µg/mL in the second bottle and 32.25 µg/mL in the third bottle. However, the final concentration of cold aqueous fruit extract was 0.0 µg/mL in the fourth bottle which was considered as a negative or untreated control.

Two ml of bacterial sample was obtained from the E. coli culture treated and untreated with cold aqueous fruit extract after 2 h, 5 h, and 24 h. The genomic DNA of E. coli for these samples was extracted according to method described previously[18]. The concentration of genomic DNA for each sample was measured using a nanodrop

spectrophotometer (GenovaNano, Jenway) and the DNA samples were stored at -20ºC for ERIC-PCR technique.

The ERIC-PCR was performed using Primer ERIC1: 5`-ATG TAA GCT CCT GGG GAT TCA C-3` and Primer ERIC2: 5-AAG TAA GTG ACT GGG GTG AGC G-3` (Ventura et al., 2003)[19]. The assay conditions for PCR master mix preparation, DNA amplification and electrophoresis conditions were conducted according to method *described **previously**[8]*, except that the amount of DNA template was 20 ng for the samples collected at time interval 2 h, and 40 ng for samples collected at interval times 5 h and 24 h. *Variations in banding pattern profile following the amplified DNA extracted from E. coli strain treated with plant extracts were taken in consideration. The changes used for genotoxicity assessment including band intensity as well as gain or loss of bands [8,20,21].*

5. CONCLUSION

Findings of the current study showed that that fruit extracts of *C. spinosa*, especially ethanolic extract has antimicrobial activity and can inhibit the growth of different types of bacteria species. In addition, results of this study highly suggest the potential genotoxic effect of cold aqueous fruit extract prepared from *C. spinosa* plant on *E. coli*. Further research is required to assess and identify the exact biological molecules and their mechanisms in the context of the genotoxicity of this plant. In vivo genotoxicity assessment or genotoxicity assessment with the presence of liver extract is recommended to evaluate the safety of using fruits for therapeutic purposes and a valuable nutrient source.

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التقييم المخبري للنشاط المضاد للبكتيريا واحتمالية السمية الجينية لمستخلصات ثمارنبات القبار *Capparis spinosa* L.

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ملخص

تم إجراء هذا البحث لتقييم الحد الأدنى من التركيز المثبط (MIC) واحتمالية السمية الجينية لمستخلصات الثمار الإيثانولية والمائية (الباردة والساخنة) من نبات القبار *Capparis spinosa* L. (C. spinosa) ضد أنواع مختلفة من السلالات البكتيرية. تم استخدام طريقة التخفيف الدقيق المتسلسل من اجل معرفة تأثير المستخلصات لهذه الثمار انواع مختلفة من البكتيريا. كما وتم تقييم احتمالية السمية الجينية باستخدام تقنية قائمة على تفاعل البوليميراز المتسلسل.(ERIC-PCR) أظهرت الدراسة أن قيم الحد الأدنى من التركيز المثبط لمستخلص الثمار الإيثانولي ضد البكتيرياالمستخدمة في الفحص كانت ما بين 12.5 ملغ/مل إلى 25 ملغ مل. بينما قيم الحد الأدنى من التركيز المثبط لمستخلصات الثمار المائية كانت ما بين 50 ملغ/مل إلى 100 ملغ/مل. لقد تم تحديد احتمالية السمية الجينية لمستخلص الثمار المائي البارد وفقا للتغيرات على ملف تعريف ERIC-PCR لسلالة البكتيريا الإشريكية القولونية المعالجة بالمستخلص النباتي مقارنة بغير المعالجة (الشاهد السلبي). تشير نتائج هذه الدراسة أن مستخلص الثمار المائي البارد قد يكون له تأثير سمية جينية على الإشريكية القولونية. هناك حاجة إلى مزيد من البحوث لتقييم وتحديد الجزيئات البيولوجية وآلياتها في سياق السمية الجينية لهذا النبات. يوصى بتقييم السمية الجينية في الجسم الحي أو تقييم السمية الجينية مع وجود مستخلص الكبد لتقييم سلامة استخدام الثمار لأغراض علاجية أو كمصدر غذائي.

الكلمات الدالة: نبات القبار، نشاط مضاد للميكروبات، السمية الجينية، مستخلص الثمار الإيثانولي، مستخلص الثمار المائي.

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