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Antidiarrheal Effect of *Capparis Spinosa* Fruits Extract

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ABSTRACT

Introduction: This research was conducted for the purpose of evaluating the antidiarrheal effect of *Capparis spinosa* fruits methanolic extract and ciprofloxacin against resistant *E. Coli.* O157:H7.

Objective: This research aimed to know the antidiarrheal effect of *Capparis spinosa* fruits extract against resistant *E. Coli.* O157:H7. **Patients and methods:** The extract dose that used in this study was 400 mg/kg of rat weight and 7.14 mg/kg of ciprofloxacin twice daily for seven days. A one ml containing concentration of 1.0×10^9cfu/ml of the activated cells from *E. Coli.* O157:H7 was obtained to be administrated orally to experimental animals**.**

Results: This extract showed antidiarrheal activity leading to return of electrolytes to nearly normal value and caused reduction in the number of stools and bacterial count. The results of this study suggest that using *C. Spinosa* fruit extract may have the perfect to be choice in treatment of diarrhea a result of *E. coli* O157:H7. The findings indicated the alcoholic *C. spinosa* fruit extract contained some biologically active compounds that may be effective against diarrhea. This finding may explain why the substance has traditionally been used to treat gastrointestinal diseases. **Conclusion:** There was evidence that the methanolic extract of *C. spinosa* fruits had antidiarrheal activity against *E. coli* O157:H7.

Keywords: Anti-diarrheal, *C. spinose***,** Fruits, Methanolic, Ciprofloxacin**.**

INTRODUCTION

The passing of loose stools and an increase in bowel frequency, weight, or volume are considered signals of diarrhea, or increase in bowel movement frequency, fluidity, or volume, and is associated with increased bowel sound frequency, wet stools, abdominal pain and reduced fluid absorption and loss of electrolytes (particularly sodium) as well as water in the small and/or large intestine resulting in abundant watery stool output. Diarrhea is either chronic, or acute. As for acute diarrhea normally caused by infection with bacteria, parasites and viruses. It continues for one to two days **(1).**

Cattle are the main reservoir for *E. coli* O157:H7, a potential bacterial foodborne zoonotic pathogen that is significant globally **(2, 3).** It results in infections that can be fatal, including renal failure, hemolytic uremic syndrome, bloody diarrhea, and abdominal pain **(4).** Antimicrobial medications are frequently used to treat calf diarrhea. The development of microbial tolerance to many antimicrobial drugs has nonetheless become a well-known phenomenon due to their broad spectrum activity, which is a major worry **(5, 6).** Synthetic medications are known to have a variety of harmful adverse effects on human health **(7).**

Synthetic drugs are known to have a range of harmful adverse effects. Using herbal products is one of the promising solutions if it is supported by scientific studies. In regards to the ongoing rise in bacterial resistance to antibiotics, the development of strains that are multi resistant, and the therapeutic issues that result. Recently, a number of data have been published in this area, allowing for the valuation and justification of medicinal plants' positive effects on health **(7, 8).** *C. spinosa* L(Caper) is a Capparidaceae perennial thorny shrubs grows furiously in open, arid wilds throughout the parched and semi-arid zones of various regions of the world **(9).**

Caper fruits were distinguished by having a green exocarp throughout all phases of growth, a decline in protein content as the fruit grew, and high levels of total phenols, flavonoids, and flavanols **(10).**

The nutritional value of Capparis species is well known, and it also has a wide range of antimicrobial properties, such as antifungal and antibacterial activity, or as antioxidant, hepatoprotective, anticancer, antiallergic, anthelmintic, antidiabetic, anti-inflammatory, cytotoxic, antiarthritic, anti-oxidant, cardiovascular, chondroprotective, hypolipidemic, antiallergic, anti-histaminic, immune modulatory. The fruits are used in the treatment of fever, diabetes, rheumatism, and headaches, while leaves, buds and roots are used to treat gastrointestinal, earache, dermatological, liver, and renal diseases **(11,12)**.

There have suggested that the aerial portions of *C. spinosa* could be a source of antibacterial substances and extracts from *C. spinosa* components have been shown to effectively prevent the growth of a variety of bacterial strains, particularly those that have developed antibiotic resistance **(13).** Also, it has antibacterial effect against *E. coli* and different type of bacteria **(14)** where it is taken internally to treat diarrhea and gastrointestinal illnesses **(15).** The fruits of capers are traditionally used for treating resistant *E. coli* and may have the perfect to be choice in clinical control **(16).** methanolic, ethanolic, ethyl acetate extracts were used successfully against growth of pathogenic bacteria**.** *Capparis spinose* extracts produced good results with respect to inhibiting pathogenic *Escherichia coli* growth and increasing its sensitivity to

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antibiotic use because it contains organic compounds, including tannins, phenolic compounds, terpins, alkaloids, resins and glucosides; a high percent of metals, such as K, Ca, Mg, and P and has a pH value that is acidic in all parts of the plant [17]. It is used internally in the treatment of gastrointestinal infections, diarrhoea [18].

The second-generation of fluoroquinolone antibiotic called ciprofloxacin have activity against differentt Gram-positive and Gram-negative bacteria and is used to treat many bacterial infections [19, 20]. When compared to Ciprofloxacin, the quinolones are a family or a group that has activity against both positive and negative gram bacteria. Ciprofloxacin works on topoisomerase II of bacteria (DNA. gyrase) and topoisomerase IV. [21]. The purpose of this study was to assess antidiarrheal properties of the methanolic extract from *C. spinosa* fruit.

MATERIALS AND METHODS

Extraction of *Capparis spinosa* Fruits:

By Ultrasound- Assisted Extraction according to method descried by **Areen *et al.*** [22].

Inducing Infection (Diarrhea)

A one ml containing concentration of 1.0 × 10^9cfu/ml of the activated cells was obtained to be administrated orally to the experimental animals [23].

Animals:

The experiment for the current investigation involved 20 male Wister albino rats, which were 200-205 g in body weight and about three months old.

Design of Experiment

Four groups of twenty male rats will be randomly divided (five rats in each group) treatment starts 24 hours later after infection induction.

1. **Group A (Negative control):** animals not infected give only distilled water orally for seven days.
2. **Group B (Positive control):** animals infected experimentally with *E. coli.* O157:H7 and left without any treatment, give only distilled water orally for seven days.

3. Group C: animals infected with *E. coli.* O157:H7 and treated with *C. spinosa* fruits methanolic extract orally (400 mg/ kg B.W.) twice daily for seven days, according to **Abbasifard *et al.*** [24].

4. Group D: animals infected with *E. coli.* O157:H7 and treated with ciprofloxacin orally (7.14 mg/kg B.W.) twice daily for seven days, according to **Ndem *et al.*** [25].

Parameters:

Fecal Examination

All animals had treatment every morning before being put into individual cages, the floors of which contained filter paper that would be changed every hour. After 1, 3, and 7 days of infection, the numbers of wet stools were counted for 6 hours.

Electrolytes and Mineral (Sodium, Potassium, Chloride and Magnesium Level)

Blood samples were collected without anticoagulant and centrifugated to obtain serum from all animals at initial, three and seven days after infection.

Fecal Bacterial Count, For *E. coli* O157: H7 Bacteria

Rectal sterile cotton swabs were used to collect feces samples. Prior to infection, 24 hours following infection, three days following treatment, and seven days following treatment. The counting of *E. coli* bacteria in fecal samples was done. 100 mg of fecal samples were suspended in 1 ml of diluents with a ratio of 1:99 containing 0.1% peptone in (0.85%) saline. The suspensions of initial nutrient broth and their tenfold serial dilutions were cultured (0.1 ml) in duplicate on sorbitol MacConkey Agar, according to: pour plate method for bacterial count. After being incubated for 24 hours at 37 °C, typical colorless or amber-like colonies were counted. A sample dilution used to inoculate plates that produced between 30 and 300 colonies per plate was analyzed [26]. The bacterial number (cfu) per gram or ml of sample was calculated according to the following equation [27]:

$$\text{Number of Colonies (CFUs)} = \frac{\text{Number of Bacteria in mL}}{\text{Dilution X Amount Plated}}$$

Statistical analysis

The Statistical Analysis System- SAS [28] program was used to detect the effect of difference factors in study parameters. Least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significant compare between means in this study.

Ethical approval: This study was ethically approved by college of veterinary medicine Committee. All procedures performed under the ethical standards.

RESULT

Effect of Infection with *E. Coli* O157:H7 on sodium ion:

The effects of *E. coli* O157:H7 in rats on Na^+ showed that there was decreasing in sodium ion in all groups after 3 days of infection except group (A) the control negative group that non infected and not treated (given only distilled water) with significant differences ($P<0.05$) compared to the initial values. The highest decreasing of Na^+ was observed in the infected non-treated group with significant difference ($P<0.05$) as compared to other groups at 7 days post-infection, while value of Na^+ was observed in group treated with ciprofloxacin, *C. spinosa* fruits extract 7 days post-infection which return nearly to normal value (Table 1).

Table (1): Na^+ mmol/L initial, after 3 and 7days in infected rats with the pathogenic *E. coli* O157: H7 and treated with *C. spinosa* fruits extract, ciprofloxacin

Groups	Initial (week before infection)	3 days treatment	7 days treatment	LSD value
Negative control	144.20 ±0.37 A a	144.40 ±0.40 A a	144.60 ±0.24 A a	1.02 NS
Positive control	143.40 ±0.40 A a	132.80 ±1.15 C b	130.20 ±0.86 C b	2.773 *
ciprofloxacin	143.50 ±0.37 A a	135.60 ±0.51 B c	138.20 ±0.37 B b	1.985 *
***C. spinosa* fruit extract**	144.40 ±0.40 A a	135.20 ±0.37 B c	137.60 ±0.24 B b	2.194 *
LSD value	1.223 *	1.938 *	1.358 *	---
There are significant distinctions between means with various big-letters in the same column and small-letters in the same row. * (P≤0.05).				

Effect of *E. Coli* O157:H7 Infection on potassium ion

Results of infection rats with *E. coli* O157:H7 on K+ concentration are summarized in table (2). Significant decline in K^+ level in all infected groups (B, C and D) except the control negative group (A) that non infected and not treated (given only distilled water). After 7 days of treatment, group treated with ciprofloxacin and *C. spinosa* fruits extract returned to nearly normal values with significant difference with group B (infected and untreated group). In comparison between groups, the highest declining in K^+ concentration was observed in group (B) infected not treated with significant differences ($P<0.05$). Comparing with the group treated with ciprofloxacin, *C. spinosa* fruits extract showed the lowest declining after 7 days (table 2).

Table (2): k^+ mmol/L initial, after 3 and 7days in infected rats with the pathogenic *E. coli* O157: H7 and treated with *C. spinosa* fruits extract, ciprofloxacin

Groups	Initial (week before infection)	3 days treatment	7 days treatment	LSD value
Negative control	4.42 ±0.03 A a	4.48 ±0.04 A a	4.60 ±0.05 A a	0.184 *
Positive control	4.40 ±0.03 A a	3.60 ±0.04 D b	3.20 ±0.04 C c	0.259 *
Ciprofloxacin	4.50 ±0.03 A a	3.72 ±0.06 D c	4.20 ±0.08 B b	0.194 *
***C. cpinosa* fruits extract**	4.40 ±0.04 A a	3.86 ±0.04 C c	4.10 ±0.07 B b	0.183 *
LSD value	0.118 *	0.134 *	0.179 *	---
There are significant distinctions between means with various big-letters in the same column and small-letters in the same row. * (P≤0.05).				

Effect of Pathogenic *E. Coli* Infection on The Chloride Ion

Table (3) after inducing infection showed that there was a significant ($P<0.05$) decrease in CL ion level in all infected group (B, C and D). Animals of group treated with ciprofloxacin, *C. spinosa* fruits extract showed faster returning to nearly normal values in seven days of treatment. While, infected group B (positive control) showed continuous decrease in CL ion concentration.

Table (3): CL^- mmol/L initial, after 3 and 7days in infected rats with the pathogenic *E. coli* O157: H7 and treated with *C. spinosa* fruits extract, ciprofloxacin

Groups	Initial (week before infection)	3 days treatment	7 days treatment	LSD value
Negative control	99.60 ±0.67 A a	99.60 ±0.67 A a	99.80 ±0.73 A a	1.46 NS
Positive control	99.40 ±0.51 A a	83.20 ±0.66 D b	80.80 ±0.73 D c	2.93 *
ciprofloxacin	99.80 ±1.11 A a	89.40 ±1.02 B b	92.20 ±1.15 B b	3.07 *
***C. spinosa* fruit extract**	100.20 ±0.86 A a	86.40 ±0.81 C b	88.60 ±0.97 C b	3.21 *
LSD value	2.489 NS	2.215 *	2.618 *	---
There are significant distinctions between means with various big-letters in the same column and small-letters in the same row. * (P≤0.05).				

Effect of *E. Coli* O157:H7 Infection on Magnesium Ion

Table (4) showed that there was significant decline in Mg^+ level in all infected groups (B, C and D) except the control negative group (A) that non infected and not treated (given only distilled water). After 7 days of treatment, groups treated with ciprofloxacin and *C. spinosa* fruits extract (C & D) showed return to nearly normal values when compared to group B (infected and not treated group). In comparison between groups, the highest decline in Mg^+ concentration appeared in group infected non-treated with significant difference ($P<0.05$) as compared to the negative control (A) after 3 & 7 days. Also, other groups treated with ciprofloxacin and *C. spinosa* fruits extract showed decline after three and seven days as compared to control group. Positive control group (B) showed no significant difference as compared to groups treated with ciprofloxacin and *C. spinosa* fruits extract.

Table (4): Mg mg/dL initial, after 3 and 7days in rats infected with the pathogenic *E. coli* O157: H7 and treated with *C. spinosa* fruits extract, ciprofloxacin.

Groups	Initial -week before infection	3 days treatment	7 days treatment	LSD value
Negative control	2.20 ± 0.08 A a	2.24 ± 0.08 A a	2.28 ± 0.06 A a	0.104 NS
Positive control	2.10 ± 0.08 AB a	1.24 ± 0.05 B b	1.20 ± 0.04 D b	0.181 *
ciprofloxacin	2.00 ± 0.04 B a	1.32 ± 0.05 B c	1.58 ± 0.06 C b	0.177 *
***C. spinosa* fruit extract**	1.98 ± 0.06 B a	1.30 ± 0.03 B c	1.56 ± 0.06 C b	0.184 *
LSD value	0.199 *	0.172 *	0.171 *	---
Significant differences exist between means with various big-letters in the same column and small-letters in the same row. * (P≤0.05).				

Effect of *E. coli* O157:H7 Infection on The Number of Watery Stool

Rats infected with *E. coli* O157:H7 regarding the number of watery stool showed that the number of the watery stool after one day post-infection was 1.00±0.31, 6.00±0.31, 3.60±0.51 and 4.20±0.20 /6hr in A, B, C and D groups respectively, with significant difference ($P<0.05$) between all groups except those that treated with ciprofloxacin and *C. spinosa* fruits extract. At day three post-infection the watery stool continued in all groups, which was 7.20±0.58 time/6hr in the infected non-treated group, 3.20±0.37 time/6hr in group treated with ciprofloxacin and 3.00±0.31 time/6hr in group treated with *C. spinosa* fruits extract, with significant difference ($P<0.05$) between all groups except between those that treated with ciprofloxacin and *C. spinosa* fruits extract. After seven days post-infection the watery stool continued only in the infected-non treated group 5.00±0.31 time/6hr (table 5).

Table (5): Number of the watery stool per six hours in infected rats with pathogenic *E. coli* O157: H7 and treated with ciprofloxacin, *C. spinosa* fruits extract or kept untreated during the experiment

Number of watery stools per six hours				
Groups	**1 days**	**3 days**	**7 days**	**LSD value**
G A –ve control	0.813 ±0.31 C a	0.813 ±0.00 C b	0.813 ±0.00 C b	0.871 *
G B +ve control	6.00 ±0.31 A ab	7.20 ±0.58 A a	5.00 ±0.31 A b	1.366 *
G C: Ciprofloxacin	3.60 ±0.51 B a	3.20 ±0.37 B a	1.20 ±0.37 B b	1.28 *
G D: *C. spinosa* fruits methanolic extract	4.20 ±0.20 B a	3.00 ±0.31 B a	1.20 ±0.37 B b	1.327 *
LSD value	0.969 *	1.087 *	0.813 *	---
Significant differences exist between means with various big-letters in the same column and small-letters in the same row. * (P≤0.05).				

Rectal Bacterial Count

Rectal bacterial counting was performed using the pour-plate-method **(40)**, which was compared to other methods to count fecal *E. coli* O157: H7. It was discovered that these methods, along with the spread plate method on sorbitol MacConkey agar were simpler to use, less time-consuming, fewer expenses, and provide results for fecal *E. coli* O157: H7 within a day.

Count Before Inducing Infection:

Table (6) showed that there was no growth and no statistically significant differences (P > 0.05).

Count After 24 hrs. Inducing Infection:

After 24 hours of infection second step was performed (appearance of diarrhea). *E. coli* O157:H7 viable count significantly increased (P < 0.05) in all infected groups, and in three challenged groups (B, C, and D) at the same time when they were compared to (-ve control, group-A). After 24 hours, there were no noticeable differences (P0.05) between the infected groups (table 6).

Count After Three Days of Treatment:

The findings demonstrated that treatment with ciprofloxacin and *C. spinosa* fruit extract both reduced fecal bacterial counts, but in varying ratios. All treated groups (C and D) had a significantly lower rectal bacterial counts than their respective counts following infection. The number of bacteria in group B infected with *E. coli* O157:H7, the count kept rising. In comparison with group B, groups C and D bacterial count had significant decrease (table 6).

Count After Seven Days of Treatment:

The findings demonstrated that treatment with *C. spinosa* fruits extract and ciprofloxacin led to lowering of bacterial count in feces and showed no significant decline (P<0.05) in rectal bacterial count after seven days of treatment relative to its count after three days and after inducing infection. While group B showed a little decrease in bacterial count (Table 6).

Table (6): Rectal bacterial count of *E. coli* O157: H7 (cfu/ml) in different groups infected and treated with ciprofloxacin, *C. spinosa* fruits extract or left untreated throughout the course of experiment.

Period / Group	Week before inducing infection	24 hours after inducing infection	After (3 days) of treatment	After (7 days) of treatment	LSD value
G B –ve control	0.0 ±0.00 A a	0.0 ±0.00 C a	0.0 ±0.00 B a	0.00 ±0.00 B a	0.00 NS
G A: +ve control	0.0 ±0.00 A c	71×10^{9}±94.86 A a	58×10^{9} ±100.0 A b	81×10^{7} ±1.64 A c	174.36 *
G E: Ciprofloxacin 7.14 mg/kg twice daily	000 ±0.00 A b	69×10^{9} ±104.89 AB a	57×10^{4} ±0.0008 B b	50×10^{3} ±0.0001 B b	138.91 *
GC: *C. spinosa* fruits extract 400 mg/kg	0.0 ±0.00 A b	69×10^{9} ±104.88 AB a	56×10^{4} ±0.0008 B b	48×10^{3} ±0.0001 B b	78.22 *
LSD value	0.00 NS	250.32 *	131.93 *	2.167 *	---
Significant differences exist between means with various big letters in the same column and small letters in the same row. * (P≤0.05).					

DISCUSSION

Ancient civilizations and cultures have long used medicinal plants, and their primary goal with their active ingredients is to return the body to a condition of natural balance [30].

Hamad *et al.* [17] reported that the concentrations of potassium ions in all parts of the *C. spinosa* plant are high compared with other metal concentrations. In the root of the plant, it is 27,520.0 mg/Kg, while in the leaves, fruits and stems the concentrations are 25,620.0, 23,420.0 and 21,340.0 mg/Kg respectively. Iron ions ranged between 20.0 mg/Kg (stems) to 45.0 mg/Kg (fruits). This is important for the plant, as it may be found in chlorophyll, which contains ferredoxins and rubredoxins, which are organic compounds that are created as electrons transfer groups [31].

Hamad *et al.* [17] reported the calcium, magnesium and phosphorus contents of the plant were very high in all of its parts. Calcium ranged from 650.0 mg/Kg (stems) to 17,650.0 mg/Kg (roots). Whilst, the magnesium content varied from 2,270.0 mg/Kg (stems) to 4,660.0 mg/Kg (roots), and the phosphorus content ranged from 1,720.0 mg/Kg (stems) to 4,270.0 mg/Kg (roots).

Count After 24 hrs. of Infection induction, findings are in line with those of **Mushtaq *et al.*** [32] who demonstrated that giving rats 1.5×10^{8} cfu/ml led to an effective colonization of *E. coli* within 24 hours of giving them pathogenic *E. coli* to induce an experimental infection. Additionally, these findings concur with those of **Gunzer *et al.*** [33] who demonstrated the increase in rectal bacterial count following infection with pathogenic *E. coli.*

Count After seven days of treatment results gave good evidence about use of C. *spinosa* fruits extract. These plants' therapeutic efficacy depends on their bioactive phytochemical components, which have significant physiological effects.

C. spinosa fruits are sources of bioactive and phytochemical such as steroids, quaternary ammonium compounds, terpenoids, alkaloids, vitamins, flavonoids, phenolic substances and many more phytoconstituents that are responsible for its medicinal value [34].

Many researchers are preferring using plant extract in place of antibiotics as conventional medicine utilizes active chemicals derived from higher plants and nearly 80% of such active ingredients show a strong link between their current medical application and conventional application. The prescription drugs, on the other hand, can cause many side effects while the herbal medicine shows better patient tolerance and are readily available for all people, especially those with low incomes [35].

CONCLUSION

There was evidence that the methanolic extract of *C. spinosa* fruits that obtained by ultrasonic waves extraction had antidiarrheal activity against *E. coli* O157:H7.

Conflict of interest: According to the authors, there is no conflict of interest.

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Author contribution: In this study, all authors contributed equally.

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