

**THE POTENTIAL ANTIOXIDANT AND HEPATOTOXICITY OF
METHANOLIC EXTRACT OF LEAVES OF LIBYAN *CAPPARIS
SPINOSA* SUBSP *ORIENTALIS* (DUH.) JAFRI IN RATS**

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ABSTRACT

Objective: The study aimed to investigate antioxidant activity, acute and sub-acute toxic potential of methanolic extract of leaves of Libyan *Capparis spinosa* subsp *orientalis* (Duh.) Jafri in rats. **Methods:** LD50 of methanolic extract of leaves of Libyan *apparis spinosa* subsp *orientalis* (Duh.) Jafri was determined according to El-Hadiyah *et al.* (2011). Changes in behavioral response were recorded. Antioxidant activity evaluated with use of DPPH scavenging assay. **Results:** LD50 of methanolic extract of the plant leaves was found to be more than 2g/kg. Regarding the effect of single dose of 1g/kg of methanolic extract of leaves of *Capparis spinose* injected IP to rats for one week, no significant changes in serum levels of liver enzymes of treated

group compared to normal group. Although histopathological examination of the liver of treated rats showed hepatocellular necrosis, congestion, heamorrhage and cytoplasmic vacuoles. Amoderate intermittent spasms started after 90 minutes and lasted for an hour

intermittently then disappeared. The study showed that the plant revealed an antioxidant activity 80% with IC_{50} $0.2\text{mg/ml} \pm 0.07$. **Conclusion:** Libyan *Capparis spinosa* has good antioxidant activity. The lethal dose of the methanolic extract of the plant leaves is more than 2000mg/kg. No significant differences showed in liver safety biomarkers; alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), but it showed hepato-changes on liver tissue.

KEYWORDS: Antioxidant, LD50, hepatotoxicity, *Capparis spinosa*.

1. INTRODUCTION

Pro-oxidants are Chemical compounds and reactions able to generate potential toxic oxygen species named free radicals which is either Nitrogen derived Oxygen derived. The most common reactive oxygen species include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), peroxy radicals ($ROO\cdot$) and reactive hydroxyl radicals ($OH\cdot$) which attack macromolecules including protein, DNA and lipid causing to cellular or tissue damage. Any chemical compound and reaction can scavenging the free radicals and suppressing their formation or opposing their actions are called antioxidants. In a normal human cell there is an pro-oxidant - antioxidant balance, but if the production of toxic oxygen increased or the antioxidant levels decreased a state named oxidative stress will precipitated which if prolonged will lead to serious cell damage (Patel *et al.*, 2013).

Liver is an organ that has a range of vital functions in biotransformation (glycolysis, lipid and amino acid metabolism) and detoxification of damaging substances (like drug metabolism). Indeed, liver injuries have become one of the most serious health problems and the available synthetic drugs are expensive and may cause additional damage (Nizar *et al.*, 2017). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) are indicators of the safety liver and indicating its normal function. Increased AST and ALT activity induces the hepatic permeability and in turn facilitates liver cell necrosis (Goldberg and Watts, 1965, Mohammad *et al.*, 2014).

Nowadays, medicinal plants have an important role in diet of people and in treatment of many diseases (Rahnavard and Razavi, 2016). These medicinal plants consider as a rich resources of ingredients and secondary metabolites (Singh, 2015), which can be used as good alternative to treat diseases (Shafiee, *et al.*, 2017). The genus *Capparis* includes about 250 species. The taxonomic classification is primarily based on morphological characters such as

presence/absence of spines, leaf shape, and flowers (Cristina *et al.*, 2005). *Capparis spinosa* is a wild species belongs to the Capparidaceae family. It is native to the Mediterranean region and growing wild on walls along roadside, on the slopes, rocky and stony coastal areas. (Rahnavard and Razavi, 2016). Traditionally, the whole *Capparis spinosa* plant is used for rheumatism (Manikandaselviet *al.*, 2016), Roots are used as diuretic, astringent, and tonic (Basma and AbdRazik 2011). The bark of the root has a bitter taste and used as an appetizer, astringent, tonic, antidiarrheal and to treat hemorrhoids and spleen disease (Rahnavard and Razavi, 2016). Previous chemical studies on *Capparis spinosa* have shown the presence of, alkaloids, indole, flavonoids, lipids, aliphatic glucosinolates and polyphenols (Mansour *et al.*, 2016) and additionally the plant recognized as a rich source of flavonoids such as rutin, kaempferol, quercetin and its derivatives (Sharaf *et al.*, 1997). These constituents display a significant role in the pharmacological activity of *Capparis spinose* including antioxidant, anti-inflammatory, anti-allergic, antihistaminic, hypolipidemic, anti-mutagenic, anti-proliferative, anti-microbial, anti-helminthic, hepato-protective and anti-nociceptive effects (Bonina *et al.*, 2002, Aghel *et al.*, 2010, Sahar *et al.*, 2017), in addition to the cytotoxic effect (Ramin and Nastaran, 2016). Furthermore, Nizar *et al.*, 2017 mentioned that there is an increasing preference for natural antioxidant rather than synthetic agents because of the safety, availability and cheapness of the natural sources. The present study was aimed to assess the antioxidant activity of Libyan *Capparis spinosa* and its performance on liver functions and tissue in rats.

2. MATERIAL AND METHOD

2.1 Plant Material

The plant was collected in November 2016 from Rocky Mountains at Cyrene (Shahat) area, east of Al Bayda city, north east of Libya. The plant was classified and authenticated by Dr. Hussein Altajouri; Botany department, Faculty of Science, Benghazi University, Libya.

2.2 Animals

Wister SWR albino rats used in this study weighing 80-140g were housed in groups and kept under controlled conditions of room temperature (25°C) and relative humidity (50%) at animal house at Pharmacology department, Faculty of Pharmacy, Africa University, Khartoum, Sudan. Animals were fed on standard laboratory rodent's food and water.

2.3 Plant extraction preparation

Capparis spinosa leaves were separated, cleaned with tap water in order to get off any dust hanged and left to air dried and then coarsely powdered. One hundred gram of the powdered material was thoroughly extracted for enough time (~ 6 hrs.) with enough quantities of Methanol (~ 250ml), using Soxhlet apparatus. The extract was filtered, evaporated under reduced pressure using Rota-evaporator. The plant material was air dried and the extract was kept in a well labelled closed container at 4°C.

2.4 Antioxiadnat Activity of *Capparis spinosa* subsp *orientalis* (Duh.) Jafri

2.2Di (4-tert-octylphenyl)-1-picryl-hydrazyl (DPPH) stable free radical scavenging assay was used. The DPPH radical scavenging was determined according to the method of Shimada *et al.*(1992) with some modifications. In 96-wells plate, the test samples were allowed to react with DPPH for half an hour at 37°C. The concentration of DPPH was kept as (300µM). The test samples were dissolved in dimethyl sulfoxide (DMSO) while DPPH was prepared in ethanol. After incubation, decrease in absorbance was measured at 517nm using multi-plate reader Spectrophotometer. Percentage radical scavenging activity by samples was determined in comparison with a DMSO treated control group. All tests and analysis were run in triplicate.

2.5 Toxicity of *Capparis spinose* subsp *orientalis* (Duh.) Jafri

Acute and sub-acute toxicities of the methanol extract from the leaves of *Capparis spinose* subsp *orientalis* (Duh.) Jafri, were studied on experimental rats.

2.5.1 Acute Toxicity (Lethality) and LD₅₀

A pilot 24 hours preliminary experiment with some modifications has been carried out to study the acute toxicity and to evaluate the lethal dose of the tested methanol extract fraction of *Capparis spinosa* leaves (El-Hadiyah *et al.*, 2011). Twenty four Albino rats weighting 80g – 140gm were divided into four groups, six rats each and the groups were designed as, Group one (G1), Group two (G2), Group three (G3) and Group four (G4). A dose of 1ml /kg of normal saline 0.9% was injected intraperitoneal to each rat of the group (G1) and this group was considered as control group, and doses of 500mg/kg, 1000mg/kg, and 2000g/kg of methanol extract of *Capparis spinosa* leaves were injected intraperitoneal to the G2, G3, and G4 respectively. The normal saline dose and the tested extract doses were injected as 24 hour single dose. Rats were observed for any death happened immediately after dosing and for 14 days.

2.5.2 Subacute toxicity of methanol extract of leaves of *Capparis spinosa*

El-Hadiyah *et al.* (2011) experiment was used with some modifications to study the sub-acute toxicity of the tested extract fractions. Two groups; six Albino rats weighing 80-140gm each was designed as group one (G1); control group and group two (G2); extract tested group. A twenty four hours single dose of 1000mg/kg of methanol extract of leaves of *Capparis spinosa* was injected IP to G2 rats for one week. Group one rats were injected with daily dose of 1ml /kg normal saline 0.9% for one week. In the eighth day all treated and control groups rats were anaesthetized via inhalation with Di-ethyl ether and a 3ml orbital blood from each rat was squeezed; 2ml collected in a clot activator blood container and 1ml was collected in an ethylene diamine tetraacetic acid (EDTA) container and immediately the containers transferred to the biochemistry and hematology laboratories at the Modern Medical Center, Khartoum, Sudan to check each of the liver function; total protein, serum albumin, serum globulin, total bilirubin, direct bilirubin, indirect bilirubin, Alkaline phosphate (ALP), Alkaline transaminase (ALT), aspartate aminotransferase (AST) and Gamma-glutamyl transpeptidase (GGT). The anaesthetized rats were sacrificed and the vital liver organ isolated and size minimized with use of blades and kept in 10% formalin in separate well labelled bottles until run for histopathology screening. During the study the groups were checked for any behavioral, neurological and autonomic response. Changes in behavioral response of rats were observed and recorded daily. The observation times was four hours daily divided into four periods; 1st period which start from zero time (immediately after extract injection) to one hour), 2nd period started from the end of 1st hour and lasts for an hour (1 – 2hr.), 3rd period started from the end of 2nd hour and lasts for an hour (2 – 3hr.) and 4th period which started from the end of the 3rd hour and lasts for an hour (3 – 4hr.).

Histological method

In the eighth day the livers were isolated and fixed in 10% neutral buffered formalin, sectioned at 5 μ and stained in Hematoxylin and Eosin (H&E) for histopathological studies. Histopathology screening was done at department of histopathology, Veterinary Research Center, Soba, Khartoum, Sudan.

Statistical Analysis

Data were expressed as mean \pm SD. Statistical examination was performed utilizing SPSS version 20, One-way analysis of variance (ANOVA) followed by the LSD Post Hoc test. The P values more than 0.05, less than ≤ 0.05 and \leq less than 0.01 were considered as not significant, significant and highly significant values respectively.

3. RESULTS AND DISCUSSION

3.1 Antioxidant Assay

The DPPH scavenging assay used in this study revealed that the methanol extract of *Capparis spinosa* leaves possess good antioxidant activity 80% with IC_{50} 0.2mg/ml \pm 0.07 compared with the standard Propyl Gallate (Table 1). Heibatullah *et al.*, 2018 also ascertained the antioxidant effects of *Capparis spinosa* but with lower IC_{50} 0.03mg/ml \pm 0.00. As this plant is well known rich in flavonoids such as such as rutin, quercetin and its derivatives, we suggested that its antioxidant activity referred to these flavonoids contents. Nizar *et al.*, 2017 reported that the plant has interesting antioxidant capacity with an effective dose similar to the positive control used; Vitamin C.

Table 1: Antioxidant of methanolic extract of leaves of Libyan *Capparis spinosa*.

Sample / Standard used	%RSA \pm standard error of mean (DPPH)	IC_{50} \pm SD mg/ml (DPPH)
<i>Capparis spinosa</i> methanol leaves extract	80 \pm 0.02	0.205 \pm 0.07
Standard Propyl Gallate	94 \pm 0.01	0.077 \pm 0.01

IC_{50} = Infective dose which scavenge 50% of DPPH RSA = Radical scavenging assay

DPPH = 2,2-Di (4-tert-octylphenyl)-1-picryl-hydrazyl

3.2 Acute toxicity (Lethality) Assay

Acute toxicity study test is required to know the range that could be toxic and the range of safety. Also could be used in the calculation of therapeutic index (LD50/ED50).

The acute assay in this study showed that during the 24 hours and till the end of 14 days, no death has been happened at the three 500mg/kg, 1000mg/kg, and 2000 mg/kg doses injected to the tested rats, the output which reveals that the lethal dose of *Capparis spinosa* leaves methanol extract is more than 2g/kg if there is (Table 2).

Table 2: Acute toxicity of methanolic extract of leaves of Libyan *Capparis spinosa* subsp *orientalis* (Duh.) Jafri in albino rats.

Treatment used	Number of treated rats	Treatment Concentration	Results after 14 days
<i>C.spinosa</i> MLE	6	500 mg/kg	+++++
<i>C.spinosa</i> MLE	6	1000 mg/kg	+++++
<i>C.spinosa</i> MLE	6	2000 mg/kg	+++++
Normal saline 0.9%	6	1ml / kg	+++++

C.spinosa MLE = *Capparis spinosa* methanol leaves extract (+) = Alive rats (-) = Dead rats.

3.4 Subacute toxicity Assay

3.4.1 Behavioral responses during sub-acute toxicity assay

Many behavioral has been monitored for one hour intervals periods for four hours starting from zero time (time immediately after injecting the dose) for both control and treated rats; Excitation, convulsion, grasp, aggressiveness, spasm, writhing, fatigability, itching, diarrhea, lacrimation, sedation. In first watching hour no behavioral changes have been seen compared with the control rats while during the middle of second hour moderate intermittent spasms in 4 out of six rats and light writhing in two out of six tested rats has been noticed. Both spasm and writhing disappeared by the half of the third hour (Table 3).

3.4.2 Liver function biochemistry

We found that most of the literature reviews concerned with the effect of Capparis plant on liver function were programmed to check for the plant extract effect on a drug-induced liver injury rather than check the effect of the extract directly on not intoxicated rats. Nurcan *et al.* (2016) study the protective effect of *Capparis ovata* in acute hepato-toxicity induced by paracetamol in rats concluded that *Capparis ovata* has a protective effect on the liver; both histopathologically and biochemically, against paracetamol-induced liver injury. Heibatullah *et al.*, 2018 adapted to induce post t-butyl hydroperoxide (t-BH) intoxication to rats pre-treated with hydro-alcoholic extract of *Capparis spinosa* L.fractions and the results ascertained the hepato-protective and antioxidant effects of *Capparis spinosa* in a dose-dependent manner.

In our study we evaluate the hepatic toxicity rather than check the hepato-protective effect of methanolic extract of *Capparis spinosa* leaves and only two similar studies were found in the literature review. Even though the results were varied but both studies have tested the same plant species of ours; *Capparis spinose* from the same solvent as well. In the present study the effect of *Cpparis spinosa* methanol leaves extract was tested on ten parameters related to liver function. As shown in Table 4, there are no significant differences in ALP, ALT, and AST levels and also in other tested parameters after seven days treatment with subacute extract dose 1000mg/kg compared to the control group except for two. Highly significance difference ($P < 0.01$) was seen in total protein and serum albumin compared to the control where the extract showed decreasing effect of both parameters (Table 4).

As the three enzymes ALP, ALT and AST are indicators of the safety liver and indicating its normal function and they are well known as biomarkers for early acute hepatic damage.

(Heibatullah *et al.*, 2018, Sahar *et al.*, 2017). This study suggested that methanol leaves extract of Libyan *Capparis spinosa* has no effect on liver function. This result agreed to extent with Heidari *et al.*, 2010 who reported that there were no significance difference in ALT and AST levels between the control and treated rats, but not agreed with us in that their study indicated that the ALP level has been increased with the *Capparis spinosa* methanol extract but ours proved that no change happened in ALP.. Meanwhile our result matches to extent with Heidari *et al.* (2010), but does not match with the output of a study run by Sahar *et al.* (2017) who conclude that *Capparis spinosa* from methanol extract can cause hepatotoxicity as dose-dependent manner.

We suggest that this matching and un matching in results might be referred to one or more of many factors; the different three regions where the plant collected from, different season they collected in, different solvents used and subsequently to the different components of the secondary metabolites.

Table 3: Pharmacological behavioral screening of Methanol extract of *Capparis spinosa* leaves.

Behavioral parameters ↓	1 ST Period Time 0 – 1 hr.	2 nd period Time 1 – 2 hr.	3 rd period Time 2 – 3 hr.	4th period Time 3 – 4 hr.
	NFR out of six rats	NFR out of six rats	NFR out of six rats	NFR out of six rats
Excitation	-	-	-	-
Convulsion	-	-	-	-
Grasp	-	-	-	-
Aggressiveness	-	-	-	-
Spasm	-	+ NFR=(4)	+ NFR= (4)	-
Writhing	-	-	-	-
Fatigability	-	-	-	-
Itching	-	-	-	-
Diarrhea	-	-	-	-
Lacrimation	-	-	-	-
Red tears	-	-	-	-
Sedation light	-	-	-	-
Sedation heavy	-	-	-	-
Convulsion	-	-	-	-
Push back legs	-	-	-	-

NFR = Number of effected rats out of total six rats (-) = No evidence (+) = Moderate evidence.

Table 4: Effect of leaves methanol extract of *Capparis spinosa* on liver function profile.

Liver function tested parameter	Control Rats Mean \pm SD	Treated Rats Mean \pm SD	Sig.
Total protein	7 \pm 0.5	6 \pm 0.3	**
Serum albumin	3.8 \pm 0.4	3 \pm 0.3	**
Serum globulin	3 \pm 0.3	3 \pm 0.3	NS.
Total bilirubin	0.09 \pm 0.02	0.1 \pm 0.00	NS.
Direct bilirubin	0.04 \pm 0.02	0.04 \pm 0.02	NS.
Indirect bilirubin	0.05 \pm 0.03	0.05 \pm 0.01	NS.
ALP	180.8 \pm 69	244 \pm 180	NS.
ALT	60 \pm 15.5	56 \pm 18.6	NS.
AST	113.7 \pm 18	126 \pm 11.6	NS.
GGT	1.7 \pm 1.8	1.5 \pm 1.4	NS.

SD = Standard deviation ALT= Alanine transaminase ALP = Alkaline phosphate AST = Aspartate aminotransferase GGT = Gamma-glutamyl transpeptidase

Sig. = Significance ** = Highly significant difference ($P \leq 0.01$)

NS. = No significant differences ($P > 0.05$) .

3.4.3 Histopathology of Liver tissue of both control and treated rats

Although the plant extract showed no effect on the liver enzymes, but the histopathological studies of livers showed an evidence of Hepatocellular necrosis, cytoplasmic vacuoles, congestion and hemorrhage appeared in liver tissue of the rat with subacute dose of 1000mg/kg methanol leaves extract of *Capparis spinosa* compared to the control normal rats (Figure1). Also Sahar *et al.* (2017) observed an infiltration of inflammatory liver cells with high dose 800mg/kg after 14 days while alt lower doses 200mg and 400mg/kg the tissues were normal. However many previous literatures reviews documented that the plant has a protective effect for liver tissues previously drug injury induced (Heibatullah *et al.*, 2018, Norcan *et al.*, 2016), the phenomena which not in line with this study result and this might be referred to that the experiments were run on crud extracts and there is a probability of presence of different secondary metabolites types and concentration variance. Any way further more detailed study should be carried to go in depth in aim to get more explanation.

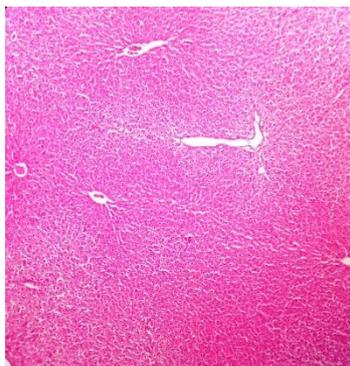


Figure 1: Liver tissue of rat treated with *Capparis spinosa* extract.

CONCLUSION

Libyan *Capparis spinosa* has good antioxidant scavenging activity against DPPH compared to the positive control used with $1C_{50}$ 0.2mg/ml and also it can be concluded that the lethal dose of the methanolic extract of leaves of Libyan *Capparis spinosa* subsp *orientalis* (Duh.) Jafri is more than 2000mg/kg if there is. No significant differences showed in liver safety biomarkers; alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

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