Preliminary Investigation into the Anticonvulsant, Sedative and Muscle Relaxant Effects of the Methanolic Extract of *Capparis spinosa* L. Leaves in Mice

Aisha Mohamed Dugani[1] Sarah Saleh Khasheba[1] Abdurazag Abdulsalam Auzzi[2]

[1] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Tripoli, Libya
[2] Department of Pharmacognosy and Natural Products, Faculty of Pharmacy, University of Tripoli, Libya

Address for correspondence Aisha Mohamed Dugani, PhD, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya (e-mail: a.dugani@uot.edu.ly).

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Abstract

Background *Capparis spinosa* L is a Mediterranean plant. In Libya, the plant grows in rocky areas and at high altitudes. It is commonly used by the inhabitants of the Mediterranean region in their kitchen and treatment of many diseases.

Aim This study was undertaken to investigate the central nervous system depressant, anticonvulsant, and the muscle relaxant activities of orally administered methanolic extract from the leaves of *C. spinosa* L. (MECS) in mice.

Methods The oral administration of three doses of the MECS in mice (500, 1000, and 2000 mg/kg) were evaluated in the picrotoxin (PC)-induced convulsion model, ketamine-induced sleep, and rota rod test. Diazepam was used as a reference drug for comparison. Results were analyzed using SPSS program version 16. Data are presented as mean ± SEM, and compared using one-way ANOVA followed by Duncan's test. The significance level was set at $p < 0.05$

Results Oral administration of MECS (1000 and 2000 mg/kg) significantly prolonged the onset of seizures ($p < 0.01$) and produced dose-dependent protection against PC-induced seizures compared with the control group (12.5% and 50% protection, respectively). MECS significantly ($p < 0.05$) and dose dependently reduced ketamine sleep latency (from 3.16 ± 0.16 to a minimum of 1.5 ± 0.22 minutes) and prolonged ketamine-induced sleeping time (from 11.33 ± 1.99 to a maximum of 33.33 ± 0.95 minutes). In the accelerated rotarod test, MECS significantly ($p < 0.01$) decreased the riding time on the rotarod (from 128.83 ± 14.6 to a minimum of 1.83 ± 0.47 seconds) as compared with the normal saline control group.

Conclusion The results showed that the MECS possesses anticonvulsant, sedative, and muscle relaxant properties in mice.

Keywords
- *Capparis spinose* L.
- sedative anticonvulsant
- muscle relaxant
- mice

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ملخص المقال باللغة العربية

تحقيق أولي في التأثيرات المضادة للاختلاج والتركين وارتخاء العضلات للمستخلص الميثانولي لأوراق نبات القبّار في القفران

المؤلفون: عائشة الدوجاني[1]، سارة خشيبة، عبدالرزاق العوزي

1 قسم علم الأدوية والصيدلة السريرية، قسم العقاقير والنواتج الطبيعية، كلية الصيدلة، طرابلس، ليبيا.

المؤلف المسؤول: عائشة الدوجاني، بريد إلكتروني: a.dugani@uot.edu.ly

الخلفية: القبّار أو الكبّر أو الشفّلح أو الأصنف (باللاتينية: **Capparis spinosa**) هي شجيرة تنتمي للفصيلة القبارية تعيش في حوض البحر الأبيض المتوسط. ينمو النبات في ليبيا في المناطق الصخرية وعلى ارتفاعات عالية. يشيع استخدامه من قبل سكان البحر الأبيض المتوسط في مطبخهم وفي علاج العديد من الأمراض.

الهدف: أجريت هذه الدراسة للتحقق من التأثير المثبط للجهاز العصبي المركزي، والمضاد للاختلاج، وارتخاء العضلات للمستخلص الميثانولي الفموي من أوراق القبّار في القفران.

الطريقة: تم تقييم الإعطاء الفموي لثلاث جرعات من مستخلص أوراق القبّار لفئران التجارب البيضاء (500، 1000، 2000 ملغم / كغم) وذلك ضد الاختلاجات التي يسببها البيكروتوكسين، والنوم الناجم عن الكيتامين، وكذلك اختبار القضيب الدوار لنشاط العضلات الهيكلية. تم استخدام الديازيبام كدواء مرجعي للمقارنة. تم تحليل النتائج باستخدام الإصدار 16 من برنامج SPSS.تم تقديم البيانات كمتوسط ± الانحراف المعياري للمتوسط. تم مقارنة النتائج باستخدام تحليل التباين أنوفا **ANOVA** متبوعة باختبار دنكن. حددت مستوى الدلالة الإحصائية عند $p<0.05$.

النتائج: أدت جرعات المستخلص الميثانولي الفموي من أوراق القبّار (1000 و2000 ملغم / كغم) إلى إطالة الفترة اللازمة لظهور الاختلاجات التي يسببها البيكروتوكسين ($P<0.01$)، كما أنها سببت في حماية تعتمد على الجرعة ضد هذه الاختلاجات مقارنة بمجموعة التحكم (حماية 12.5٪ و50٪ على التوالي). كما سبب المستخلص في تقصير المدة اللازمة لحدوث النوم بسبب الكيتامين بدلالة إحصائية ($p<0.05$) معتمدا على الجرعة (من 3.16 ± 0.16 إلى الحد الأدنى 1.5 ± 0.22 دقيقة). كما سبب المستخلص إطالة وقت النوم الناجم عن الكيتامين (من 11.33 ± 1.99 إلى 33.33 ± 0.95 دقيقة كحد أقصى). أما في اختبار القضيب الدوار فإن المستخلص أنقص وقت الركوب على القضيب الدوار (من 128.83 ± 14.6 إلى 1.83 ± 0.47 ثانية كحد أدنى) مقارنة بمجموعة التحكم بدلالة إحصائية عالية ($P<0.01$).

الخلاصة: أظهرت النتائج أن المستخلص الميثانولي من أوراق القبّار يمتلك خصائص مضادة للاختلاج، ومركنة، ومرخية للعضلات في القفران.

الكلمات المفتاحية: **Capparis spinose L**، أوراق القبّار، مركنة، مضاد للاختلاج، مرخي للعضلات، القفران

Introduction

Epilepsy is one of the most common neurological diseases affecting about 50 million people worldwide.[1] Despite the availability of treatments to control seizures including drugs, diet, neuromodulatory devices, and surgery, complete control of symptoms and seizures in all patients with epilepsy is sometimes not possible, forcing them in some cases to use natural alternatives such as herbs. Moreover, the World Health Organization (WHO) has estimated that perhaps 80% of the world's population relies chiefly on traditional medicines for primary healthcare needs, particularly in low- and middle-income countries.[2,3]

Among the natural remedies that were proven effective in the treatment of epilepsy are *Brassica nigra*, *Myristica fragrans*, *Crocus sativus*, *Glycyrrhiza glabra*,[4–7] and many more.

Capparis spinosa L. is an important source for industries, known as the Mediterranean plant. In Libya, the plant grows in rocky areas and at high altitudes.[8] It is commonly used by the inhabitants of the Mediterranean region in their kitchen and treatment of many diseases including renal colic, infections accompanied by frequent vomiting, and in the treatment of anal infections associated with hemorrhoids.[8] In this article, we are examining the anticonvulsant, sedative, and muscle relaxant effects of the methanolic extract of *capparis spinose L* (CSL) leaves collected locally from the city of Gharian, Libya.

Materials and Methods

Plant Collection and Identification

Fresh leaves of CSL collected from the Gharian area, Western Mountain, Libya in October 2018 and was authenticated by Prof. A. Auzzi, Department of Pharmacognosy and Natural Products, Faculty of Pharmacy, University of Tripoli, Libya.

Plant Extraction

The leaves of CSL were thoroughly washed with running tap water and shade dried at room temperature for 2 weeks and

then coarsely powdered. The coarse powder (300 g) was extracted by Soxhlet apparatus with methanol (1250 mL) for 24 hours at room temperature. The extract was then filtered through Whatman No.1 filter paper and was concentrated using a rotary evaporator with the water bath set at 70 °C. The yield was 27g (9%). This was stored in the refrigerator at 4°C and was used throughout the experiment.

Experimental Animals

Male Swiss albino mice, weighing about 18 to 35 g were used in the experiments. The animals were acclimatized in the laboratory for 2 weeks before experimentation and were fed with a standard diet and allowed water ad libitum.

The animals were divided into three groups. Plant extract-treated group, reference anticonvulsant drug-treated 'test' group, and normal saline-treated 'control' group.

Drugs and Chemicals

Picrotoxin (PC; Sigma-Aldrich, Germany) was dissolved in physiological saline. Diazepam (DZP; Wockhardt UK Ltd.). Sodium chloride 0.9% (normal saline; Otuska Pharmaceutical Co., SAE, Cairo, Egypt).

Evaluation of the Anticonvulsant Activity

Picrotoxin was used to test the anticonvulsant activity according to the method of Velluci and webster 1984,[9] as modified by Amabeoku, et al.[10] Picrotoxin (PCT, 10 mg/kg) was given by intraperitoneal injection and the animals were observed for 30 minutes for signs of neurological deficits, especially hindlimb tonic seizures or convulsions.

Animals were divided randomly into five groups of eight animals each. Group I served as the vehicle control group treated with normal saline (0.2 mL/20 g, i.p.); groups II, III, and IV served as test groups and treated with the extract (500, 1000, and 2000 mg/kg, i.p.), respectively, and group V served as the reference group treated with diazepam (5 mg/kg, i.p). All treatments were given have an hour before picrotoxin, then each animal was observed for half an hour after picrotoxin for any signs of convulsions. Onset of convulsions was recoded for each animal, together with percentage protection for each group.

Evaluation of Sedative Activity

The effect of the MECS on ketamine-induced sleeping time was measured as described by Erden et al,[11] where mice were divided into five groups ($n = 8$). The first group served as a control and was given normal saline (0.2 mL/20 g, i.p. group 1), the other groups (2–4) were given different doses of MECS (500, 1000, and 2000 mg/kg, i.p.). Thirty minutes later, each rat was given ketamine (100 mg/kg, i.p.). The sleep latency was measured as time in minutes after treatment with ketamine and the loss of righting reflex. While the time in minutes between the loss and regain of the righting reflex was taken as sleeping time, group 5 served as the reference group and treated with diazepam (2 mg/kg, i.p.).[11]

Evaluation of Skeletal Muscle Relaxant Activity

Accelerating rotarod (TSE RotaRod System) was used to assess motor coordination and balance. Mice were placed on a horizontal metal coated rod with rubber (3 cm diameter) rotating at an initial speed of 10 rpm/min. The terminal speed of the rod was 20 rpm in accelerated studies and the rotational velocity of the rod was linearly increased from 10 to 20 rpm within 20 seconds. The time each animal was able to maintain its balance walking on top of the rod was measured. The riding ability of the animals was checked before the beginning of all experiments. Thus, the mice were initially put on a rotating rod, and mice that immediately dropped off (within 30 s) were removed from the experiment.

Animals were divided into five groups each consisting of six mice. Diazepam (1 mg/kg), MECS (500, 1000, and 2000 mg/kg), and normal saline (10 mL/kg) were injected for 30 and 60 minutes, respectively, before the rotarod test.[12]

Statistical Analysis

Data were analyzed using SPSS version 17.0 (SPSS Inc., USA). Values are expressed as means ± standard error of the mean (SEM). The significance of the differences between the means of different treatments in comparison with control was done by one-way ANOVA followed by Duncan's test. The *p*-Values less than 0.05 were considered significant.

Results

Anticonvulsant Activity

MECS at the dose of 500 mg/kg significantly ($p < 0.05$) delayed the onset of convulsions induced by picrotoxin. Moreover, the higher doses of the extract (1000 and 2000 mg/kg) showed a more prominent, highly significant ($p < 0.01$) anticonvulsive activity. The reference anticonvulsant drug (diazepam 5 mg/kg, i.p.) profoundly delayed the onset of seizures significantly ($p < 0.01$) (►**Fig. 1**). Animals treated with MECS (1000 mg/kg and 2000 mg/kg) showed 12.5% and 50% protection, respectively, whereas diazepam provided 62.5% protection in PC-induced convulsions (►**Fig. 1**).

CNS Depressant Activity

In control animals, the righting reflex was lost after 3.16 minutes from ketamine injection. MECS at doses of 500, 1000, and 2000 mg/kg significantly ($p < 0.05$) reduced the latency to sleep when compared to control as did the reference drug diazepam (2 mg/kg) (►**Table 1**).

The mean total sleeping time in control animals was 11.33 minutes. MECS at doses of 500, 1000, and 2000 mg/kg significantly increased the ketamine-induced sleep time when compared with control as did the reference drug diazepam (2 mg/kg) (►**Table 1**).

Skeletal Muscle Relaxant Activity

In the rotarod test, MECS in the first trial at the doses of 500, 1000, and 2000 mg/kg showed a significant ($p < 0.05$) decline in motor function relative to the control group given normal

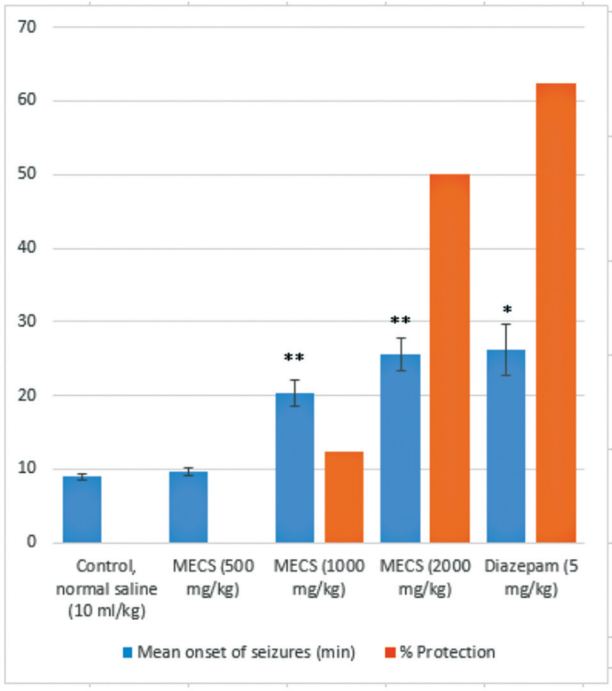

Fig. 1 Effect of C. spinosa methanolic extract on the mean onset of picrotoxin-induced seizures and % protection. One-way ANOVA followed by Duncan's test. Values are mean ± S.E.M. $n = 8$ in each group. $^{*}p < 0.05$; $^{**}p < 0.01$ when compared with the control group. Percentage protection was calculated by dividing the number of non-convulsing mice/total number of animals in each group multiplied by 100.

saline (10 mL/kg) (►**Table 2**). In the second trial MECS in doses of 500, 1000 ($p < 0.01$), and 2000 ($p < 0.05$) mg/kg significantly decreased the riding time on the rotarod compared to the control (►**Table 2**).

Discussion

A seizure reflects an imbalance between excitatory and inhibitory activities in the brain, with an increment of excitation over inhibition. Gamma amino butyric acid (GABA) is one of the major inhibitory neurotransmitters that is implicated in epilepsy. The enhancement and inhibition of the neurotransmission of GABA will attenuate and enhance convulsion, respectively.[13]

C. spinosa has been reported to be a safe plant and there are no reports available in the scientific literature on its toxic manifestations after acute, sub-acute, or chronic treatment except for allergic contact dermatitis.[14] There are a number of synthetic anticonvulsant drugs available in the market for use in the management, control and/or treatment of individuals with epilepsy. However, most of these synthetic drugs are not only inaccessible and unaffordable but also possess many toxic effects. It is, therefore, necessary to develop cheap, effective, and safe anticonvulsant agents from plants and other natural resources.

The present study revealed that the methanolic extract of leaves of *C. spinosa* L. delayed the onset of seizures induced by picrotoxin. The most effective dose was 2000 mg/kg

Table 1 Effect of *C. spinosa* methanolic extract on latency and duration of sleep in ketamine-induced sleeping time

Treatment	Sleep latency (min)	Sleep duration (min)
Control, normal saline (10 mL/kg)	3.16 ± 0.16	11.33 ± 1.99
MECS (500 mg/kg)	2.0 ± 0.25*	22.33 ± 0.76*
MECS (1000 mg/kg)	1.83 ± 0.47*	28.16 ± 2*
MECS (2000 mg/kg)	1.50 ± 0.22*	33.33 ± 0.95*
Diazepam (5 mg/kg)	1.33 ± 0.21*	37.67 ± 2.2*

One way ANOVA followed by Duncan's test. Values are mean ± S.E.M. $n = 8$ in each group.
$^{*}p < 0.05$ when compared with the control group.

Table 2 Effect of *C. spinosa* methanolic extract on motor coordination of mice in the Rotarod Test

Treatment	First trial (s)	Second trial (s)
Control, normal saline (10 mL/kg)	128.83 ± 14.68	128.83 ± 14.68
MECS (500 mg/kg)	15.00 ± 3.49*	34.33 ± 7.90***
MECS (1000 mg/kg)	5.50 ± 0.76*	63.33 ± 10.29***
MECS (2000 mg/kg)	1.83 ± 0.47*	79.16 ± 11.91*
Diazepam (5 mg/kg)	27.67 ± 3.54*	75.67 ± 5.67*

One-way ANOVA followed by Duncan's test. Values are mean ± S.E.M. $n = 6$ in each group.
$^{*}p < 0.05$
$^{***}p < 0.01$, when compared with the control group.

($p < 0.01$). Picrotoxin, a well-known potent selective GABA-A receptor antagonist,[6], can prevent the entry of chloride causing seizures by blocking the chloride-ion channels linked to GABA-A receptors.[15] Thus, it is likely that *C. spinosa* probably produced its anticonvulsant effect directly by acting as an orthosteric GABA-A agonist,[16,17] or indirectly by enhancing GABAergic neurotransmission through allosteric agonism.[18–20] The phytochemical studies on *C. spinosa* extract showed that the extract had saponins, tannins, and flavonoid constituents.[19] Natural and synthetic flavonoids have shown anticonvulsant and anxiolytic activities in rats. These compounds exert their effects through the central benzodiazepine receptors.[21,22] Actually, many flavonoids were found to be ligands for the GABA-A receptor in the central nervous system, which led to the hypothesis that they act as benzodiazepine such as molecules, probably in the place of specific action on the receptor GABA-A. Their behavioral effects in animal models support this suggestion.[23] The existence of flavonoids in *C. spinosa* can explain many of its beneficiary effects,[24] which might have resulted from an affinity for GABA-A receptors.[25,26]

The ketamine-induced sleeping time is an experiment normally carried out to determine the effect of a test agent on CNS depression. Two parameters are measured, latency of sleep, and total sleeping time.[27] Like the standard drug

diazepam, MECS reduced sleep latency and increased total sleeping time induced by ketamine when compared with the control. Ketamine produces sleep by acting as ionotropic glutamatergic n-methyl-D-aspartate receptor (NMDAR) antagonist. Thus, the potentiation of the sleeping effect suggests that MECS may be acting through the GABA-A receptors as explained before.[16–20] The effect on ketamine-induced sleeping time is in agreement with work on some plants such as *Cissus cornifolia*, *Nepeta persia* which potentiated ketamine-induced sleeping time.[28,29]

The test for motor coordination (rotarod performance) was adopted to evaluate the effect of the extract on physical performance, endurance, and possible neuromuscular inhibition. The study revealed that the extract produced an effect on motor coordination. The decrease in the motor activity gives an indication of the level of excitability of the CNS[30] and this decrease may be related, in part, to sedation resulting from depression of the CNS.[31] Other phytochemical constituents identified in the methanolic extract from *C. spinosa* including saponins, anthraquinones, and tannins have been reported in the literature to possess anticonvulsant, sedative, and muscle-relaxant activities.[32–34] Therefore, these ingredients may act simultaneously with flavonoids to provide such effects.

Conclusion

This preliminary investigation has shown that the methanolic extract of *C. spinosa* showed significant anticonvulsant, sedative, and muscle-relaxant activities in mice. However, further studies are needed to identify the phytochemical component responsible for these actions and elucidate the mechanisms responsible for them.

Conflict of Interest
None declared.

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