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Sedative-Hypnotic Effects of Different Extracts and Fractions of *Capparis spinosa* L. in Mice

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Abstract:

Introduction: *Capparis spinosa* L. (Caper) is an aromatic plant growing in dry regions around the Mediterranean area. *C. spinosa* is shown to have several compounds such as tannins, sterols, alkaloids, polyphenols and flavonoids. Previous studies showed that flavonoids have sedative and hypnotic effects. The aim of this study was evaluating the sedative-hypnotic effects of various extracts and fractions of *C. spinosa* in different doses.

Methods and Results: Maceration method was used for extraction of the aerial part of the plant. All experiments conducted on male NMRI mice (18-25g weight). For evaluation the hypnotic and sedative effects of plant, open field and pentobarbital induced sleep test were used. In this study, animals were treated with different doses of aqueous extract, methanolic extract, methanolic fraction and dichloromethane fraction (i.p.). In pentobarbital induced sleep test, the duration of lack of righting reflex was reported. In open field test, the locomotor activities of mice were calculated by measuring total distance moved in the open field arena. According to the results, the dichloromethane fraction decreased the total distance moved in the open field test (ED_{50} = 66.6 mg/kg) and also increased the sleep duration in pentobarbital induced sleep test (ED_{50} =18.7 mg/kg) compared with other extract and fractions groups.

Conclusion: In conclusion, the dichloromethane fraction of *C. spinosa* has hypnotic and sedative effects compared to the other extract and fraction groups. Further studies are necessary to find the active components responsible for the several effects of the dichloromethane fraction and the exact mechanism of action of these effects.

Keywords: *Capparis spinosa* L.; Sedative; Hypnotic; Mice; Open field test; Pentobarbital-induced sleep test

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1. Introduction

Traditional medicine has a long history and was developed in various cultures before the modern medicine. nowadays, in some parts of the world, the majority of the population rely on traditional medicine for treating diseases [1,2]. Generally, the use of herbs is a major part of traditional medicines [3]. According to a survey by the National Center for Complementary and Alternative Medicine (NCCAM), herbal medicine along with vitamins and minerals were the most commonly used treatments in societies [4]. Herbal medicines include herbal materials and herbal products, that contain active component parts of plants. Due to the probable higher efficacy and lower adverse effects and bioactive components of herbal medicine, it could be used as an alternative therapy for the treatment of several diseases. Caper (*Capparis spinosa* L.) is one of the reasonable herbs that is been used for many years in traditional medicine of many societies, and commonly distributed in

all of the world. Capparis is the largest genus of the family *Capparidaceae* that originated in the tropics and Mediterranean zone. They are used as a resource for medicine, food, soil fertility, fuel and livestock feed [5–7]. The flower buds (capers) are used for seasoning and flavoring meat, and the fruits (caper berries) are usually consumed as pickled. Two species, *C. cartilaginea* and *C. spinosa* and three variety, *var. spinosa*, *var. parviflora* and *var. mucronifolia* are found in Iran [6]. *C. spinosa* or Flinders rose, is an aromatic and perennial plant with an aesthetic blossom and fleshly leaves. It is distributed in all regions of Iran, especially in the south of Iran [8,9]. It is used as a diuretic, in the treatment of malaria, joint diseases, rheumatism, digestive problems, headache, and toothache [10–13].

Previous studies showed that *C. spinosa* has various biological effects like anti-oxidative and anti-bacterial effects, but there are no evidence about neurobehavioral outcomes such as hypnotic and sedative effects of *C. spinosa* [14]. Since central nervous system disorders such as insomnia may lead to other health problems and diseases that reduce the quality of life in humans, the aim of our study was assessment of the sedative and hypnotic effects of aqueous extract, methanolic extract, methanolic fraction, and dichloromethane fraction of *C. spinosa* using pharmacological experiments such as open field and pentobarbital-induced sleep test respectively.

2. Materials *&* Methods

2.1. Preparation of plant extract and fraction:

In this study we collected *Capparis spinosa L.* from Kohgiluyeh and Boyer-Ahmad Province, Iran. After identifying the samples by a qualified botanist at Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Science, Tehran, Iran (THRC498), we dried and powdered the aerial parts of *Capparis spinosa*.

At first, we separated the powdered dried plant into 3 parts, the First part for preparation of the aqueous extract, the second part for preparation of the methanolic extract, and the third part for preparation of the fractions. We used maceration method for preparing the plant extracts. For preparing the extracts, we macerated the powdered dried aerial parts of the plants in distilled water and methanol solvents, and permitted to shake for 1 day, and filtered through a paper filter, then concentrated by rotary evaporator. For preparing the fractions, we fractioned the extract (third part of powdered dried plant) by methanol and dichloromethane solvents. For removing the solid particles, we filtered the achieved fractions using paper filter and then concentrated by rotary evaporator. Finally, we suspended the plant extracts and the fractions intraperitoneally in 1% tween in normal saline and injected the suspensions (10 ml/kg, i.p.) 30 min before each experiment.

2.2. Animals

In this study, we used male NMRI mice (6-8 weeks old, 18-25 grams) supplied from the Animal House of School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We kept the animals in controlled condition, standard rodent diet, 12-hour light/dark cycles, at temperature 20-24 °C, humidity 45-55% and in groups of eight mice. We performed all pharmacological experiments between 9:00 to 15:00 and prepared the solutions of the extracts and the fractions of *C. spinosa* freshly. We carried out all the experiments in according to instructions of ethical standards of Institutional Animal Care and Use Committee (IACUC) of Shahid Beheshti University of Medical Sciences with approval code IR.SBMU.RETECH.REC.1398.708. In this study, we randomly divided animals in to experimental groups including control, 12.5, 25, 50, 100, 200, 400 mg/kg of the aqueous extract, the methanolic extract, the methanolic fraction and the dichloromethane fraction, flumazenil (antagonist of BZD receptors), naloxone (antagonist of opioid receptors) and diazepam groups.

2.3. Open filed test:

We used the open filed test to evaluate the locomotor activity (indicating sedative effects) of *Capparis spinosa*. A Plexiglas box (40 × 40 × 40 cm) with transparent walls forms the open field chamber was used for this test. We placed each mouse individually in the center of the chamber and recorded the movement of the animals by a digital camera during 10 minutes. We analyzed the recorded videos by an automated tracking system (Ethovision XT, Noldus, The Netherlands) and reported the total distance movement of each mouse. Reduction of locomotor activity may indicate the sedative effects of the extract or the fractions [15–17].

2.4. Pentobarbital-induced sleep test:

We used the pentobarbital-induced sleep test to evaluate the hypnotic effects of *Capparis spinosa* and performed pentobarbital-induced sleep test according to the method described by Tabatabai et al [18]. We injected

pentobarbital (40 mg/kg, ip) 30 minutes following administration of the extracts or the fractions for sleep induction. We measured the duration between loss and recovery of righting reflex as sleep duration [19,20].

2.5. Statistical analysis:

In this study, we carried out the analysis of the data by GraphPad Prism software, and for determination of the difference between groups used one-way analysis of variance followed by Tukey's post hoc tests. We described the results as significant at $P<0.05$ and represented all the data as mean ± standard error of the mean (SEM). To identify the ED_{50} values (The dose of the extracts or the fractions which decreases the total distance movement or increase sleep duration 50% compared to control group is reported as ED_{50} in open field test or pentobarbital induced sleep test, respectively) with 95% confidence interval, we used the non-linear regression analysis of the log dose–response curve.

3. Results

The extraction and the fractions yield of 300 g dried plant material are presented in Table 1. Maximum extraction yield was 25% for aqueous extract. and minimum fraction yield was 3.82% for dichloromethane fraction of *Capparis spinosa*.

Table 1. Yield of the extracts and the fractions of *Capparis spinosa*

	Yield of aqueous extract (%)	Yield of methanolic extract (%)	Yield of methanolic fraction (%)	Yield of dichloromethane fraction (%)
Areal part of *Capparis spinosa L.*	25	22.33	7.75	3.82

3.1. Sedative effects in open field test:

We used the open filed test to evaluate the effect of *C. spinosa* on locomotor activity. Total distance movement was measured as the locomotor activity of mice, which were treated with different doses of the extracts, the fractions, and diazepam (as a positive control) and compared with the control (vehicle) group. As shown in Figure 1 (a), doses of 100 and 200 mg/kg of aqueous extract, reduced the total distance movement ($P<0.001$). In Figure 1 (b), doses of 25, 50, 100, 200 and 400 mg/kg of methanolic extract, reduced the total distance movement ($P<0.01$, $P<0.001$, $P<0.001$, $P<0.0001$ and $P<0.0001$, respectively). In Figure 1 (c), doses of 100, 200 and 400 mg/kg of methanolic fraction, reduced the total distance movement by mice ($P<0.001$, $P<0.001$ and $P<0.0001$, respectively). In Figure 1 (d), doses of 12.5, 25, 50 and 100 mg/kg of dichloromethane fraction, reduced the total distance movement by mice ($P<0.05$, $P<0.01$, $P<0.001$ and $P<0.0001$, respectively).

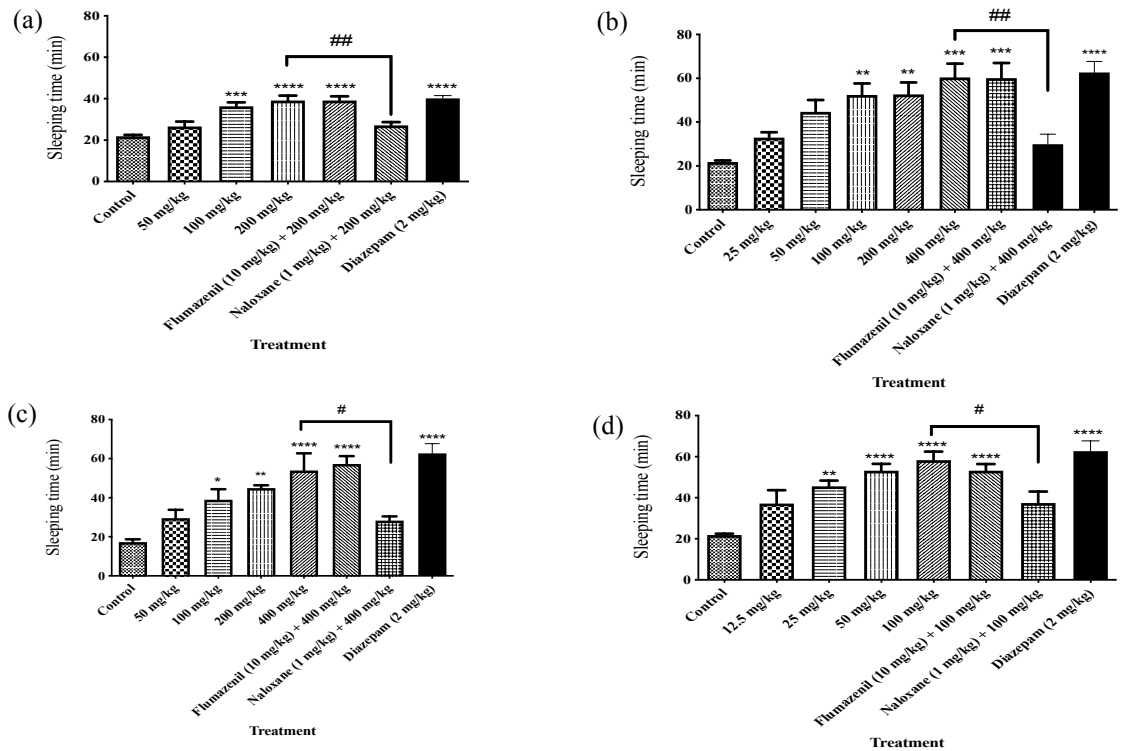

Figure 1. Effects of *Capparis spinosa* on locomotor activity in open field test in NMRI mice (n=8). (a) aqueous extract. (b) methanolic extract. (c) methanolic fraction. (d) dichloromethane fraction. Data are presented as mean ± SEM. * $P < 0.05$ compared to control; ** $P < 0.01$ compared to control; *** $P < 0.001$ compared to control; **** $P < 0.0001$ compared to control; ## $P<0.01$ compared to the indicated group.

According to the results, flumazenil (10 mg/kg) as a standard benzodiazepine antagonist did not prevent the sedative effects of the aqueous and the methanolic extracts, and also the methanolic and the dichloromethane fractions. However, naloxone (1 mg/kg) as an opioid antagonist was able to prevent the sedative effects of the aqueous and the methanolic extracts, as well as the methanolic and the dichloromethane fractions (P<0.01). It means that the sedative effect of *Capparis spinosa* was significantly antagonized by the administration of naloxone. Also, diazepam (2 mg/kg) as a positive control decreased the total distance movement (P<0.0001). We reported the ED_{50} values of sedative effects of the extracts and the fractions in Table 2.

Table 2. The ED_{50} values of the extracts and the fractions of *Capparis spinosa.*

	ED_{50} (95% CI*) (mg/kg) Open field test	ED_{50} (95% CI) (mg/kg) Pentobarbital induced sleep test
Dichloromethane fraction	66.6 (46.8 to 94.7)	18.7 (14.9 to 23.3)
Methanolic fraction	136.5 (116.0 to 160.5)	56.6 (32.5 to 98.4)
Methanolic extract	201.5 (168.1 to 241.5)	131.2 (99.2 to 173.6)
Aqueous extract	322.7 (266.4 to 390.8)	223.5 (176.5 to 283.0)

* Confidence interval

3.2. Hypnotic effects in pentobarbital induced sleep test:

We used the pentobarbital induced sleep test to determine the hypnotic effects of *Capparis spinosa*. Sleeping time was considered as the hypnotic effects of *Capparis spinosa* in mice, which were treated with different doses of the extracts, the fractions, and diazepam as appositive control and compared with the control (vehicle) group. As shown in Figure 2 (a), doses of 100 and 200 mg/kg of aqueous extract, increased the sleeping time (P<0.001 and P<0.0001, respectively). In Figure 2 (b), doses of 100, 200 and 400 mg/kg of methanolic extract, increased the sleeping time (P<0.01, P<0.01 and P<0.001, respectively). In Figure 2 (c), doses of 100, 200 and 400 mg/kg of methanolic fraction, increased the sleeping time (P<0.05, P<0.01 and P<0.0001, respectively). In Figure 2 (d), doses of 25, 50 and 100 mg/kg of dichloromethane fraction, increased the sleeping time (P<0.01, P<0.0001 and P<0.0001, respectively). According to the results, flumazenil (10 mg/kg) as a standard benzodiazepine antagonist did not prevent the hypnotic effects of the aqueous and the methanolic extracts, and also the methanolic and the dichloromethane fractions. However, naloxone (1 mg/kg) as an opioid antagonist was able to prevent the hypnotic effects of the aqueous and methanolic extracts, as well as the methanolic and dichloromethane fractions (P<0.01, P<0.01, P<0.05 and P<0.05, respectively). It means that the hypnotic effects of *Capparis spinosa* were significantly antagonized by the administration of naloxone. Also, diazepam (2 mg/kg) as a positive control increased the sleeping time (P<0.0001). We reported the ED_{50} values of the extracts and the fractions from pentobarbital induced sleep test in Table 2.

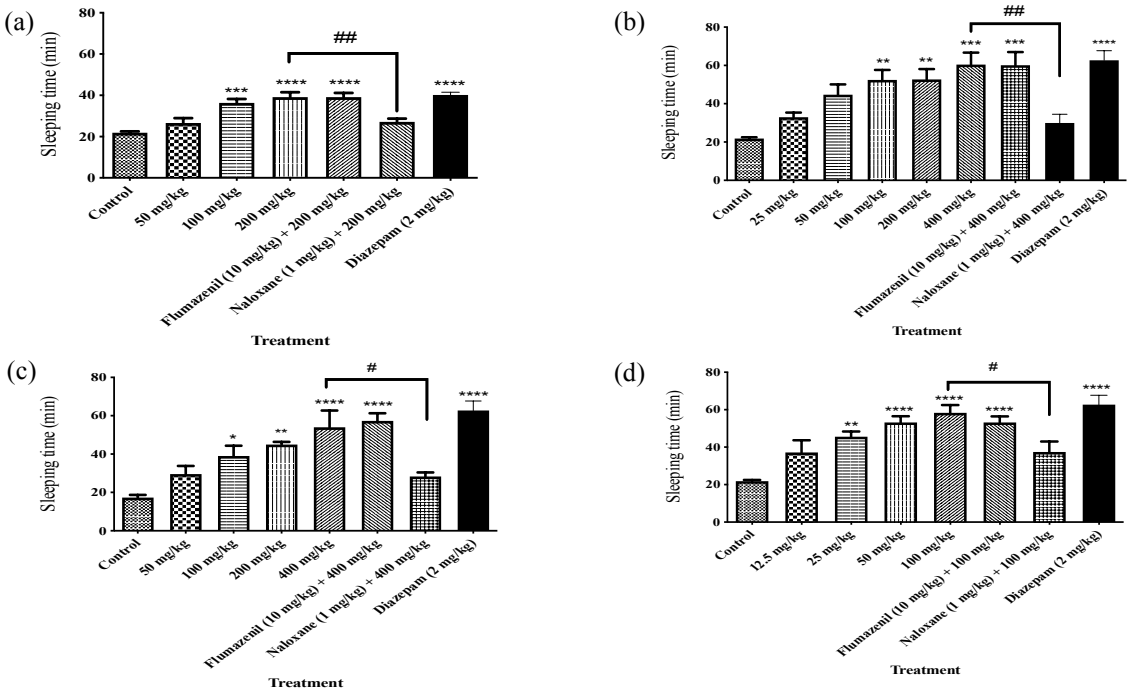

Figure 2. Effects of *Capparis spinosa.* on sleeping time pentobarbital induced sleep test in NMRI mice (n=8). (a) aqueous extract. (b) methanolic extract. (c) methanolic fraction. (d) dichloromethane fraction. Data are presented as mean ± SEM. * P < 0.05 compared to control; ** P < 0.01 compared to control; *** P < 0.001 compared to control; **** P < 0.0001 compared to control; # P<0.05 compared to the indicated group; ## P<0.01 compared to the indicated group.

4. Discussion and Conclusion

In the last century, due to the development of technology and industrial life, disorders of the central nervous system including insomnia have been increased. Unfortunately, most of treatments for insomnia and sleep disorders have adverse effects, toxicity, high cost and drug resistance in patients. There is a possibility that herbal medicines may show less adverse effects compared to the chemical drugs, and their efficacy and toxicity should be tested [21–23]. Herbal medicines contain several active components, that they may have additive effects or interaction with each other. *Capparis spinosa* is commonly used in traditional medicine. The roots, fruits and flowers of *Capparis spinosa* are conventionally used for the treatment of diseases. Whereas in the latest studies, some useful properties of *Capparis spinosa* like antioxidant, antibacterial ,and antifungal properties were reported, but there is no study on the pharmacological activities of *Capparis spinosa* as sedative and hypnotic herbal medicine [24–27].

In this study, we investigated the sedative and hypnotic effects of aqueous extract, methanolic extract, methanolic fraction and dichloromethane fractions of *Capparis spinosa* using the pentobarbital induced sleep test and open field test in male NMRI mice. For making the comparison easier between the extracts and the fractions of *Capparis spinosa*, we calculated ED_{50} values by non-linear regression. All of the extracts and fractions of *Capparis spinosa* showed the hypnotic and sedative effects compare to the control group. Based on the ED_{50} values, the dichloromethane fraction had the highest hypnotic and sedative effects with ED_{50} values 18.7 (14.9 to 23.3) mg/kg and 66.6 (46.8 to 94.7) mg/kg, respectively. Among the other extracts and fractions, the aqueous extract did not have proper efficacy in pentobarbital induced sleep test and open field test with the lowest ED_{50} values 223.5 (176.5 to 283.0) mg/kg and 322.7 (266.4 to 390.8) mg/kg, respectively. Considering that the dichloromethane fraction has more non-polar and less polar compounds than the aqueous extract, and based on the results, the dichloromethane fraction had the highest and aqueous extract had the lowest sedative-hypnotic effects. Therefore, the non-polar compounds may cause the sedative-hypnotic effects. To assess the mechanism of the extracts and the fractions of the *Capparis spinosa*, we administrated flumazenil (an antagonist of benzodiazepine receptors) at the dose of 10 mg/kg and naloxone (an antagonist of opioid receptors) at dose of 1 mg/kg. We noticed that, Flumazenil could not prevent the hypnotic and sedative effects of the extracts and the fractions of the *Capparis spinosa* indicating that the benzodiazepine receptors are not involved in these effects. However, pretreatment with naloxone as an antagonist of opioid receptors prevented the hypnotic and sedative effects of the *Capparis spinosa*. These experiments demonstrated that the extracts and the fractions of *Capparis spinosa* had hypnotic and sedative effects and opioid receptors are involved in these effects. *Capparis spinosa* is source of flavonoid compounds such as rutin and quercetin, and other compounds for example α-tocopherol, isothiocyanate and phenol, that were identified and measured in several studies and researches. The antioxidant and anti-platelet properties of capers are due to the attendance of these compounds [28–30]. Several studies have been performed for determination and measurement of fatty acids and tocopherols in *Capparis spinosa*, such as linoleic acid, oleic acid, cis-oleic and palmitic acid and gamma-tocopherol, that have pharmacological, industrial and nutritional values. Established on previous studies, taste of raw caper is very bitter and several washing and processing of the caper improve the taste. It seems that one of the causes for bitter taste of caper, is owing the attendance of alkaloids. Alkaloids play various roles and usually induce a bitter taste in herbals [31–33]. To recognize the active components and find the mechanism of action of the component, further studies and additional researches are needed.

This is the first effort to evaluate the hypnotic and sedative effects of aqueous extract, methanolic extract, methanolic fraction and dichloromethane fractions of *Capparis spinosa*. In this study, we determined the sedative-hypnotic effects of *Capparis spinosa* in animal models. We showed that the dichloromethane fraction has the highest and the aqueous extract has lowest effect compare to the other extract and fractions. Since the naloxone was able to antagonize the hypnotic and sedative effects of *Capparis spinosa*, we can conclude that the involvement of opioid receptors is the possible mechanism of action. Nevertheless, further studies are necessary to identify the active components and the mechanism of action of the reported effects. Eventually, in this research, we noticed that the traditional medicine could play an essential role help people and improve human life.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethics

Ethics Code: IR.SBMU.RETECH.REC.1398.708

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