

Full Length Research Paper

Medicinal characteristics of *Smyrniurn cordifolium* Boiss. plant extract in rats

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The most common sleep disorder is insomnia and about 35% of all people suffer from this disturbance. A trend in using herbal medications for this disorder is increasing globally. Current study aimed to investigate the hypnotic characteristics of *Smyrniurn cordifolium* Boiss (SCB) plant extract. From an experimental study, 96 healthy male Wistar rats were equally divided into 12 groups. For hypnotic evaluations, a negative control with normal saline (10 mg/kg), a positive control with diazepam (1 mg/kg) and 3 treatment groups with different dosages of plant extract (100, 200 and 300 mg/kg) were selected and injected intraperitoneally. Sleep start time and sleep duration time were then measured in different groups. For relaxant effects of the plant, a negative control with normal saline (10 mg/kg), 3 positive controls with diazepam (0.125, 0.25 and 0.5 mg/kg) and 3 treatment groups of plant extract (200, 300 and 400 mg/kg) were allocated and injected intraperitoneally. Finally, the mean time of sleeping, sleep start time and holding bar (marker of muscle relation) were compared between treatment and control groups appropriately. SCB plant extract (300 mg/kg), compared to diazepam and normal saline (N/S) shortened the sleep start time significantly ($p < 0.001$). All 3 dosages of SCB plant extract (100, 200 and 300 mg/kg), compared to diazepam and normal saline, increased sleep duration significantly ($p < 0.001$) and as the SCB dosage was increased the sleep duration was increased too. The relaxant effects of the plant extract did not indicate a significant difference. SCB plant extract as a natural product showed hypnotic effects even better than diazepam and needs to be investigated in human by further studies.

Key words: *Smyrniurn cordifolium* Boiss, hypnotic, insomnia, relaxant, Iran.

INTRODUCTION

One of the essential needs for human body is sleep phenomenon. Sleep is a dynamic time, necessary

for mental and physical restoration during which some physiological processes such as recovering, remaking of

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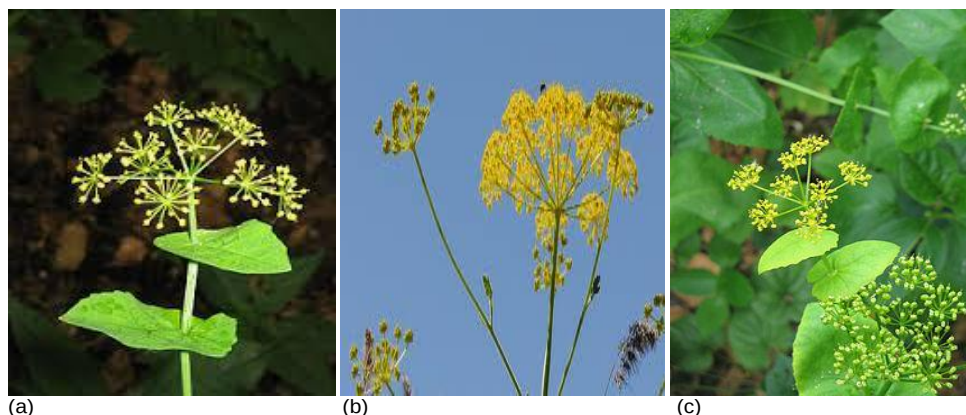


Figure 1. Natural picture of *Smyrniurn cordifolium* plant.

cells and structural growth occur.

A study reported that sleep deprivation caused some abnormal signs in rats, including a weak and slimy appearance, weight loss, dermal lesions, increment of food and energy consumption, decrease in body temperature and sudden death (Zavesicka et al., 2008).

Sleep duration among 90% of adults is between 6 to 9 h and a sleep duration < 3.5 and > 9 h compared to those with 7 h increases the chance of death by 15% (Sadock et al., 2002). Insomnia is defined as the presence of long sleep latency, frequent nocturnal awakenings, or prolonged periods of wakefulness during the sleep period or even frequent transient arousals (Thomas, 2007). Drug based methods, for insomnia, are used when non medicinal methods are failed. Medications used for insomnia have a calmatve effect on central nervous system (CNS). A good treatment for insomnia is characterized by a good start and continuity of sleep, high quality of sleep and the least side effects on CNS and also a lack of dependency during interruption (Sadock et al., 2002).

Benzodiazepines are the most common used drugs for insomnia. These kinds of medications have some disadvantages including withdrawal syndrome, drug accumulation, daily acedia, amnesia and relapse of insomnia (Pena and Krauss, 1999). Barbiturates are other types of medications used for insomnia with almost similar complications to benzodiazepines (Gillian and Byerley, 1990). Some kinds of plants have been traditionally used for insomnia and a trend in use of herbal products has been increased recently.

Smyrniurn cordifolium Boiss is a spring plant which was traditionally used as diuretic and expellant for kidney stones (Ahvazi et al., 2012) and also an antibacterial effect of this plant has been reported (Ulubelen et al., 1985). This plant is grown in Central Asia, Iran, Turkey and West of Afghanistan and it is widely distributed in Iran, particularly in Ilam Province and is used as an

herbal medication in human and as a feed by herbivorous animals (Mehrabi and Mehrabi, 2011). As consumption of this plant caused a moderate drowsiness and confusion among local consumers, the author decided to investigate the hypnotic and relaxant effects of *S. cordifolium* Boiss in rats in comparison with the current medications used for these purposes (Figure 1).

METHODOLOGY

The spring samples of *S. cordifolium* plant were collected from hillsides of Zagross mountains of Ilam province in west of Iran and then were confirmed by the Pharmacy Faculty of Mashhad and the Agricultural researches centre of Jahad Keshavarzi Directorate of Ilam Province. By an experimental study, 96 healthy male Wistar rats (weights 250 to 300 g), prepared from Pastor Institution in Iran and kept at the same conditions, dampness ($38\% \pm 2$), light (12 h darkness and 12 h lightness intermittently), temperature ($22 \pm 2^\circ$) and freely access to food and water, were divided into 12 equal groups among them, 5 groups were allocated for hypnotic evaluation and 7 groups for investigation of the relaxant effects of the plant. For hypnotic evaluations, a negative control with normal saline (10 mg/kg), a positive control with diazepam (1 mg/kg) and 3 treatment groups with different dosages of plant extract (100, 200 and 300 mg/kg) were selected and injected via insulin syringes intraperitoneally. Sleep start time and sleep duration time were then measured in different groups. Rats in the negative group were first injected by 10 mg/kg N/S intraperitoneally and 60 min later by another 10 mg/kg N/S and 90 min from the second injection a dosage of 30 mg/kg pentobarbital was applied intraperitoneally (Venkateswarlu and Rama, 2013).

For those in the positive control, 1 mg/kg diazepam was firstly injected intraperitoneally and 60 min later the second dosage of diazepam (1 mg/kg) was injected and 90 min from the second injection a dosage of 30 mg/kg pentobarbital was applied by the same method with negative control. Rats in treatment groups were firstly injected with the different dosages of plant extract (100, 200 and 300 mg/kg appropriately) and 60 min later the next dosages (similar to the previous dosages) of plant extracts were injected for the relevant groups. 30 mg/kg of pentobarbital was injected for rats in different groups, 90 min after the second injection (Table 1). After these steps, rats were put upwards on a cottony and warm (37°)

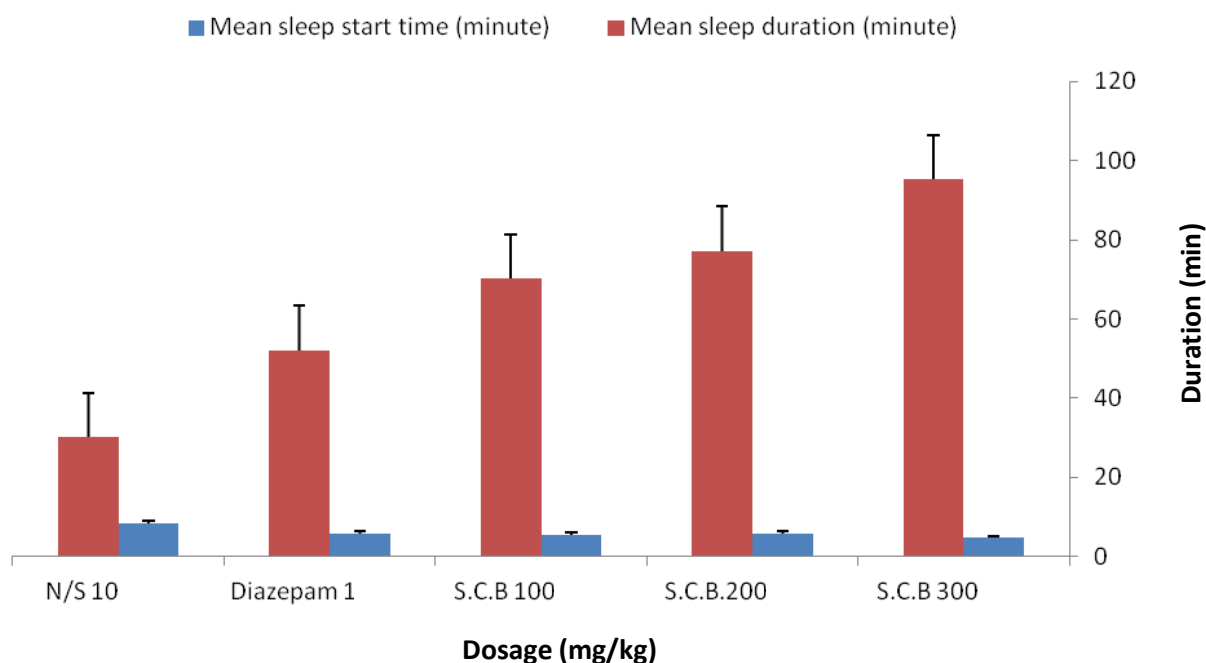


Figure 2. Comparison between mean sleep start time and sleep duration among rats due to different dosages of *S.C.B* plant extract and other tested variables. N/S: Normal saline, SCB: *Smyrniun cordifolium* Boiss. Bars: standard error.

surface. Time spent for righting (a duration in which rats could not amend their upwards positions) was considered as the sleep start time. Sleep termination time was considered if rats could amend their upwards positions, at least 3 times in a minute, remained on their feet and walked.

For relaxation test, a bar with 100 cm length and 50 mm diameter and a height of 30 cm from the surface was fixed in each cage and rats were hanged by two hands on the bar. If the animal could return to the normal position during 5 s, and hold is able to the bar with hands, it meant that the drug did not show any relaxant effect. Lacking the ability of holding the bar was considered as a relaxant effect of the drug. The mean duration of holding the fixed bar, as the marker of muscle relaxation, was measured among different rats groups. For relaxant effects of the plant, a negative control with normal saline (10 mg/kg), 3 positive controls with diazepam (0.125, 0.25 and 0.5 mg/kg) and 3 treatment groups of plant extract (200, 300 and 400 mg/kg) were allocated and were injected intraperitoneally. A score between 0 to 5 was considered as the marker of relaxation in rats and those that held the bar strongly and were not affected by medications, were given zero score and those that left the bar quickly were given a score of 5.

The score of zero meant that the drug did not show a relaxant effect. Monitoring for holding the bar was performed 30 and 60 min after injections and finally the mean time of sleeping, sleep start time and holding the bar were compared between treatment and control groups appropriately. Data was analysed using statistical package for social sciences (SPSS) version 16.0 and the mean and standard deviation of sleeping period, sleep start time and bar holding time among different rats groups were compared by paired T-test or analysis of variance (ANOVA) and Bonferroni test appropriately. A p-value less than 0.05 was considered as significant.

This research was conducted in accordance with the Principles of Laboratory Animal Care (NIH publication, revised in 1985) and was approved prospectively by Ethics Committee of Ilam University of Medical Sciences.

RESULTS

According to the results of this study, SCB plant extract (300 mg/kg), compared to diazepam (1 mg/kg) and N/S (10 mg/kg), shortened the sleep start time significantly ($p < 0.001$). The shortest time for sleep start was related to SCB at the dosage of 300 mg/kg. Using N/S (10 mg/kg) as negative control, the mean time for sleeping start was 8.25 min; however, using diazepam (1 mg/kg) as positive control, this time was lower (5.85 min). Using the dosages of 100, 200 and 300 mg/kg of SCB plant extract, in different groups of rats, the mean sleep start time was reduced to 5.55, 5.6 and 4.6 min, respectively. All 3 dosages of SCB plant extract (100, 200 and 300 mg/kg), compared to diazepam and normal saline, increased the mean sleep duration time significantly ($p < 0.001$) and as the SCB dosage was increased the sleep duration was increased too (Tables 1 and 2). Diazepam at the dosages of 0.25 and 0.5 mg/kg showed a significant relaxant effect; however, different dosages of plant extract did not indicate a significant relaxant effect in rats (Table 3 and Figure 2).

Table 1. Mean and 95% confidence intervals of sleep start time and sleep duration by rats in different groups.

Treatment	Dosage (mg/kg)	Mean (95%CI) of sleep start (min)	Mean (95%CI) of sleep duration (min)
Normal saline	10	8.25 (7.6-8.9)	30.02 (28.4-31.7)
Diazepam	1	5.85 (5.02-6.7)	52.1(50.8-53.4)
	100	5.55 (4.9-6.2)	70.2 (69.6-70.7)
S.C.B extract	200	5.62 (5.2-6.1)	77.2 (76.6-77.8)
	300	4.61 (4.2-5.03)	95.3 (94.8 -95.8)

Group N/S: Normal saline 10mg/kg (start) + N/S 10 mg/kg (60 min later) + pentobarbital 30 mg/kg (90 min after 2nd injection).
 Group Diazepam: Diazepam 1mg/kg (start) diazepam 1mg/kg (60 min later) + pentobarbital 30mg/kg (90 min after 2nd injection).
 Group Extract 100: Extract 100 mg/kg (start) + extract 100mg/kg (60 min later) + pentobarbital 30mg/kg (90 min after 2nd injection).
 Group Extract 200: Extract 200 mg/kg (start) + extract 200mg/kg (60 min later) + pentobarbital 30mg/kg (90 min after 2nd injection).
 Group Extract 300: Extract 300mg/kg (start) + extract 300 mg/kg (60 min later) + pentobarbital 30 mg/kg (90 min after 2nd injection).

Table 2. Comparison between hypnotic effects of different dosages of S.C.B plant extract and other tested variables.

Comparison variable		Mean (min)	Mean difference (min)	P-value	Significant
Sleep start time	N/S vs. diazepam	8.25 vs. 5.85	2.40	0.0001	Yes
	N/S vs. Extract 100	8.25 vs. 5.55	2.60	0.0001	Yes
	N/S vs. Extract 200	8.25 vs. 5.62	3.63	0.0001	Yes
	N/S vs. Extract 300	8.25 vs. 4.61	4.64	0.0001	Yes
	Diazepam vs. extract 100	5.85 vs. 5.55	0.30	1.0	No
	Diazepam vs. extract 200	5.85 vs. 5.62	0.23	1.0	No
	Diazepam vs. extract 300	5.85 vs. 4.61	1.24	0.02	Yes
	Extract 100 vs. extract 200	5.55 vs. 5.62	-0.07	1.0	No
	Extract 100 vs. extract 300	5.55 vs. 4.61	0.94	0.16	No
Sleep duration	Extract 200 vs. extract 300	5.62 vs. 4.61	1.01	0.09	No
	N/S vs. diazepam	30.02 vs. 52.1	-22.08	0.0001	Yes
	N/S vs. Extract 100	30.02 vs. 70.2	-40.18	0.0001	Yes
	N/S vs. Extract 200	30.02 vs. 77.2	-47.18	0.0001	Yes
	N/S vs. Extract 300	30.02 vs. 95.3	-65.28	0.0001	Yes
	Diazepam vs. extract 100	52.1 vs. 70.2	-18.1	0.0001	Yes
	Diazepam vs. extract 200	52.1 vs. 77.2	-25.1	0.0001	Yes
	Diazepam vs. extract 300	52.1 vs. 95.3	- 43.2	0.0001	Yes
	Extract 100 vs. extract 200	70.2 vs. 77.2	-7.0	0.0001	Yes
	Extract 100 vs. extract 300	70.2 vs. 95.3	-25.1	0.0001	Yes
	Extract 200 vs. /extract 300	77.2 vs. 95.3	-18.1	0.0001	Yes

Table 3. Comparison between relaxant effects of SCB plant with diazepam and normal saline.

Variable	Dosage mg/kg	Mean relaxant score	P value
Normal saline	10	0	-
	0.125	0	-
Diazepam	0.25	2.6	0.02
	0.5	5	0.0001
Extract	200	0.05	-
	300	0.1	-
	400	0.5	-

DISCUSSION

About one third of human life is spent by sleeping and any disturbance of this phenomenon would be strongly annoying and needs interventional issues by physicians or psychologists. The most common sleep disorder is insomnia, with a prevalence rate of 35% among general population (Mellinger et al., 1985). The most important drugs used for insomnia were benzodiazepines; however, some older medications such as barbiturates, glutethimide meprobamate, chloral hydrate and paraldehyde or new drugs such as zolpidem and zaleplon are also applied for this purpose (Sadock et al., 2002). Herbal medications have also been used for insomnia and because of their natural sources as well as physiological adaptation to human body, are interested globally (Uporety et al., 2012; Asadollahi et al., 2010). Row forms of *S. cordifolium* Boiss plant are consumed commonly in Ilam province as a spring plant and its application is usually accompanied with mild confusion and drowsiness.

The current study investigated the hypnotic and relaxant effects of this plant compared with routine drugs among rats. The current study showed that, using diazepam (1 mg/kg) as positive control reduced the sleep start time to 5.55 min; however, using plant extract at the dosages of 100, 200 and 300 mg/kg reduced this time to 5.85, 5.62 and 4.61 min, respectively, all statistically significant in comparison with normal saline ($p < 0.0001$). In comparison with diazepam, the only dosage of plant which showed a significant difference for sleep start time was 300 mg/kg ($p < 0.02$); however, all 3 dosages of plant extract increased the length of sleep significantly ($p < 0.0001$). Increasing the dosage of SCB plant extract caused a rise at the sleep duration but more than 750 mg/kg was toxic and caused rats' mortality.

We could not find a similar study in the literature to compare the hypnotic or relaxant effects of SCB plant extract; therefore, the current study is the first investigation of the hypnotic or relaxant effect of this plant. One of the most common used herbal medications for insomnia was *Valerian officinalis* L. (Schulz et al., 1994). A study indicated that *V. officinalis* applied for 28 days had good and very good effects on insomnia compared to placebo (Kuhlmann et al., 1999). Another study reported a reduction of sleep start time by *V. officinalis* at the dosages of 450 and 900 mg/kg (Wheatley, 2001) which was in accordance to the effects of SCB plant. However, a systematic review of *Valerian* reported that evidences in support of the effectiveness of this plant are uncertain (Taibi et al., 2007). Some other herbal medications such as *Kavakava* (Cupp, 1999), *Rhodiola sachalinensis* (Muller and Ehrenstein, 1977), *Passiflora incarnate* (Speroni and Minghetti, 1988; Delaveau et al., 1989), *Lavandula angustifolia* (Gyllenhaal et al., 2000), *Mimosa blossoms* (Muceniece

et al., 2008), *Matricaria chamomile* (Perez-Ortega et al., 2008), *Tilia Americana* var, *Mexicana inflorescences* (Li et al., 2008), *Spikenarol* (Adeyemi et al., 2007), *Sansevieria liberica* Gerome (Herrera-Arellano et al., 2007), *Galphimia gluca* (Rakhshandah and Hosseini, 2006), *Rosa damascene* (Huang et al., 2008) and *Keampferia galangal* (Linfang et al., 2008) have been used and tested for insomnia by various studies in different societies including European, Asian and American countries.

The relaxant effects of SCB plant extract was compared to diazepam and there was not found a significant difference. Diazepam did not show any relaxant effect at the dosages of 0.125 mg/kg; however, at the dosages of 0.25 and 0.5 mg/kg showed mean relaxant effects of 2.6 and 5, respectively. A study performed in 2007 showed that a China plant (*Rhodiola sachalinensis*) caused loss of righting reflex in rats at the dosage of 150 mg/kg. The method used in their study was similar to ours but they reported a positive relaxant effect (Muller and Ehrenstein, 1977). The reason behind this difference may be associated with different cell receptors of extracts or their central or peripheral effectiveness.

Conclusion

SCB plant extract as a natural product showed hypnotic effects even better than diazepam and needs to be investigated in humans by further studies; however, the relaxant effects of this plant did not show a significant effect.

Conflict of Interests

The author(s) have not declared any conflict of interests.

ACKNOWLEDGMENT

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ABBREVIATIONS

SCB, *Smyrniun cordifolium* Boiss; **N/S**, normal saline; **Ip**, intraperitoneally.

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