© 2023 Journal of Pharmacy & Pharmacognosy Research, 11 (6), 1072-1078, 2023
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1579_11.6.1072

*Original Article*

# Central nervous system depressant effect of ethanol extract of *Senna spectabilis* (DC.) H.S.Irwin & Barneby in mice

[Efecto depresor del sistema nervioso central del extracto etanólico de *Senna spectabilis* (DC.) H.S.Irwin & Barneby en ratones]

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**Abstract**

*Context*: *Senna spectabilis* (DC.) H.S.Irwin & Barneby which belongs to *Fabaceae* family is widely used traditionally in the treatment of various diseases and disorders such as constipation, insomnia, anxiety, epilepsy, malaria and skin diseases.

*Aims*: To investigate the central nervous system (CNS) depressant effect of 70% ethanol extract of *S. spectabilis* leaves (70SSEE) using different neuropharmacological models in mice.

*Methods*: The CNS depressant effect of 70SSEE was investigated by the classical models of depression as elevated plus maze (EPM), hole cross (HC), and thiopental sodium (TS)-induced sleeping time tests in mice. The EPM test was used to assess the anxiolytic activity of 70SSEE at doses of 10, 50, and 100 mg/kg, while HC and TS-induced sleeping time tests at doses of 100, 250, and 500 mg/kg were used to assess the locomotor and sedative activity in mice.

*Results*: In EPM test, 70SSEE at doses of 50 and 100 mg/kg significantly ($p<0.05$) increased the number of open arm entries and time spent in open arm by mice compared to controls. In HC test, 70SSEE significantly inhibited the movement of animals across the hole in a dose-dependent manner. In addition, the administration of 70SSEE to mice significantly ($p<0.05$) decreased sleep latency time and increased sleep duration of TS-induced mice.

*Conclusions*: 70SSEE has CNS depressant effects which is a rational explanation for its use in traditional medicine. From these findings, it is hoped that this plant could be used in the treatment of various neurological disorders, including anxiety and insomnia.

*Keywords*: central nervous system depressants; depression; mice.

**Resumen**

*Contexto*: *Senna spectabilis* (DC.) H.S.Irwin & Barneby, que pertenece a la familia *Fabaceae*, se utiliza tradicionalmente en el tratamiento de diversas enfermedades y trastornos como estreñimiento, insomnio, ansiedad, epilepsia, malaria y enfermedades cutáneas.

*Objetivos*: Investigar el efecto depresor del sistema nervioso central (SNC) del extracto etanólico al 70% de hojas de *S. spectabilis* (70SSEE) utilizando diferentes modelos neurofarmacológicos en ratones.

*Métodos:* El efecto depresor del SNC de 70SSEE se investigó mediante los modelos clásicos de depresión como el laberinto elevado plus (EPM), el cruce de agujeros (HC) y las pruebas de tiempo de sueño inducidas por tiopental sódico (TS) en ratones. La prueba EPM se utilizó para evaluar la actividad ansiolítica de 70SSEE a dosis de 10, 50 y 100 mg/kg, mientras que las pruebas de tiempo de sueño inducidas por HC y TS a dosis de 100, 250 y 500 mg/kg se utilizaron para evaluar la actividad locomotora y sedante en ratones.

*Resultados*: En la prueba EPM, 70SSEE a dosis de 50 y 100 mg/kg aumentó significativamente ($p<0,05$) el número de entradas en brazo abierto y el tiempo de permanencia en brazo abierto de los ratones en comparación con los controles. En la prueba HC, 70SSEE inhibió significativamente el movimiento de los animales a través del agujero de forma dosis-dependiente. Además, la administración de 70SSEE a los ratones disminuyó significativamente ($p<0,05$) el tiempo de latencia del sueño y aumentó la duración del sueño de los ratones inducidos por TS.

*Conclusiones*: El 70SSEE tiene efectos depresores del SNC, lo que constituye una explicación racional de su uso en la medicina tradicional. A partir de estos hallazgos, se espera que esta planta podría ser utilizada en el tratamiento de diversos trastornos neurológicos, incluyendo la ansiedad y el insomnio.

*Palabras Clave*: depresión; depresores del sistema nervioso central; ratones.

ARTICLE INFO
Received: January 11, 2023.
Accepted: September 4, 2023.
Available Online: October 4, 2023.

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**Abbreviations:** 70SSEE: 70% ethanol extract of *Senna spectabilis* leaves; CNS: central nervous system; EPM: elevated plus maze; $GABA_A$: gamma-aminobutyric acid type A; HC: hole cross; Na-CMC: carboxymethyl cellulose sodium; TS: thiopental sodium.

## INTRODUCTION

Depressive and anxiety disorders are common mental health disorders in adults. Worldwide prevalence for general mental health disorders is 4 to 10% (NCCMH, 2011). In 2019, 280 million people lived with depression, including 23 million children and adolescents, and 301 million people lived with anxiety disorders, including 58 million children and adolescents (IHME, 2019). Anti-anxiety and anti-depressant drugs are used in the treatment of depression and some anxiety disorders, most of these drugs have unfavourable risk along with benefit ratios, and their prominent side effects are still a barrier to long-term treatment with these drugs (Newman et al., 2004). Medicinal plant therapy or phytomedicine can be an effective alternative in the treatment of depression because it has fewer side effects than synthetic drugs.

*Senna spectabilis* (DC.) H.S.Irwin & Barneby (*Fabaceae*), which is commonly known in Indonesia as *Ramayana*, is an ornamental plant in tropical and subtropical regions. It is native to Central America and the North and South America regions, and is widely distributed in East African as well as Southeast Asian countries (Jothy et al., 2012a). This species has been used in Asia and many other countries to treat various diseases based on its antimicrobial, laxative, antiulcerogenic, analgesic, and anti-inflammatory properties (Viegas et al., 2004). Traditionally, *S. spectabilis* leaf infusions are used to treat constipation, insomnia, and anxiety, while the decoction is used to treat malaria, dysentery, and headache (Bum et al., 2010).

A number of studies have revealed that *S. spectabilis* has several biological activities, such as antinociceptive (Viegas et al., 2008), antimicrobial (Sangetha et al., 2009), antioxidant, hepatoprotective (Jothy et al., 2012b), anti-ulcer (Paguigan et al., 2014), leishmanicidal (Melo et al., 2014), antimalarial (Ekasari et al., 2018), and anti-acetylcholinesterase (Suciati et al., 2020). However, there is a lack of scientific reports to support this suspected central nervous system (CNS) depressant activity in mice. The purpose of this study is to evaluate the pharmacological activity of 70% ethanol extract from *S. spectabilis* leaves (70SSEE) on the CNS using various animal models to explain the traditional use of this plant in the treatment of anxiety and insomnia.

## MATERIAL AND METHODS

### Plant material

*Senna spectabilis* leaves were collected and identified by the Indonesian Institute of Science (LIPI) - Purwodadi Botanical Garden Plant Conservation Center, Pasuruan, Indonesia (No.: 0371/IPH.06/HM/III/2019) (7°47'51.4"S 112°44'12.8"E). Dried leaf powder (500 g) was macerated with 70% ethanol with occasional stirring at room temperature for three days. Then, the filtrate was housed and concentrated using a rotary evaporator. Finally, concentrated extracts were stored in darkness in glass vials at room temperature for further use in the entire research series.

### Experimental animals

Male adult BALB/c mice (25–30 g) came from the Pharma Veterinary Center (PUSVETMA), Surabaya, Indonesia, and were placed in the veterinary laboratory of the Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia, under standard laboratory conditions (room temperature of 22 ± 2°C; 12 h light/dark cycle). Animals were given access to drinking water as well as food pellets and acclimatized to the experimental environment for one week before the experiment. All experimental protocols used in this study have been approved by the Animal Care and Use Committee, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia (No. 2.KE.082.07.2021 for elevated plus maze test; No. 2.KE.083.07.2021 for hole cross test; No. 2.KE.084.07.2021 for thiopental sodium-induced sleeping time test).

### Elevated plus maze (EPM) test

The method used in this experiment was adapted from the method described by Pellow et al. (1985) with slight modifications. The instrument used was a plus labyrinth raised above the floor level, consisting of two closed arms (30 × 6 × 15 cm) facing perpendicularly with two open arms (30 × 6 cm) and a central area measuring 6 × 6 cm. The experimental animals were randomly divided into five groups, with five mice in each group. The negative control group received 0.5% carboxymethyl cellulose sodium (Na-CMC, 10 mL/kg, p.o.), the positive control group received diazepam (standard drug, 1.5 mg/kg, p.o.), and the three test groups received 70SSEE at three different doses (10, 50, and 100 mg/kg, p.o.). After 60 min of oral administration of Na-CMC, diazepam, or 70SSEE, each mouse was placed individually in the centre area of the EPM with the head facing open hand and left to explore for five minutes. Mouse behaviour was recorded using an overhead video camera for subsequent quantification. Various types of parameters include the number of entries in the open arm, the time spent in the open arm, the number of

entries in the closed arm, and the time spent in the closed arm are recorded. In addition, other ethological parameters, such as the number of rears (vertical standing of rodent on two hindlegs) could also be observed.

### Hole cross (HC) test

The method used in this experiment was adapted from the method described by Takagi et al. (1971) with slight modifications. The instrument used was a cage measuring 30 × 20 × 14 cm with a fixed partition at a height of 7.5 cm in the middle, which had a hole with a diameter of 3 cm. The experimental animals were randomly divided into five groups, with five mice in each group. The negative control group received 0.5% Na-CMC (10 mL/kg, p.o.), the positive control group received diazepam (standard drug, 1 mg/kg, p.o.), and the three test groups received 70SSEE at three different doses (100, 250, and 500 mg/kg, p.o.). Immediately after oral administration of Na-CMC, diazepam, or 70SSEE, each mouse was allowed to cross the hole from one chamber to another. The animals were observed for three minutes, and the number of holes crossed was recorded before and at 30, 60, 90, and 120 min after treatment.

### Thiopental sodium (TS)-induced sleeping time test

The method used in this experiment was adapted from the method described by Hossain et al. (2010) with slight modifications. The experimental animals were randomly divided into five groups, with five mice in each group. The negative control group received 0.5% Na-CMC (10 mL/kg, p.o.), the positive control group received diazepam (standard drug, 1 mg/kg, p.o.), and the three test groups received 70SSEE at three different doses (100, 250, and 500 mg/kg, p.o.). After 30 min of oral administration of Na-CMC, diazepam, or 70SSEE, each mouse was treated with thiopental sodium (TS, 60 mg/kg, i.p.) intraperitoneally to induce sleep. The experimental animals were observed by placing them on different V-shape beds to record the latent period (time between TS administration to loss of righting reflex) and the duration of sleep (time between the loss and recovery of righting reflex).

### Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analysis was performed using one way analysis of variance (ANOVA) followed by Dunnett's post hoc test. Differences between groups were considered significant at the level of $p<0.05$.

## RESULTS

### Elevated plus maze (EPM) test

In EPM test, the behavior of the mouse model, as observed, confirmed the anxiolytic activity of 70SSEE and diazepam, as shown in Table 1. At a 70SSEE dose of 100 mg/kg ($p<0.05$), significantly increased the number of mice admissions to the open arm and time spent in the EPM open arm. The number of entries in the closed arm and the time spent in the closed arm decreased significantly in the extract treatment group comparable to the standard diazepam. In addition, 70SSEE at a dose of 100 mg/kg ($p<0.05$) and diazepam significantly reduced the number of rearing compared to the control.

### Hole cross (HC) test

In HC test, the behavior of the mouse model, as observed, confirmed the locomotor activity of 70SSEE and diazepam, as shown in Table 2. 70SSEE showed a significant decrease in motion ($p<0.05$) at doses of 100, 250, and 500 mg/kg from its initial value of 0 min to 120 min. The number of holes crossed from one chamber to another by mice from standard diazepam drugs (1 mg/kg, p.o.) decreased from 0 min to 120 min. Extracts showed dose-dependent activity, and the maximum depressive effect at a dose of 500 mg/kg was observed in the fourth observation period (90 min).

**Table 1.** Anxiolytic activity of 70% ethanol extract of *S. spectabilis* (70SSEE) and diazepam on elevated plus maze test in mice.

| Treatment | Dose (mg/kg) | Number of entries in | | Time (s) spent in | | Number of rearing |
|---|---|---|---|---|---|---|
| | | Open arm | Close arm | Open arm | Close arm | |
| Control | - | 7.00 ± 1.00 | 7.00 ± 3.30 | 225.00 ± 3.79 | 50.83 ± 1.40 | 18.33 ± 3.01 |
| Diazepam | 1.5 | 2.00 ± 0.40* | 9.00 ± 0.40 | 57.83 ± 6.92* | 229.83 ± 5.61 | 0.83 ± 0.75* |
| 70SSEE | 10 | 2.00 ± 0.30 | 5.00 ± 0.70 | 53.33 ± 2.32 | 254.33 ± 6.13 | 17.33 ± 3.56 |
| | 50 | 4.00 ± 0.40 | 6.00 ± 0.50 | 115.67 ± 5.81 | 175.17 ± 5.88 | 16.50 ± 3.27 |
| | 100 | 7.00 ± 0.50* | 7.00 ± 0.80 | 185.67 ± 2.32* | 109.67 ± 2.99 | 7.00 ± 4.86* |

Data are expressed as mean ± SEM (n = 5). *p<0.05 compared to the control group (one-way ANOVA followed by a Dunnett's post hoc test).

**Table 2.** Locomotor activity of 70% ethanol extract of *S. spectabilis* (70SSEE) and diazepam on hole cross test in mice.

| Treatment | Dose (mg/kg) | Number of holes crossed | | | | |
|---|---|---|---|---|---|---|
| | | 0 min | 30 min | 60 min | 90 min | 120 min |
| Control | - | 3.60 ± 3.56 | 4.00 ± 4.00 | 6.40 ± 3.44 | 4.00 ± 2.61 | 1.00 ± 0.45 |
| Diazepam | 1 | 8.60 ± 3.61* | 1.60 ± 1.60 | 1.60 ± 1.60 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| 70SSEE | 100 | 8.00 ± 3.42* | 2.60 ± 1.78* | 2.00 ± 1.38* | 1.00 ± 1.00 | 4.20 ± 2.69 |
| | 250 | 5.20 ± 4.46 | 2.60 ± 2.60 | 2.40 ± 2.16 | 1.20 ± 1.20 | 0.00 ± 0.00 |
| | 500 | 3.20 ± 1.39* | 2.20 ± 1.74* | 1.00 ± 0.63 | 0.00 ± 0.00 | 0.00 ± 0.00 |

Data are expressed as mean ± SEM (n = 5). *p<0.05 compared to the control group (one-way ANOVA followed by a Dunnett's post hoc test).

**Table 3.** Sedative activity of 70% ethanol extract of *S. spectabilis* (70SSEE) and diazepam on thiopental sodium-induced sleeping time test in mice.

| Treatment | Dose (mg/kg) | Onset of sleep (s) | Duration of sleeping time (min) |
|---|---|---|---|
| Control | - | 289.25 ± 76.06 | 99.20 ± 26.01 |
| Diazepam | 1 | 119.20 ± 8.27* | 240.05 ± 12.92* |
| 70SSEE | 100 | 128.25 ± 21.96* | 166.57 ± 43.52 |
| | 250 | 180.20 ± 19.70 | 225.83 ± 42.08* |
| | 500 | 121.40 ± 11.78* | 166.87 ± 52.06 |

Data are expressed as mean ± SEM (n = 5). *p<0.05 compared to the control group (one-way ANOVA followed by a Dunnett's post hoc test).

### Thiopental sodium (TS)-induced sleeping time test

In the TS-induced sleeping time test, the behavior of the mouse model, as observed, confirmed the sedative activity of 70SSEE and diazepam, as shown in Table 3. 70SSEE decreased the onset of sleep and increased the length of sleep, which was comparable to standard diazepam. 70SSEE at doses of 100 and 500 mg/kg produced significant effects at bedtime onset compared to the controls ($p<0.05$). Meanwhile, 70SSEE at a dose of 250 mg/kg produced a significant effect on the duration of sleep compared to the controls ($p<0.05$). Standard drug diazepam (1 mg/kg, p.o.) also showed statistically significant effects on sleep onset and duration of sleep ($p<0.05$).

## DISCUSSION

This study was conducted to explain the effect of central nervous system (CNS) depressant from 70% ethanol extract of *S. spectabilis* leaves (70SSEE) in mice. The effect of CNS depressants from 70SSEE was studied using three classical neuropharmacological models, namely elevated plus maze (EPM), hole cross (HC), and thiopental sodium (TS)-induced sleeping time.

EPM is one of the most widely used animal anxiety models currently and is very sensitive to the effect of anxiolytic and anxiogenic drugs that work on the $GABA_A$-benzodiazepine complex (Dhonnchadha et al., 2003). This test is based on the rodents' natural tendency to explore new environments and their innate avoidance of unprotected, bright, and tall places (represented by open arms) that describe signs of anxiety in the animals. Exposure to anxiolytic drugs may increase exploration of the open arms. In this study, administration of 70SSEE at different doses (10, 50, and 100 mg/kg) produced an anxiolytic-like effect in mice, where a dose of 100 mg/kg produced the strongest dose-response effect. This was demonstrated by a significant increase in the number of open-arm entries and time spent in the EPM open-arm when compared to control animals. This effect is comparable to diazepam (1.5 mg/kg) given as a standard anxiolytic drug. Research conducted by Thongsaard et al. (1996) on *Senna siamea* (Lam.) H.S.Irwin & Barneby for anxiolytic activity reported that water extracts of *S. siamea* leaves and flowers at doses of 1, 6, and 12 g/kg of human body weight, which when converted to experimental animals, were 130, 780, and 1560 mg/kg of mouse body weight, with oral administration showing a decrease in the duration of time spent on the open arm and did not significantly increase the number of locomotors, both of which were indicators of anxiolytic effect parameters in the EPM test.

Locomotor activity is considered to be an index of alertness, and its reduction is indicative of CNS depressant activity (Dey et al., 2011). This decrease in spontaneous motor activity can be attributed to the CNS depressant effect of plant extracts (Rakotonirina et al., 2001). In this study, 70SSEE showed a significant decrease in movement frequency in HC test in

mice. The results of this study provide evidence that 70SSEE reduces locomotor activity, confirming its CNS depressant effect. Another species of the *Fabaceae* family that exhibits the same locomotor activity is *Dalbergia candenatensis* Prain. A research by Anisuzzman et al. (2017) showed that the administration of 98% ethanol extract of *D. candenatensis* leaves orally at doses of 100, 250, and 500 mg/kg led to a decrease in the number of holes passed and lethargy to the new environment, which is the opposite of CNS stimulating agents. Suppression effects were found at 30 min and continued up to 120 min after leaf extract administration. All doses tested resulted in significant locomotor inhibition. Inhibition of locomotors by inducing crude extracts of *D. candenatensis* shows its potential to suppress the central nervous system.

CNS-like depressive behavior is also demonstrated by the barbiturate-induced prolongation of sleep time, such as TS (Castañeda et al., 2022). Thiopental is essentially a hypnotic agent that can induce hypnosis by potentiating GABA-mediated postsynaptic inhibition through allosteric modification of the $GABA_A$ receptor (Hardman and Limbird, 2001). Substances that have CNS depressant activity can reduce sleep onset, prolong sleep duration, or both induced by TS (Nyeem et al., 2006). In this study, 70SSEE significantly reduced sleep onset and prolonged sleep duration compared to the control animals. The effect produced by 70SSEE at doses of 100 and 500 mg/kg is comparable to that of standard diazepam (1 mg/kg). This could explain how the extract works similarly to diazepam. This is in line with research by Bum et al. (2010), where ethanol extract of *S. spectabilis* leaves greatly increases the total sleep time caused by diazepam. Anxiolytic, muscle relaxant, and sedative-hypnotic activities of benzodiazepines such as diazepam are mainly caused by an increased $GABA_A$ activity (Doyno and White, 2021). Based on research conducted by Nkantchoua et al. (2018), it was revealed that *S. spectabilis* plant extract has anticonvulsant activity on the GABAergic pathway because it can inhibit seizures induced by selective antagonist compounds on the effect of GABA inhibition. This may indicate that the CNS depressant effect induced by *S. spectabilis* is likely to be mediated through the GABA pathway.

In addition to having anxiolytic, anti-depressant, and sedative-hypnotic activities, *S. spectabilis* was also reported to have anticonvulsant activities, with iso-6-spectaline as the active compound responsible for these activities (Bum et al., 2010; Silva et al., 2009; 2011). Although the exact mechanism of action of iso-6-spectaline is unclear, the GABAergic neurotransmitter system may be involved. This further strengthens the evidence that *S. spectabilis* has an effect on CNS.

## CONCLUSION

The study of locomotor activity measured by elevated plus maze and hole cross test showed that 70SSEE significantly decreased locomotor activity as an indication of CNS depressant effect. 70SSEE also showed significant sedative effects through reduction of sleep onset and prolongation of sleep duration in mice induced by TS. Therefore, the use of *S. spectabilis* in folkloric treatment may be due to the effect on CNS, as evidenced by these findings. However, further research is needed to determine the active compound and mechanism of action responsible for the biological activity of 70% ethanol extract of *S. spectabilis* leaves.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## ACKNOWLEDGMENTS

Authors acknowledge the Faculty of Pharmacy, Universitas Airlangga, for the PUF research grant 2021 [grant number 212/UN3/2021].

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Concepts or ideas | x | | | | | | | | | | | |
| Design | x | | | | | | | | | | | |
| Definition of intellectual content | x | | | | | | | | | | | |
| Literature search | | | | | | | x | x | x | x | x | |
| Experimental studies | | | | | | | x | x | x | x | x | |
| Data acquisition | | | | | | | x | x | x | x | x | |
| Data analysis | x | | | | | | x | x | x | x | x | |
| Statistical analysis | x | x | x | x | x | | x | x | x | x | x | |
| Manuscript preparation | x | x | x | x | x | x | x | x | x | x | x | x |
| Manuscript editing | x | | | | | | | | | | | x |
| Manuscript review | x | x | x | x | x | x | x | x | x | x | x | x |

**Citation Format:** Ekasari W, Widyowati R, Wahyuni TS, Suciati, Oktarina RD, Ardianto C, Prameswari ES, Suri WAA, Kurnia AI, Wirabuana RK, Angembani VMA, Sahu RK (2023) Central nervous system depressant effect of ethanol extract of *Senna spectabilis* (DC.) H.S.Irwin & Barneby in mice. J Pharm Pharmacogn Res 11(6): 1072–1078. https://doi.org/10.56499/jppres23.1579_11.6.1072