



Central Nervous System Effects of Iso-6-spectaline Isolated from *Senna Spectabilis* var. *Excelsa* (Schrad) in Mice

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ABSTRACT

The central nervous system (CNS) depressant and anticonvulsant activities of iso-6-spectaline (SPEC) were investigated in animal models. The SPEC from *Senna spectabilis* var. *excelsa* (Schrad) (0.1, 0.5 and 1.0 mg/kg) injected by oral route (p.o.) in mice caused a significant decrease in the motor activity up to 30 days after the administration and in the dose of 1.0 mg/kg significantly reduced the remaining time on the Rota-rod apparatus. Additionally, SPEC (0.1, 0.5 and 1.0 mg/kg, p.o.) was also capable of promoting increase of latency for development of convulsions induced by pentylenetetrazole. This SPEC was also capable of promoting an increase of latency for development of convulsions induced by picrotoxin at highest dose. In the same way, the anticonvulsant effect of SPEC was affected by pretreatment with flumazenil, a selective antagonist of the benzodiazepine site of the GABA_A receptor. These results suggest possible CNS depressant and anticonvulsant activities in mice that needs further investigation.

Key words: Fabaceae, open field, pentylenetetrazole, picrotoxin, *senna spectabilis*

INTRODUCTION

Numerous herbal medicines are recognized as active in the central nervous system (CNS), and they have at least a hypothetical potential to affect chronic conditions such as anxiety, depression, headaches or epilepsy, that do

not respond well to conventional treatments. Thus, iso-6-spectaline (SPEC) may possess a modulatory role in the treatment of neurodegenerative diseases, since their piperidine alkaloid compound can interrupt cellular oxidative processes in the CNS. The effects of SPEC on the CNS have not yet been determined, therefore, would be important to conduct these studies to clarify its brain action mechanism.

Piperidine alkaloids are abundant in nature and many of them are known to exhibit some biological activity. In our search for potential anxiolytic, antidepressant or anticonvulsant agents employing a mechanism-based yeast bioassay for CNS-modifying agents,^[1] we have isolated iso-6-spectaline (SPEC; 14-[(2R,3R,6R)

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-3-hydroxy-2-methylpiperidine]-tetradecan-13-one), piperidine alkaloids, is a heterocyclic organic not aromatic compound [Figure 1] found in many plant species. It was isolated for the first time from *Cassia sp.*, species previously known as *Cassia excelsa*, hence the term cassine.^[2] Piperidine alkaloid derivatives with CNS effects include SPEC which exerts neuroprotective effects against depression model.^[2]

In Brazilian northeast folk medicine, *Senna spectabilis* is used as anti-inflammatory, analgesic, laxative, purgative, antimicrobial and antiulcerogenic.^[3-5] Studies have shown that the extract of *Senna sp.* inhibits lipid peroxidation of bovine brain phospholipids, indicating its antioxidant activity.^[6] Then, the excessive production of free radicals in the organism, and the imbalance between the concentrations of these and the antioxidant defenses may be related to the pathogenesis of neurodegenerative diseases.^[7,8]

The genus *Cassia* possesses about 600 species distributed worldwide, being well known due to its diverse biological and pharmacological properties.^[4] *Senna spectabilis* (DC) Irwin and Barneby var. *spectabilis* (*Cassia spectabilis* DC) is widely grown as an ornamental plant in tropical and subtropical areas, and has been commonly used in traditional medicine for many years. It has also been used in traditional Brazilian medicine for the treatment of flu and cold, as a laxative and purgative.^[9,10]

Preliminary behavioral screening realized with the SPEC demonstrates that it reduces lipid peroxidation in pilocarpine-induced seizures, increasing survival rate and reducing number of seizures in rats. Additionally, there is no work demonstrating SPEC effects in neurodegenerative diseases in animal models of anxiety, depression or epilepsy. Therefore, we decided to assess the SPEC effects on the CNS of mice.

MATERIALS AND METHODS

Plant material and chemistry study

The plant was collected in September 2003, at Boa Viagem, State of Ceará, Brazil, and was identified by

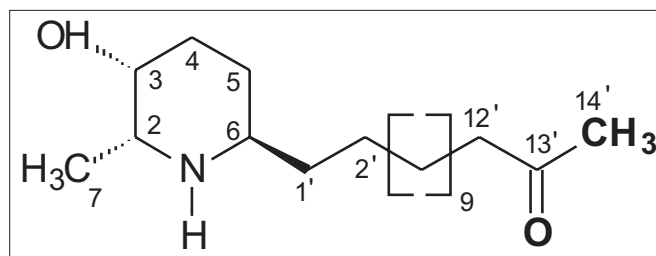


Figure 1: Chemical structure of iso-6-spectaline (SPEC; 14-[(2R,3R,6R)-3-hydroxy-2-methylpiperidine]-tetradecan-13-one)

Prof. A.G. Fernandes, in the Department of Biology of the Federal University of Ceará. The voucher specimen is deposited at the Prisco Bezerra Herbarium under the voucher number 33013.

The botanical material, leaves (1.5 kg), stem (5.1 kg) and roots (3.8 kg), were triturated and exhaustingly extracted with ethanol and concentrated in rotative evaporator, producing 39 g, 27.5 g and 42 g respectively. The leaf extract (39 g) was then submitted to technical of selective extraction of alkaloids a fraction rich in alkaloids (FA) and a non alkaloids (FNA) were obtained. The alkaloid fraction was submitted to chromatography on SEPHADEX, with methanol as movable phase. The dichloromethane fraction (7.6 g) was submitted to the same chromatography process.

The analysis of the fractions was made in chromatography in thin layer (CCD), which revealed the purity of the rich fraction in SPEC (30 mg) which when subjected to the test with the reagent Dragendoff revealed an orange stain, and was thus positive for alkaloids.^[11] Its spectra of NMR RMN¹H, RMN¹³C, DEPT 135, COSY, HMBC e HSQC¹ were obtained and compared with the data from the literature for identification. The iso-6-spectaline is an amorphous white solid with M.P. 130.8-132.3°C; the value of TLC in MeOH/EtOAc (1:1), R_f = 0.58; NMR spectra description of ¹H is ¹H NMR (MeOD, 500 MHz) δ_H 3.83 (1H, H-3); 3.30 (1H, H-6); 3.23 (1H, H-2); 2.47 (2H, H-12); 2.15 (3H, H-14); 1.44 (3H, H-7); 1.29-1.33 (12H, H-4' - H-9); NMR spectra description of ¹³C is ¹³C NMR (MeOD, 125 MHz) δ_C -212.4 (C, C-13); 66.1 (CH, C-3); 58.8 (CH, C-2); 57.7 (CH, C-6); 44.4 (CH₂, C-12); 34.9 (CH₂, C-1); 31.2 (CH₂, C-4); 29.9 (CH₃, C-14); 30.9 (CH₂, C-3); 30.5 (CH₂, C-10); 30.5-30.9 (CH₂, C-4'-C-9); 26.4 (CH₂, C-2); 23.8 (CH₂, C-5); 23.8 (CH₂, C-11); 16.1 (CH₃, C-7). In the present work, the iso-6-spectaline was suspended in 0.5% Tween 80 distilled in water, and sonicated before use. Agents were administrated orally (p.o.) and intraperitoneally (i.p.) at a dose volume of 0.1 ml/10 g.

Animals

Male Swiss mice (25-30 g), two months of age were used. The animals were randomly housed in appropriate cages at 23 ± 2°C on a 12-h light/dark cycle (lights on 08:00 a.m. – 18:00 p.m.) with free access to food (Purina®) and water. All experiments were carried out between 08:00 a.m. and 18:00 p.m. in a quiet room. Experimental protocols and procedures were approved by the Ethics Committee on Animal Experiments at the Federal University of Piauí (CEEA/UFPI # 44/09).

Behavioral effects, locomotor activity and motor coordination test (rota-rod test)

Behavioral screening ($n = 7$, per group) was performed following parameters described by Almeida *et al.*,^[12] and animals were observed at 30 days after oral (p.o.) administration of SPEC (0.1, 0.5, and 1.0 mg/kg, p.o.).

Mice were divided into four groups (seven animals each). Vehicle (saline/Tween 80 0.5%; control group) and SPEC (0.1, 0.5, and 1.0 mg/kg, p.o.) were injected. The spontaneous locomotor activity of the animals was assessed in a cage activity (50 cm × 50 cm × 50 cm) after 30 days of treatment.^[13]

A Rota-rod treadmill device (AVS®, Brazil) was used for the evaluation of motor coordination.^[14] Initially, the mice able to remain on the Rota-rod apparatus longer than 180 s (9 rpm) were selected 24 h before the test. Thirty minutes after 30 days of administration of either SPEC (0.1, 0.5, and 1.0 mg/kg, p.o.), vehicle (saline/Tween 80 0.5%; control group) or diazepam (DZP, 2.0 mg/kg, i.p.), each animal was tested on the Rota-rod apparatus and the time(s) remained on the bar for up to 180 s was recorded after 30 days of treatment.

Pentylentetrazole-induced convulsions

Pentylentetrazole (PTZ) (60 mg/kg, i.p.) was used to induce clonic convulsions.^[15] Mice were divided into five groups ($n = 7$ per group). First group received vehicle (two drops of Tween 80 0.5% in distilled water, the solvent for SPEC) while the second group was treated with diazepam (DZP, 2.0 mg/kg, i.p.). The remaining groups received an injection of SPEC (0.1, 0.5, and 1.0 mg/kg, p.o.). After 30 days of drug administration, the mice were treated with PTZ (i.p.) at a dose of 60 mg/kg. The latency and percentage of inhibition clonic convulsions were registered. The incidence of deaths was noted until 24 h after the injection of PTZ.

The effect of selective GABA_A-BZD receptor antagonist flumazenil^[16] on the anticonvulsant activity of SPEC was investigated. In the experimental groups, mice were given flumazenil (FLU) (10 mg/kg, i.p.) 30 min before the administration of SPEC (1.0 mg/kg, p.o.) (30 days before the injection of PTZ). In the standard group, the animals received FLU 30 min before the administration of diazepam (DZP, 2.0 mg/kg, i.p.) (30 days before the injection of PTZ). The anticonvulsant activity of SPEC and DZP in mice pretreated with FLU was assessed.

Picrotoxin-induced convulsion

The method has been described previously.^[17,18] Animals were divided into five groups ($n = 7$ per group). Control

group received vehicle and standard group was treated with diazepam (DZP, 2.0 mg/kg, i.p.). The remaining groups were treated with 0.1, 0.5 and 1.0 mg/kg (p.o.) of SPEC. After 30 days of drug administration, the mice were treated with PIC at a dose of 8 mg/kg (i.p.). Immediately after the injection of the convulsant, mice were individually placed in plastic boxes and observed for the time to onset of clonic convulsion (latency), percent clonic convulsion and deaths. The incidence of deaths was noted until 24 h after the injection of PIC.

Statistical analysis

The data obtained were evaluated by one-way analysis of variance (ANOVA) followed by Student-Neuman-Keuls *t*-test. The incidence (%) of clonic or tonic-clonic convulsions as well as the mortality were evaluated by Fisher's Exact Test. Differences were considered to be statistically significant when $P < 0.05$.

RESULTS AND DISCUSSION

Analysis of the ¹H NMR and ¹³C NMR spectra showed that SPEC presented analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of the compound was determined by analysis of the ¹H NMR and ¹³C NMR.

SPEC at doses of 0.1, 0.5 and 1.0 mg/kg (p.o.) showed behavioral changes in animals 30 days after of treatment: Decrease of spontaneous activity, palpebral ptosis, ataxia, analgesia, and sedation. Behavioral changes were more evident on the second day of treatment. The doses of 0.1, 0.5 and 1.0 mg/kg (p.o.) of SPEC caused significant decrease of 30%, 30% and 59% of ambulation (number of crossings) 30 days after administration, respectively [Figure 2]. In this test only the highest dose (1.0 mg/kg, p.o.) reduced (40%) the remaining time of animals on the Rota-rod apparatus [Figure 3].

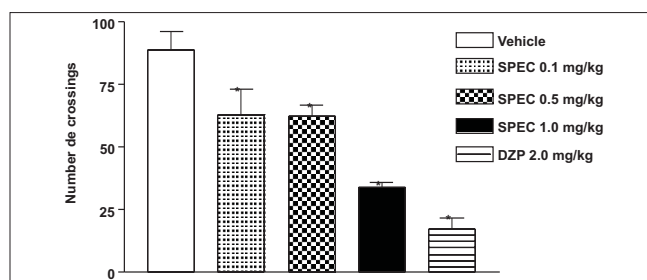


Figure 2: Effects of iso-6-spectraline (0.1, 0.5 and 1.0 mg/kg, p.o., SPEC) or diazepam (DZP, 2.0 mg/kg, i.p.) on locomotor activity of mice. The parameters evaluated were the total number of pulses of crossings in activity cage. Values are mean ± S.E.M. for seven mice per group. * $P < 0.001$ as compared to control (Vehicle), one-way ANOVA followed by Student-Neuman-Keuls *t*-test

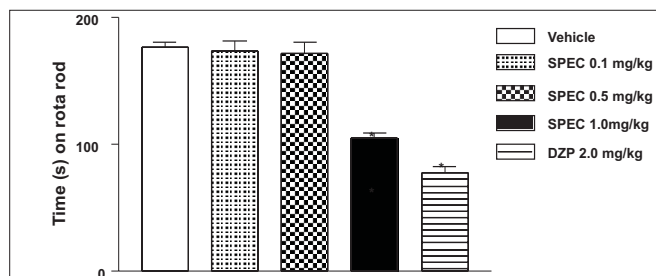


Figure 3: Time (s) on the Rota-rod observed in mice after oral route treatment with Vehicle (control), iso-6-spectaline (0.1, 0.5 and 1.0 mg/kg, p.o., SPEC) or DZP (2.0 mg/kg, i.p.). The motor response was recorded for the following 180 s after drug treatment. Values are mean ± S.E.M. for seven mice per group. * $P < 0.001$ as compared to control (Vehicle), one-way ANOVA followed by Student-Neuman-Keuls t -test

Table 1 shows that (PTZ) consistently induced clonic convulsions in 100% of mice. SPEC (0.1, 0.5 and 1.0 mg/kg, p.o.) delayed the onset of PTZ-induced tonic convulsion significantly and (1.0 mg/kg, p.o.) protected 80% ($P < 0.001$) of mice against the convulsion. Diazepam completely protected the animals against the tonic convulsion elicited by PTZ.

As described in Table 1, the administration of FLU (10 mg/kg, i.p.) antagonized the effect of SPEC (1.0 mg/kg, i.p.) and DZP (2 mg/kg, i.p.) in the prolongation of convulsion latency. When given i.p., only the highest dose of SPEC (1.0 mg/kg, i.p.) increased the latency for convulsions induced by PIC significantly when compared to the control ($P < 0.001$) [Table 2].

The antidepressant and anticonvulsant effects of SPEC isolated from *S. spectabilis* were emphasized in the present work since the management of neurodegenerative diseases faces a number of problems including limited number of effective antidepressant agents and toxicity of the available anticonvulsant agents. In folk medicine of the Brazilian Northeast, the *Senna spectabilis* is used as an anti-inflammatory, analgesic, laxative, purgative, antimicrobial and antiulcerogenic.^[3,4] In pharmacological behavioral screening, the animals treated with SPEC showed decrease of response to the touch, palpebral ptosis, ataxia, analgesia, sedation and reduction of motor activity. These data are indicative of the depressive activity of the CNS,^[2] indicating effects on the CNS similar to drugs that reduce the CNS activity.^[5,10,19-23]

The reduction of the locomotor activity observed after treatment with SPEC can be due to either an inhibitory effect of the SPEC in the CNS or by muscular relaxant activity in the periphery. Our results suggest that SPEC could show a neuro-sedative activity or a profile for a hypnotic drug.

Table 1: Effects of iso-6-spectaline (0.1, 0.5 and 1.0 mg/kg, p.o., SPEC) on PTZ-induced convulsion in mice

Treatments	Dose (mg/kg)	Latency (s)	% inhibition of convulsion	% inhibition of death
Vehicle	-	156.3 ± 11.9	0	0
SPEC 0.1	0.1	279.0 ± 22.6 ^a	0	0
SPEC 0.5	0.5	376.8 ± 38.0 ^{a, b}	10	20 ^c
SPEC 1.0	1.0	582.5 ± 33.5 ^{a, b, c}	80 ^d	30 ^d
ISO + FLU	1.0 + 10	271.8 ± 38.9	0	10 ^c
DZP	2	862.9 ± 10.0 ^a	100 ^d	100 ^d
DZP + FLU	2 + 10	171.2 ± 15.2	0	15

Values are mean ± S.E.M. for seven mice per group. ^a $P < 0.05$ (ANOVA followed by Student-Neuman-Keuls t -test), significantly different from control; ^b $P < 0.01$ (ANOVA followed by Student-Neuman-Keuls t -test), significantly different from SPEC 0.1; ^c $P < 0.001$ (ANOVA followed by Student-Neuman-Keuls t -test), significantly different from SPEC 0.5; ^d $P < 0.001$ (Fisher's test), significantly different from control. ^e $P < 0.05$ (Fisher's test), significantly different from control

Table 2: Effects of iso-6-spectaline (0.1, 0.5 and 1.0 mg/kg, p.o., SPEC) on PIC-induced convulsion in mice

Treatment	Dose (mg/kg)	Latency (s)	% inhibition of convulsion	% inhibition of death
Vehicle	-	516.2 ± 14.5	0	0
DZP	2	1336.0 ± 10.0 ^a	100 ^a	100 ^a
SPEC 0.1	0.1	518.5 ± 21.01	0	0
SPEC 0.5	0.5	517.5 ± 45.9	10	10
SPEC 1.0	1.0	1125.9 ± 29.3 ^a	50 ^a	50 ^a

Values are mean ± S.E.M. (n = 7 per group). ^a $P < 0.05$ (ANOVA followed by Student-Neuman-Keuls t -test) compared to control; ^b $P < 0.001$ (Fisher's test) compared to control

Our results suggest that the higher dose of SPEC produces loss of motor coordination in mice. Thus, the lack of motor coordination is characteristic of a drug that reduces the CNS activity such as anxiolytics, sedatives and hypnotics.^[12,24,25]

Pentylentetrazole, picrotoxin and strychnine are all convulsant agents.^[26,27] Data from this study show that the onset of tonic-clonic convulsion produced by PTZ was significantly delayed by SPEC [Table 2] and mortality was significantly reduced ($P < 0.05$). According to De Sarro *et al.*,^[28] PTZ may be exerting its convulsing effect by inhibiting the activity of gamma aminobutyric acid (GABA) at GABA_A receptors. Gamma aminobutyric acid is the major inhibitory neurotransmitter implicated in epilepsy. The enhancement and inhibition of GABA neurotransmission will attenuate and enhance convulsion, respectively.^[29] Since the SPEC delayed the occurrence of PTZ convulsion, it is probable that it may interfere in GABAergic mechanisms to exert its anticonvulsant effect.

In order to determine the role of BZD receptors in the SPEC-induced anticonvulsant effects, flumazenil (FLU), a specific antagonist of the benzodiazepine site in the GABA-benzodiazepine receptor complex, was used.^[16] The results obtained from PTZ-induced convulsion model in mice pretreated with FLU suggest that SPEC could facilitate the inhibitory activity of the GABAergic system

probably through a competitive agonist action in the BZD site of the GABA receptors. The significant effect on the motor coordination, in high doses, might support this theory, as GABAergic drugs usually are sedative.^[30]

According to previous studies, picrotoxin, a GABA_A-receptor antagonist, produces seizures by blocking the chloride-ion channels linked to GABA_A-receptors, preventing the entry of chloride ions into the brain and, consequently, inhibitory transmission in the brain.^[31] Therefore, the findings of the present study suggest that SPEC (1.0 mg/kg, p.o.) might have inhibited and/or attenuated the PIC-induced convulsions by interfering with GABAergic neurotransmission.^[32]

Summarizing our data, the results suggest depressant CNS and anticonvulsant effects of iso-6-spectaline from *Senna spectabilis*. The precise mechanisms of the possible behavioral effects of iso-6-spectaline are not clear, however, the GABAergic neurotransmitter system might be involved. So, more studies will be required for elucidation of this effect in the CNS.

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