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Iso-6-spectaline effects on convulsions induced in epilepsy models

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ABSTRACT

The central nervous system (CNS) and anticonvulsant activities of iso-6-spectaline (SPEC) from *Senna spectabilis* 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 24 h 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 (PIC) only 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 anticonvulsant activities in mice that needs further investigation.

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

INTRODUCTION

Several herbal medicines are recognized as active in the central nervous system (CNS), and they have at least a hypothetical potential to affect neurodegenerative conditions including epilepsy, that do not respond well to conventional treatments. Thus, iso-6-spectaline (SPEC) may possess a neuromodulatory role in the treatment of seizures, since this piperidine alkaloid compound can interrupt cellular oxidative processes and monoaminergic system changes in the hippocampus and striatum. The effects of SPEC on these cerebral areas have not yet been determined, therefore, would be important to conduct these studies to clarify its brain action mechanism.

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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) -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]

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 excessive production of free radicals, and the imbalance between the concentrations of these and the antioxidant defenses may be related to the pathogenesis of seizures.[6-8]

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]

Previous studies about behavioral screening realized with the SPEC demonstrates that it produces antioxidant effects in vitro and reduces lipid peroxidation in hippocampus of adult mice after pilocarpine-induced seizures, increasing survival rate and reducing number of seizures in mice. Additionally, there is no work demonstrating SPEC effects in neurodegenerative diseases in animal on epilepsy models.

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 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.

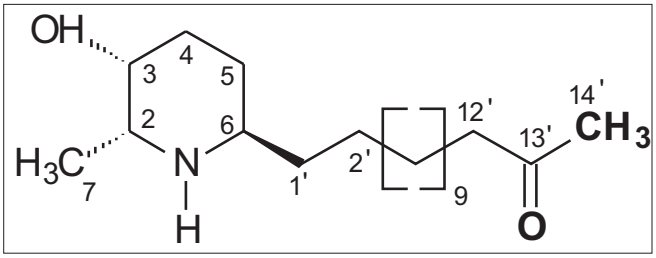

Figure 1: Chemical structure of iso-6-spectaline (SPEC; 14-[(2R,3R,6R)-3-hydroxy-2-methylpiperidine]-tetradecan-13-one)

The botanical material, leaves (3.0 kg), stem (10.2 kg) and roots (7.6 kg), were triturated and exhaustingly extracted with ethanol and concentrated in rotative evaporator, producing 78 g, 55 g and 84 g respectively. The leaf extract (78 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 (15.2 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 RMN^{1}H, RMN^{13}C, DEPT 135, COSY, HMBC e HSQC[1] were obtained and compared with the data from the literature for identification. The iso-6-spectaline is an amorphous white solid with M.P. 130.8-132.3ºC; the value of TLC in MeOH/EtOAc (1:1), Rf = 0.58; NMR spectra description of ^{1}H is ^{1}H 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 ^{13}C is ^{13}C 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 (CH_2, C-12'); 34.9 (CH_2, C-1'); 31.2 (CH_2, C-4); 29.9 (CH_3, C-14'); 30.9 (CH_2, C-3'); 30.5 (CH_2, C-10'); 30.5-30.9 (CH_2, C-4'-C-9'); 26.4 (CH_2, C-2'); 23.8 (CH_2, C-5); 23.8 (CH_2, C-11'); 16.1 (CH_3, 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 Piaui (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 14 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 24 h 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 (16 rpm) were selected 24 h before the test. Thirty minutes after 24 h 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 24 h of treatment.

Pentylenetetrazole-induced convulsions

Pentylenetetrazole (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 24 h 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.) (24 h 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.) (24 h 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 24 h 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 ^{1}H NMR and ^{13}C NMR spectra showed that SPEC presented analytical and spectroscopic data in full agreement with its assigned chemical structure [Figure 1]. The chemical purity of the compound was determined by analysis of the ^{1}H NMR and ^{13}C NMR.

SPEC at doses of 0.1, 0.5 and 1.0 mg/kg (p.o.) showed behavioral changes in animals 24 h after of treatment: Decrease of spontaneous activity, palpebral ptosis, ataxia and analgesia. 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) 24 h 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].

Table 1 shows that (PTZ) consistently induced clonic

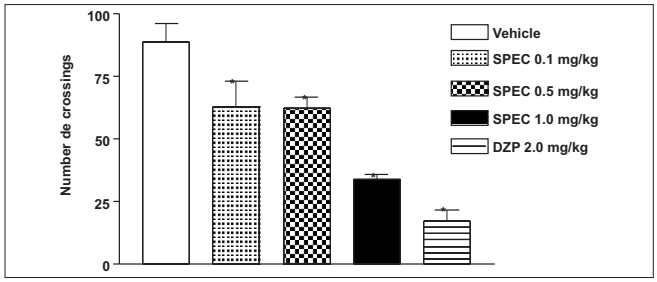

Figure 2: Effects of iso-6-spectaline (0.1, 0.5 and 1.0 mg/kg, p.o., SPEC) or diazepam (DZP, 2.0 mg/kg, i.p.) on locomotor activity of mice. The parameters evaluated were the total number of pulses of crossings in activity cage. Values are mean ± S.E.M. for seven mice per group. *$P < 0.001$ as compared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

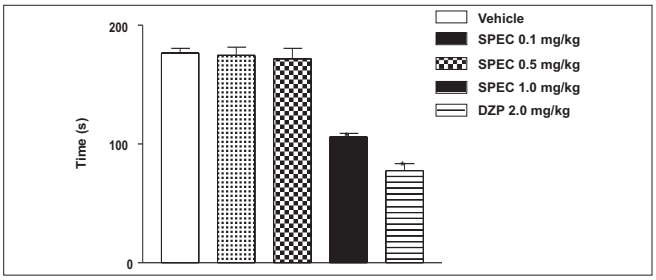

Figure 3: Time (s) on the Rota-rod observed in mice after oral route treatment with Vehicle (control), iso-6-spectaline (0.1, 0.5 and 1.0 mg/kg, p.o., SPEC) or DZP (2.0 mg/kg, i.p.). The motor response was recorded for the following 180 s after drug treatment. Values are mean ± S.E.M. for seven mice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

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 and reduced in 30% the mortality rate in PTZ model. 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 and reduced in 50% the mortality rate in PIC model induced by PIC significantly when compared to the control ($P < 0.001$) [Table 2].

The anticonvulsants 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. Previous studies showed that *Senna spectabilis* is used as an anti-inflammatory, analgesic, laxative, purgative, antimicrobial and antiulcerogenic by popular medicine in Brazil.[3,4] In neuropharmacological behavioral screening, the animals treated with SPEC showed decrease of response to the touch, palpebral ptosis, ataxia and analgesia. These results suggest that SPEC could exert a depressive activity in rodents.[2] indicating effects on the CNS similar to iso-6-cassine isolated from *Senna spectabilis* var. excelsa (Schrad) in mice and others drugs that reduce the brain function.[5,10, 19-23]

The reduction of the locomotor activity observed after treatement with SPEC an 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 SEPC could show a

Table 1: Effects of iso-6-spectaline (0.1, 0.5 and 1.0 mg/kg, o.r., 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[b]	10	20[e]
SPEC 1.0	1.0	582.5 ± 33.5[c]	80[d]	30
SPEC + FLU	1.0 + 10	271.8 + 38.9	0	10
DZP	2	862.9 ± 10.0[c]	100[d]	100[d]
DZP + FLU	2 + 10	171.2 + 15.2	0	15

Values are the mean ± S.E.M. for 7 mice (per group). [a]p<0.05 (ANOVA followed by t-Student-Neuman-Keuls test), significantly different from control. [b]P<0.01 (ANOVA followed by t-Student-Neuman-Keuls test), significantly different from control. [c]P<0.001 (ANOVA followed by t-Student-Neuman-Keuls test), significantly different from control. [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

neuro-sedative activity or a profile for a hypnotic drug. The results of present study no suggest these effects.

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]

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<0.001). Previous studies about PTZ model [1,26] showed that this convulsivant agent may be exerting its convulsing effect by inhibiting the activity of gamma aminobutyric acid (GABA) at gabaergic ($GABA_A$) receptors. The literature reports that GABA is the inhibitory neurotransmitter implicated in human epilepsy. The enhancement and inhibition of GABA neurotransmission will attenuate and enhance convulsion, respectively.[27]

Our results showed that SPEC delayed the occurrence of PTZ convulsion and decreased the mortality rate in mice, it is probable that it may interfere in GABAergic mechanisms to exert its anticonvulsant effect in this epilepsy model..

In order to determine the anticonvulsant effects of SPEC, a specific antagonist of the benzodiazepine site in the

GABA-benzodiazepine receptor complex, was used in experiments.[16]

The results obtained from PTZ model in mice pretreated with flumazenil suggest that this compound could facilitate the GABAergic system activity. The significant effects on the motor coordination, in doses of 1.0 mg/kg, might support this hypothesis.[28]

Previous studies showed that picrotoxin, a $GABA_A$-receptor antagonist, produces seizures by blocking the chloride-ion channels, preventing the entry of chloride ions into the cerebral regions and, consequently, inhibitory transmission of central nervous system.[29] Therefore, the findings of the present study suggest that SPEC might have inhibited attenuated the PIC-induced convulsions and reduced in 50% the mortality rate in this epilepsy model.[30]

In conclusions, the results suggest anticonvulsant effects of iso-6-spectaline from *Senna spectabilis*. The possible behavioral effects produced by iso-6-spectaline are not clear, however, the GABAergic, noradrenergic and setoninergic neurotransmitter systems might be involved. So, future studies will be required for elucidation of these action mechanisms.

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