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Heteropterys aphrodisiaca (extract BST0298): a Brazilian plant that improves memory in aged rats

S.M.P. Galvão, L.C. Marques, M.G.M. Oliveira, E.A. Carlini *

Departamento de Psicobiologia, Universidade Federal de São Paulo, Rua Botucatu, 862, 1º andar, Vila Clementino, CEP 04023-062, São Paulo, Brazil

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Abstract

Literature report is lacking on pharmacological studies of the plant *Heteropterys aphrodisiaca*, endemic to the scrublands of Brazil. The present study was carried out to investigate the effects of oral dosing with extract BST0298 from this plant, on learning and on memory, in young (3–6-month-old) and aged (20–28-month-old) rats. The aged animals presented significant memory deficits in both the passive avoidance and T-maze left/right discrimination tests. Treatment for 7 days (50 mg/kg) or 26 days (100 mg/kg) with extract BST0298 restored the memory deficits in the passive avoidance test. However, no improvement in memory was observed after acute administration of extract BST0298 (100 mg/kg) in aged rats. An improvement in learning was also observed in the left/right discrimination test in aged rats treated for 109 days with BST0298 at a dose of 50 mg/kg. These results suggest that treatment for 7 days or more with *H. aphrodisiaca* improves learning and memory deficits in aged rats.

Keywords: *Heteropterys aphrodisiaca*; Ageing; Memory; Medicinal plants; Aged rats

1. Introduction

'Nó-de-cachorro' was described by Hoehne (1920) as a plant with stimulant and aphrodisiac properties and was given the botanical name *Heteropterys aphrodisiaca* O. Mach. (Malpighiaceae) by Othon Machado in 1949 (Machado, 1949). The plant is found mainly in the scrubland regions of the States of Mato Grosso and Goiás in Brazil (Pio Corrêa, 1984) and is also known as 'Nó-de-porco' and 'Cordão-de-São-Francisco' (Pott and Pott, 1994).

Among the general population, *H. aphrodisiaca* roots are used as an 'aphrodisiac', 'tonic' or 'stimulant' and in the treatment of 'nervous debility' and 'nervous breakdown' (Pio Corrêa, 1984; Pott and Pott, 1994). These terms, used popularly to refer to symptoms with a broad meaning, are very imprecise and are open to various interpretations. Based on the results of ethnobotanical field studies, Rizzini (1983) affirmed that the root of *H. aphrodisiaca* is a stimulant and this plant is one of 65 psychoactive plant species found in Brazil. Other species included guaraná (*Paullinia cupana* Mart. Sapindaceae), which is used by the general population as a tonic and has become the subject of many studies (Galduróz and Carlini, 1994, 1996; Espinola et al., 1997; Mattei et al., 1998). Acute and chronic administration of guaraná in animals has been shown to restore impaired memory induced by administration of scopolamine (Espinola et al., 1997). Guaraná has also been shown to exert an antioxidant effect by inhibiting the process of lipid peroxidation in vitro (Mattei et al., 1998).

Guaraná and *H. aphrodisiaca*, as well as other plants considered as a tonic by the general population, are taken chronically (in a continuous manner) with the aim of improving general health and for their preventive effect in relation to a wide range of health problems, as are adaptogenic plants.

The concept of adaptogenic effect has been developed during the past 30 years as the scientific basis for the popular use of plants as a 'tonic', but which do not show any effects when studied by classical methods (Brekhman and Dardymov, 1969; Carlini, 1991). These

* Corresponding author. Fax: +55-11-5084-2793.
E-mail address: carlini@psicobio.epm.br (E.A. Carlini).

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plants, however, promote a non-specific increase in the body's resistance to various naturally occurring harmful physical, chemical and biological agents (Carlini, 1991; Wagner et al., 1994; Rege et al., 1999).

Various studies have shown that adaptogenic plants affect the nervous system, improving cognitive functions by slowing down the deterioration of cognitive processes observed in elderly people. *Panax ginseng*, an adaptogenic plant, has been shown to restore learning and memory deficits in old rats in a two-way active avoidance test (Petkov and Mosharrof, 1987) and in the eight-arm radial maze (Nitta et al., 1995) and also to restore impaired acquisition of ethanol-treated rats in passive avoidance performance (Lee et al., 2000). Multiple formulations of plants used in traditional Chinese medicine, such as S-113m and Kamikihi-To, have also been shown to have beneficial effects on learning and memory in both young and old mice performing passive avoidance and two-way active avoidance tests (Nishizawa et al., 1991; Nishiyama et al., 1995, 1996).

This information led us to investigate the effects of extract BST0298 prepared from the roots of *H. aphrodisiaca* on the memory and learning capacity of aged rats.

2. Materials and methods

2.1. Animals

The animals used were male Wistar rats, aged 3–5 months (young) and 19–28 months (old) at the start of the experiment. They were housed in plastic cages in groups of four to five and kept in a room with a controlled temperature (23 ± 1 °C) and light:dark cycle (lights on from 07:00 to 19:00 h). Food and water were freely available.

2.2. Plant material

Roots of *H. aphrodisiaca* were collected in March, 1996, in Mato Grosso State, Brazil and identified by Dr Miramy Macedo, curator of the herbarium of the Federal University of Mato Grosso. A voucher herbarium specimen of the plant was deposited in the herbarium of the Federal University of Mato Grosso UFMT under acquisition number 219.

2.3. Preparation of extract BST0298

The roots were crushed and powdered using a grinding mill. The standardized extract, designated BST0298, was prepared by turbolysis, as described by Voigt (1993). For this purpose, the extract was concentrated by evaporation to $\approx 10\%$ of its original volume and was then lyophilized. Each 100 g of powdered roots yielded 21 g of the lyophilized material. BST0298 solution was prepared by dissolving the lyophilized material in distilled water, in order to deliver through oral route (gavage) the desired dose of 0.1 ml per 100 g body weight; for example, a 50 mg/kg dose in a 500 g animal would require 0.5 ml of a 50 mg/ml solution.

2.4. Preliminary phytochemical qualitative analysis

The chemical constituents of the extract were investigated using the usual pharmacognostic techniques, as recommended by Harbone (1984).

2.5. Passive avoidance test

2.5.1. Apparatus

The passive avoidance apparatus consisted of two boxes, one illuminated, the other kept dark, measuring $30 \times 21 \times 30$ cm and connected by a door. The floor of the dark box consisted of a metal grid connected to a Grason-Stadler 700 shock generator, which was used to apply the shock to the animals' paws. The shock lasted 1 s and varied between 0.4 and 0.6 mA, depending on the experiment.

2.5.2. Experiment 1: treatment of aged naïve rats for 26 days

The purpose of this experiment was to verify whether a long-term treatment could improve the performance of aged rats in a passive avoidance task. Two groups of naïve old rats, aged between 19 and 22 months at the start of the experiment, were treated with 100 mg/kg extract BST0298 ($N = 29$) or water ($N = 24$) for 5 days a week, for 26 days. A group of young 3-month-old rats ($N = 15$) received water under the same schedule. On the twenty-ninth and thirtieth day, 3 days after the last extract administration, the animals were evaluated in the passive avoidance test.

Each rat was placed in the lit compartment of the passive avoidance apparatus with the door closed. After 10 s, the door was opened and the time taken for the animals to cross into the dark compartment was recorded (acquisition training). As soon as the animal entered the dark compartment, the door was closed and five 0.6 mA shocks were administered at 15-s intervals. Immediately afterwards, the animal was removed from the apparatus. The individual who performed the experiment did not know which treatment (water or plant) each animal had received.

After 24 h, each animal was again placed in the lit compartment with the door closed. After 10 s, the door was opened and the time taken for the animals to cross into the dark compartment was recorded (retention test). The maximum time allowed for an animal to cross into the dark compartment was 300 s (Bueno et al., 1993).

2.5.3. Experiment 2: treatment of naïve aged rats for 7 days

This experiment was conducted in order to verify whether a smaller dose and a shorter period of treatment would also be effective. Two groups of rats, aged 21 months at the start of the experiment, were treated for 7 days with 50 mg/kg extract BST0298 ($N = 12$) or water ($N = 12$). A group of young 3-month old rats ($N = 10$) received water under the same schedule. On the eighth and ninth days, 24 h after the last extract administration, the animals were evaluated in the passive avoidance test using the same training and test procedures as in Experiment 1, except for the time limit allowed for crossing into the dark compartment, which was increased to 600 s.

2.5.4. Experiment 3: acute treatment of naïve aged rats

Two groups of naïve old rats, aged between 20 and 28 months at the start of the experiment, were treated with 100 mg/kg extract BTS0298 ($N = 10$) or water ($N = 9$). A group of young 5-month-old rats ($N = 11$) received water.

After treatment (2 h), the rats were submitted to the same experimental procedure as described in Experiment 1, but the time limit for crossing to the dark compartment was 600 s.

2.6. Left/right discrimination test

2.6.1. Apparatus

The animals were individually trained and tested in a T maze with arms 60 cm long by 10 cm wide and walls 3 cm high. The maze was raised 1 m above the floor. A 150-mg milk-caramel sweet was placed at the end of each arm as reinforcement. The apparatus was placed in the centre of a room that contained spatial cues and was cleaned with 20% alcohol after each run to prevent olfactory cues during training.

2.6.2. Experiment 1: chronic treatment of naïve old rats

The same animals employed in Experiment 1 were used. Following the passive avoidance test, the animals were left for 25 days without treatment, after which they were treated with 50 mg/kg extract BST0298 ($N = 19$) or water ($N = 22$) for 5 days a week. A group of young 3-month-old rats ($N = 15$) received water under the same schedule. On the 37th day of treatment, the animals started the learning phase in the T maze. The treatment was given in the morning and the training in the afternoon (between 13:00 and 18:00 h).

The animals were placed individually in the maze for 5 min without the presence of reinforcement. This procedure was performed on alternate days and was repeated five times. Following this test, the reward was placed at the end of each of the maze arms and the animals, which had been starved for the preceding 20 h, were placed individually in each arm for 1 min. This procedure was performed on alternate days and was repeated four times.

In the performance of the T maze left/right discrimination task (Pisa and Cyr, 1990), 50% of the rats from each group were randomly selected and reinforcement placed on the right arm, while for the other 50%, reinforcement was placed on the left arm. The reinforced (correct) arm remained constant throughout the training period. On alternate days, the animals were submitted to training sessions, each of which was composed of six consecutive runs. Each run started with the animal being placed at the start-arm and if it chose the correct side-arm, it received the reward. If the animal chose the incorrect side-arm, it was confined in the arm for 30 s without a reward. The animal was then placed at the start-arm for the next run. The time limit for the animal to enter one of the side-arms was 5 min. The rats were trained until they achieved the learning criteria of at least two consecutive sessions without an error (12 correct runs) or until they had had 20 training sessions (the training ceiling). The entire experiment took 109 days to complete. During this period, body weights were recorded weekly and blood analysis and anatomo-pathological examinations were performed on the viscera, to detect eventual toxic effect of the extract.

2.7. Statistical analysis

The latency to entry into the dark box in the passive avoidance test was analyzed using the Kruskal–Wallis test (one-tailed), which was followed, when necessary, by the Mann–Whitney *U*-test (one-tailed).

The number of sessions required to achieve the learning criteria in the left/right discrimination task was analyzed using an ANOVA test and was followed, when necessary, by Duncan's post hoc test.

3. Results

3.1. Preliminary qualitative phytochemical analysis

The following compounds were detected in the extract: flavonoid glycosides, cardiac glycosides with steroidal nucleus, aromatic glycosides, cardiac glycosides with pentagonal lactonic ring, saponins, hydrolyzable and condensed tannins and aliphatic nitro compounds.

3.2. Passive avoidance test

3.2.1. Experiment 1: treatment of naïve aged rats for 26 days

As shown in Fig. 1, as expected, there was no statistical difference between the groups in the acquisition

phase of the passive avoidance task (Kruskal–Wallis: $H = 2.4068$; $P = 0.15$). However, in the retention phase, statistically significant differences were found between the groups (Kruskal–Wallis: $H = 10.9536$; $P = 0.0021$). Thus, 24 h after the application of the shock, the animals in the young control group presented a high latency for entry into the dark compartment. On the other hand, the animals in the aged control group entered the dark compartment with a much lower latency. The difference between the two control groups (young and old) was statistically significant (Mann–Whitney: $U = 74$; $P = 0.001$) (Fig. 1). In contrast, the aged rats treated with 100 mg/kg extract BST0298 had a statistically significant higher latency than the aged control animals (Mann–Whitney: $U = 160$; $P = 0.037$).

3.2.2. Experiment 2: treatment of aged rats for 7 days

In the acquisition phase, there was no statistically significant difference between the groups (Kruskal–Wallis: $H = 4.8868$; $P = 0.08$). However, as shown in Fig. 2, the groups differed in the retention phase (Kruskal–Wallis: $H = 9.0777$; $P = 0.005$). The aged control rats entered the dark compartment with a lower latency, in comparison to the young control rats (Mann–Whitney: $U = 19$; $P = 0.0025$). On the other hand, the aged rats treated with 50 mg/kg extract BTS0298 showed better retention, with statistically significant higher latency than the aged control animals (Mann–Whitney: $U = 39$; $P = 0.026$).

3.2.3. Experiment 3: acute treatment of aged rats

Fig. 3 shows the performance of the animals in the acquisition training phase and in the retention test. In the acquisition phase, the young and aged controls and the aged treated animals all showed the same performance (Kruskal–Wallis: $H = 3.1827$; $P = 0.10$). In the retention phase, a statistically significant difference was observed between the groups (Kruskal–Wallis: $H = 5.2201$; $P = 0.036$). The animals of the aged control group entered the dark compartment with a lower latency. On the other hand, the animals in the young control group showed a higher latency in entering the dark compartment. The difference between the two control groups (young and aged) was statistically significant (Mann–Whitney: $U = 25$; $P = 0.029$). However, acute treatment of the aged rats with extract BST0298 ($N = 10$) also showed memory impairment in the passive avoidance task when compared with the young control group (Mann–Whitney: $U = 27$; $P = 0.023$) (Fig. 1).

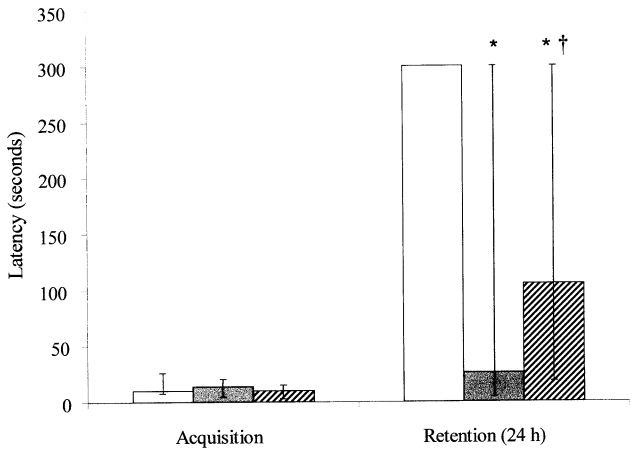

Fig. 1. Latency for the acquisition and retention (24 h later) phases of the passive avoidance test by young control rats (□), aged control rats (▩) and aged rats treated with 100 mg/kg extract BST0298 for 26 days (▨). The values are expressed as medians. * Indicates statistical difference from the young control group. † Indicates statistical difference from the aged control group.

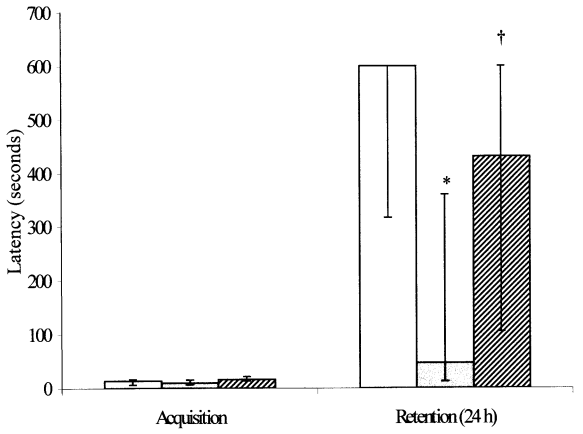

Fig. 2. Latency for the acquisition and retention (24 h later) phases of the passive avoidance test by young control rats (□), aged control rats (▩) and aged rats treated with 50 mg/kg extract BST0298 for 7 days (▨). The values are expressed as median. * Indicates statistical difference from the young control group. † Indicates statistical difference from the aged control group.

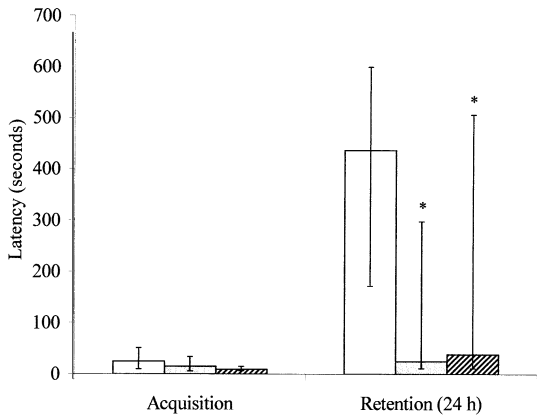

Fig. 3. Latency for the acquisition and retention (24 h later) phases of the passive avoidance test by young control rats (□), aged control rats (▩) and aged rats treated acutely with 100 mg/kg extract BST0298 (▨). The values are expressed as medians. * Indicates statistical difference from the young control group.

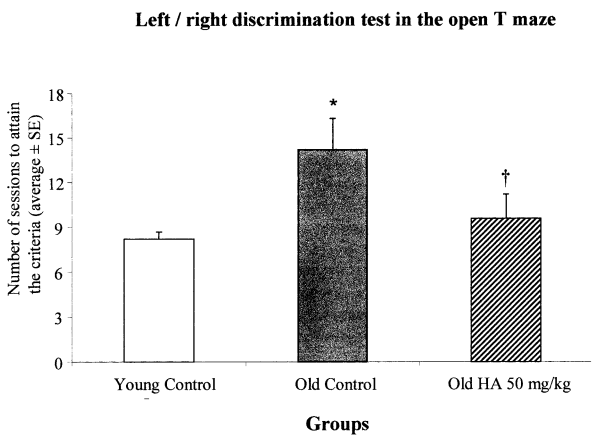

Fig. 4. Number of sessions required to attain the learning criteria in the T maze by young control rats (□), aged control rats (▩) and aged rats treated with 50 mg/kg extract BST0298 (▨) for 109 days. The values are expressed as mean ± S.E. * Indicates statistical difference from the young control group. † Indicates statistical difference from the aged control group.

3.3. Left/right discrimination test

3.3.1. Experiment 1: chronic treatment of old naïve rats

As can be seen in Fig. 4, there was a statistically significant difference between the groups (one way ANOVA: $F\ 2.29 = 5.8973$; $P = 0.007$). Duncan's post hoc test ($P = 0.01$) showed that the rats of the aged control group needed a greater number of sessions to attain the learning criteria when compared with the young control group. The aged rats treated chronically with extract BST0298 showed a significantly better performance when compared with the aged control rats (Duncan: $P = 0.03$) and similar performance to the young control group (Duncan: $P = 0.44$).

4. Discussion and conclusions

Many authors have described deteriorations in learning and memory which occur with aging and have correlated them with anatomical and biochemical alterations in the central nervous system (Kubanis and Zornetzer, 1981; Bartus et al., 1982; Perry et al., 1999). In this context, it is possible to study drugs that may reduce or restore learning and impaired memory in old age (Hock, 1987; Bartus, 1990; Ohta et al., 1991). In the present study, aged rats and young control animals were treated for 7 or 26 days either with water or with a 50 or 100 mg/kg extract BST0298 and were evaluated in the passive avoidance apparatus (Figs. 1 and 2). The treatment with extract BST0298 increased the performance of aged rats in this memory task. This effect, however, was not observed following acute treatment with extract BST0298 at 100 mg/kg (Fig. 3). It is pertinent that the improvement obtained following 26 days of extract administration was observed 3 days after the last treatment; similarly, the results following 7 days of extract administration were observed 24 h after the treatment. This suggests that the effect of the extract went beyond any acute pharmacodynamic property it may possess and that an enduring change probably took place in the central learning and memory mechanism.

The memory of laboratory animals in this passive avoidance model is also improved by drugs which stimulate the CNS, such as caffeine (Cestari and Castellano, 1996), nootropics, such as oxiracetam, aniracetam and piracetam (Spignoli and Pepeu, 1987), precursors of acetylcholine (Hock, 1987; Lopez et al., 1991), certain plants, such as *P. ginseng*, *Withania somnifera* and *Biota orientalis* and chronic treatment with combinations of oriental plants (S-113m and Kamikihi-To) (Nishizawa et al., 1991; Nishiyama et al., 1995, 1996; Lee et al., 2000).

The results obtained with the T maze confirmed the positive effects of extract BST0298. The aged rats treated with the 50 mg/kg extract for 109 days attained the learning criteria in a number of sessions practically equal to the number required by the young animals and well below the number required by the aged control animals (Fig. 4). In this paradigm, the BST0298 extract restored the memory impairment observed in aged rats. The learning difficulties presented by aged rats in maze tasks have been well described in the literature, as have the beneficial effects of certain plants and substances. The positive effects of *P. ginseng* (an adaptogenic plant) in resorting the impairments to learning and memory induced by scopolamine (Yamaguchi et al., 1996) or related to age (Petkov and Mosharrof, 1987; Yamaguchi et al., 1997) have been well studied. Furthermore, drugs which inhibit the metabolism of acetylcholine, such as physostigmine (Ohta et al., 1991) and direct cholinergic agonists, such as aerocholine, oxitremorine and betanechol (Merlini and Pinza, 1989) also have beneficial effects on memory.

It is open to discussion whether or not the effects of the nó-de-cachorro extract could be attributed to one or more of its chemical constituents. It seems improbable that a cholinergic action could explain the effects of extract BST0298 on learning and memory as typical cholinergic effects, such as tremors and chromodacryorrhea (Espinola et al., 1999), which were not observed. It is possible that the effects were those typical of adaptogenic plants which act in non-specific ways and whose effects on learning and memory have yet to be explained. On the other hand, it is known that many plants protect against the effects of oxidative stress (Cavin et al., 1998; Sastre et al., 1998; Ravikumar and Anuradha, 1999) and that their antioxidant capacity is attributable to the presence of substances as flavonoids, tannins, saponines and others (Hässig et al., 1999; Ng

et al., 2000). In fact, the BST0298 extract possesses a rather marked anti-oxidant property (Mattei et al., in press). However, as the extract was effective in aged animals, in which the loss of learning and memory abilities had already occurred, it is unlikely that an antioxidant preventive effect is responsible. Finally, among other biological effects which should also be considered is a psycho-stimulant action, which could positively affect learning and memory in animals, as has been shown with amphetamine in the Lashley III maze task (Breda et al., 1969).

Some alternative explanations may be offered to explain the observed effect. Passive avoidance uses shock as motivation, so it is not possible to rule out the possibility of the treatment increasing shock sensitivity or decreasing locomotion activity of the aged animals. This possible effect on motor activity, however, could not explain the results observed in the T maze test since learning is not accessed through the animal's speed in running for food. Alternatively, chronic treatment could alter food-seeking motivation (raising the level of hunger). Further research is required in order to address these issues.

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References

Bartus, R.T., 1990. Drugs to treat age-related neurodegenerative problems. Geriatrics 38, 680–695.

Bartus, R.T., Dean, R.L., Beer, B., Lippa, A.S., 1982. The cholinergic hypothesis of geriatric memory dysfunction. Science 217, 408–417.

Breda, J.B., Carlini, E.A., Sader, N.F.A., 1969. Effects of chronic administration of (+)-amphetamine of the rat. British Journal of Pharmacology 37, 79–86.

Brekhman, I.I., Dardymov, I.V., 1969. New substances of plant origin which increase non-specific resistance. Annual Review of Pharmacology 9, 419–432.

Bueno, O.F.A., Oliveira, M.G.M., Pomarico, A.C., Gugliano, E.B., 1993. A dissociation between the proactive ECS effects on inhibitory avoidance learning and on classical fear conditioning. Behavioral and Neural Biology 59, 180–185.

Carlini, E.A., 1991. Efeito adaptógeno ou resistógeno de algumas plantas. In: Buchillet, D. (Ed.), Medicinas Tradicionais e Medicina Ocidental na Amazônia. Edições Cejup, Belém, PA.

Cavin, A., Hostettmann, K., Dyatmyko, W., Potterat, O., 1998. Antioxidant and lipophilic constituents of *Tinospora crispa*. Planta Medica 64, 393–396.

Cestari, V., Castellano, C., 1996. Caffeine and cocaine interaction on memory consolidation in mice. Archives Internationales de Pharmacodynamie et de Therapie 331, 94–104.

Espinola, E.B., Dias, R.F., Mattei, R., Carlini, E.A., 1997. Pharmacological activity of guaraná (*Paullinia cupana* Mart.) in laboratory animals. Journal of Ethnopharmacology 55, 223–229.

Espinola, E.B., Oliveira, M.G.M., Carlini, E.A., 1999. Differences in central and peripheral responses to oxitremorine in young and aged rats. Pharmacology Biochemistry and Behavior 62, 419–423.

Galduróz, J.C.F., Carlini, E.A., 1994. Acute effects of the *Paullinia cupana*, 'guaraná' on the cognition of normal volunteers. São Paulo Medical Journal 112, 607–611.

Galduróz, J.C.F., Carlini, E.A., 1996. The effects of long-term administration of guaraná on the cognition of normal, elderly volunteers. São Paulo Medical Journal 114, 1073–1078.

Harbone, J., 1984. Phytochemical Methods: a Guide to Modern Techniques of Plant Analysis, second ed. Chapman Hall, London, p. 288.

Hässig, A., Liang, W.X., Schwabl, H., Stampfli, K., 1999. Flavonoids and tannins: plant-based antioxidants with vitamin character. Medical Hypotheses 52, 479–481.

Hock, F.J., 1987. Drug influences on learning and memory in aged animals and humans. Neuropsychobiology 17, 145–160.

Hoehne, F.C., 1920. O que Vendem os Hervanários da Cidade de São Paulo. Casa Duprat, São Paulo.

Kubanis, P., Zornetzer, S.F., 1981. Age-related behavioral and neurobiological changes: a review with an emphasis on memory. Behavioral and Neural Biology 31, 115–172.

Lee, S.C., Moon, Y.S., You, K.H., 2000. Effects of red ginseng saponins and nootropic drugs on impaired acquisition of ethanol-treated rats in passive avoidance performance. Journal of Ethnopharmacology 69, 1–8.

Lopez, C.M., Govoni, S., Bergamaschi, S., Longoni, A., Giaroni, C., Trabucchi, M., 1991. Effect of a new cognition enhancer, alpha-glycerylphosphorylcholine, on scopolamine-induced amnesia and brain acetylcholine. Pharmacology Biochemistry and Behavior 39, 835–840.

Machado, O.X.B., 1949. Nova espécie do gênero *Heteropterys* Kunth. Rodriguésia 11–12, 113–119.

Mattei, R., Dias, R.F., Espínola, E.B., Carlini, E.A., Barros, S.B.M., 1998. Guaraná (*Paullinia cupana*): toxic behavioral effects in laboratory animals and antioxidant activity in vitro. Journal of Ethnopharmacology 60, 111–116.

Mattei, R., Barros, M.P., Galvão, S.M.P., Bechara, E.J.H., Carlini, E.A. *Heteropterys aphrodisiaca* O. Machado: effects of extract BST0298 on the oxidative stress of young and old rat brains, Phytotherapy Research (in press).

Merlini, L., Pinza, M., 1989. Trends in searching for new cognition-enhancing drugs. Progress in Neuropsychopharmacology and Biological Psychiatry 13, S61–S75.

Ng, T.B., Liu, F., Wang, Z.T., 2000. Antioxidative activity of natural products from plants. Life Sciences 66, 709–723.

Nishiyama, N., Chu, P.J., Saito, H., 1995. Beneficial effects of Biota, a traditional Chinese herbal medicine, on learning impairment induced by basal forebrain-lesion in mice. Biological and Pharmaceutical Bulletin 18, 1513–1517.

Nishiyama, N., Chu, P.J., Saito, H., 1996. An herbal prescription, S-113m, consisting of Biota, Ginseng and Schizandra, improves learning performance in senescence accelerated mouse. Biological and Pharmaceutical Bulletin 19, 388–393.

Nishizawa, K., Saito, H., Nishiyama, N., 1991. Effects of Kamikihi-To, a traditional Chinese medicine, on learning and memory performance in mice. Phytotherapy Research 5, 97–102.

Nitta, H., Matsumoto, K., Shimizu, M., Ni, X.-H., Watanabe, H., 1995. *Panax ginseng* extract improves the performance of aged Fischer 344 rats in radial maze task but not in operant brightness discrimination task. Biological and Pharmaceutical Bulletin 18, 1286–1288.

Ohta, H., Ni, X.H., Matsumoto, K., Watanabe, H., 1991. Working memory deficit in aged rats in delayed nonmatching to position task and effect of physostigmine on performance of young and aged rats. Japanese Journal of Pharmacology 56, 303–309.

Perry, E., Walker, M., Grace, J., Perry, R., 1999. Acetylcholine in mind: a neurotransmitter correlate of consciousness? Trends in Neurosciences 22, 273–280.

Petkov, V.D., Mosharrof, A.H., 1987. Age- and individual-related specificities in the effects of standardized ginseng extract on learning and memory (experiments on rats). Phytotherapy Research 1, 80–84.

Pio Corrêa, M., 1984. Diccionário das Plantas Úteis do Brasil e das Exóticas Cultivadas, vol. 5. Ministério da Agricultura/Instituto Brasileiro de Desenvolvimento Florestal, Rio de Janeiro, p. 293.

Pisa, M., Cyr, J., 1990. Regionally selective roles of the rat's striatum in modality-specific discrimination learning and forelimb reaching. Behavioral Brain Research 37, 281–292.

Pott, A., Pott, V.J., 1994. Plantas do Pantanal. EMBRAPA–SPI, Corumbá, p. 101.

Ravikumar, P., Anuradha, C.V., 1999. Effect of fenugreek seeds on blood lipid peroxidation and antioxidants in diabetics rats. Phytotherapy Research 13, 197–201.

Rege, N.N., Thatte, U.M., Dahanukar, S.A., 1999. Adaptogenic properties of six *Rasayana* herbs used in ayurvedic medicine. Phytotherapy Research 13, 275–291.

Rizzini, C.T., 1983. Efeitos psicotrópicos de plantas brasileiras parte II: aspectos botânicos. Ciência e Cultura (São Paulo) 35, 434–438.

Sastre, J., Millán, A., Asunción, J.G., Plá, R., Juan, G., Pallardó, F.V., Conner, E.O., Martin, J.A., Lefaix, M.T.D., Viña, J., 1998. A *Ginkgo biloba* extract (EGb 761) prevents mitochondrial aging by protecting against oxidative stress. Free Radical Biology and Medicine 24, 298–304.

Spignoli, G., Pepeu, G., 1987. Interactions between oxiracetam, aniracetam and scopolamine on behavior and brain acetylcholine. Pharmacology, Biochemistry and Behavior 27, 491–495.

Voigt, R., 1993. Pharmazeutische Technologie, seventh ed. Ullstein Mosby, Berlin, pp. 496–504.

Wagner, H., Nörr, H., Winterhoff, H., 1994. Plant adaptogens. Phytomedicine 1, 63–76.

Yamaguchi, Y., Higashi, M., Kobayashi, H., 1996. Effects of ginsenosides on impaired performance caused by scopolamine in rats. European Journal of Pharmacology 312, 149–151.

Yamaguchi, Y., Higashi, M., Kobayashi, H., 1997. Effects of ginsenosides on maze performance and brain choline acetyltransferase activity in scopolamine-treated young rats and aged rats. European Journal of Pharmacology 329, 37–41.