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Original article

Effects of *Boswellia Papyrifera* Gum Extract on Learning and Memory in Mice and Rats

*[1,2]Amir Farshchi, [1,2]Golbarg Ghiasi, [3]Samireh Farshchi, [4]Peyman Malek Khatabi

Abstract

Objective(s)
Learning is defined as the acquisition of information and skills, while subsequent retention of that information is called memory. The objective of the present study was to investigate the effect of aqueous extract of *Boswellia papyrifera* on learning and memory paradigms in mice and rats.
Materials and Methods
This study was held at the Department of Pharmacology, Faculty of Pharmacy, Kermanshah University of Medical Science, Kermanshah, Iran from September 2006 to March 2008. Male Wistar rats and male NMRI mice were randomly divided into control, *B. papyrifera* treated (50, 100, 150 mg/kg, p.o.), and piracetam (150 mg/kg) groups. Radial arm maze (RAM) and Morris water maze (MWM) were the screening tests used to assess the activity of *B. papyrifera* extract.
Results
The mice treated with *B. papyrifera* (50, 100 and 150 mg/kg) or piracetam (150 mg/kg) showed a decrease in number of days required to learned ($P< 0.05$) and time taken to find food by the learned mice in radial arm maze ($P< 0.01$). In Morris water maze, rats treated with the above mentioned doses showed dose dependent improvement in spatial learning. Escape latency during swimming in water maze in piracetam and *B. papyrifera* treated animals was significantly lower ($P< 0.01$) than control. Swimming distance was also significantly lower ($P< 0.05$) in the treated groups.
Conclusion
The results show facilitation of spatial learning and memory processes and thereby validate *B. papyrifera* traditional use of intelligence improving. The presence of alkaloids, flavonoids and saponins might be responsible for this activity of *B. papyrifera*.

Keywords: *Boswellia papyrifera*, Cognition, Morris water maze, Radial arm maze, Spatial learning and Memory

1- School of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran
2- Department of Pharmocoeconomy and Pharmaceutical Management, Shcool of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
3- Department of otolaryngology, Amiralam Hospital, Tehran University of Medical Sciences, Tehran, Iran
4- Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khoramabad, Iran
*Corresponding author: Tel: +98-918-8563290; Fax: +98-831-8369850; email: farshchi_a@razi.tums.ac.ir

Introduction

Learning is the process of acquiring knowledge about the world and memory is the retention of the acquired knowledge, which can be retrieved as and when, required (1). Poor learning abilities, impaired memory, lower retention and slow recall are the common problems in stressful situations. Moreover, age, stress and emotions are conditions that may lead to impaired learning, memory loss, amnesia, and dementia or to more ominous threats like Schizophrenia and Alzheimer's disease (2). As memory involves many interwoven brain functions, there are several different types of memories and virtually any type of brain damage can result in one or other type of memory loss (3). Working memory is a type of memory which refers to storage and manipulation of the information necessary for complex cognitive tasks like language, comprehension, learning and reasoning (4). Piracetam, the prototype of the so-called 'nootropic' drugs (5), is used in many countries to treat cognitive impairment in aging, brain injuries, as well as dementia (6, 7). Piracetam is used as protective agent because of its antioxidant properties (8-12). Additionally, *Boswellia papyrifera*, an Iranian folk medicinal plant, has been reported traditionally to have beneficial effects like analgesia, antiinflammation, antitumor, antirheumatism, improving intelligence, etc (13). However, its effects on spatial learning and memory have not been scientifically documented so far. In the present study, effects of *B. papyrifera* on spatial learning and memory using two procedures, namely radial arm maze (RAM) and Morris water maze (MWM), have been investigated.

Materials and Methods

Preparation of B. papyrifera extract

Aqueous extract of *B. papyrifera* was received as a gift sample in September 2006 from Goldaru phytolaboratory, Isfahan, Iran and authenticated by the School of Agricultural Sciences, Razi University, Kermanshah, Iran. *B. papyrifera* gum was extracted with distilled water for 24 hr and concentrated. The concentrated mass was washed with petroleum ether several times to remove the resinous part. This mass was diluted with distilled water, filtered using Whatman No. 1 filter paper and concentrated and dried to get a fine powdered form of the extract. This powdered extract was dissolved in an appropriate quantity of normal saline and administered orally with oral feeding needle. The standard piracetam liquid was purchased from Darou Pakhsh Pharmaceutical Company, Tehran, Iran.

Animals

Male NMRI mice (25-30 g) and male Wistar rats (200-250 g) were provided by the Iranian Razi Institute and kept at the Laboratory Animal Centre in Pharmacy School, Kermanshah University of Medical Sciences, Iran. Animals were housed in standard cages with free access to food (standard laboratory rodent's chow) and water *ad libitum*. The animal house temperature was maintained at 23±3 °C with a relative humidity and 12 hr light/dark cycle (light on from 06:00 to 18:00 hr). The ethical guidelines for the investigation of experimental animals were followed in all tests. All efforts were made to minimize animal suffering and to reduce the number of animals. Animals were transferred to the laboratory at least one hour before the start of the experiment and all experiments were carried out from 08:00 am to 16:00 pm.

Treatment

Mice and rats were divided into five groups (ten animals in each) for RAM or MWM tests, respectively. The following groups were designed: Animals received normal saline (10 ml/kg, p.o.) as sham BP treated, or oral dose of 50, 100, and 150 mg/kg of *B. papyrifera* extract and positive control group received piracetam (150 mg/kg) orally for comparison as a reference standard (6). Normal saline, *B. papyrifera* or piracetam were administrated 30 min before the tests. Animals were tested everyday for either RAM or MWM performance.

Radial arm maze (RAM)

Locally fabricated wooden radial arm maze elevated 50 cm above the floor consisting of

an octagonal central hub 36 cm in diameter with eight radial arms was used. Each arm 43 cm long, 15 cm wide with 12 cm sides, had small black plastic cups mounted at 30 cm from the central hub (14, 15). The mice were trained for RAM performance by conducting daily training trial which consisted of two sessions wherein one food pellet was placed in fixed arm and then in the variable arm to record the effect of extract on spatial reference and spatial working memory respectively. Mice maintained at 85% of their total diet were placed individually in the central hub and were allowed to choose the arm freely to get the food with upper cut off limit of 300 sec. The time taken by each mouse to find the food along with number of re-entries was considered to assess RAM performance. Mouse was considered to be learned when found the food with maximum one re-entry for three consecutive days. The number of days required for making the mice learned and the latency to find the food along with number of initial correct entries (i.e. before first re-entry) of learned mouse were recorded as the effects of the drug on learning and memory process. One-hour interval was kept between the spatial reference and spatial working memory evaluation. The apparatus was cleaned with damp cloth after each trial to avoid place preference and the influence of olfactory stimuli (14-17).

Morris water maze task (MWM)

MWM was constructed from a circular black colored water tank, 140 cm in diameter and 80 cm in height that was located in the center of small room and was surrounded by numerous extramaze cues on the wall in the room. The tank was divided into four quadrants (N, E, W and S) and filled with water 40 cm in depth. The experimenter stood in the southwest corner of the room. Invisible round disk platform (made of Plexiglas) 10 cm in diameter was used and located 1cm beneath the surface of the water. In the first 4 days of experiment, location of platform was constant throughout the sessions (see below). An automated infrared tracking system (CCTV B/W camera, SBC-300 (P), Samsung Electronic Co, Ltd, Korea) recorded the position of the rat in the tank. The camera was mounted 2.5 m above the central surface of the water (18).

A) Handling

Each rat received once daily, 10 min handling period for three days, after which the animals were trained for two days to stand on the platform. On the first day, rats were placed on the platform which was at the center of the tank without water for 60 sec, and on the second day, the rats were placed again on the platform under the same conditions but the tank was filled with water, room temperature (25±2 ºC). When the rat climbed off the platform, the experimenter guided the rat to go back onto the platform (19).

B) Training procedure

Extra maze landmarks (window, door, etc.) in the room were spatial cues for learning of platform's position for animals. The position of the platform was fixed throughout the experiments. The platform was located in the north-west quarter of MWM tank with 20 cm distance from the edge of the tank, and 1 cm beneath the surface of water. Each rat was tested for 5 sessions. Each session consisted of 4 trials in a day. In the first sessions, a trial began by releasing the rat into the water facing the wall of the tank from one of the four quadrants (N, S, E or W). The sequence of starting location was chosen in a pseudorandom manner by computer in such a way that the starting location was different from the immediate preceding trial. The trial was stopped when the rat found the platform or 60 sec after start of the trial. If the rat could not reach the platform within 60 sec, the experimenter led the rat to the platform and the rat remained on the platform for 30 sec, then released into the water from the next starting location. After the last trial in each session, the rat was towel-wiped and placed in a drying chamber for 5 to 15 min and then returned to the home cage. For evaluation of accuracy and validity of initial learning, probe trial was performed on the fifth day, in which, platform was expelled and animal during one session (consisting of 4 trials) was released into water exclusively from one of the above mentioned

directions (East) that was determined by computer for all rats (18).

Preliminary phytochemical screening

The *B. papyrifera* extract was screened for alkaloids, flavonoids, triterpenoids and saponins by thin layer chromatography (20). In order to chemically screen the extract, Dragendorff's reagent (potassium bismuth iodide) was used for alkaloids, Mg^{2+} and HCl for flavonoids, Liebermann–Burchard method for terpenoids, and the ability to produce foam for saponins.

Acute toxicity

Six groups of rats of both sex (ten animals per group, five females and five males) and weighing about 200-250 g were administered orally a single dose of either 2, 3, 4 and 5 times of effective dose of aqueous extract of *B. papyrifera*. Then rats were observed for gross behavioral, neurologic, autonomic and toxic effects at short time intervals for 24 hr. Food consumption, fecal matter and urine were also examined at 2 hr and then at 6 hr intervals for 24 hr (21).

Statistical analysis

The data was expressed as mean±SEM. Statistical analysis was performed using one way analysis of variance (ANOVA) and two-way repeated measures followed by Tukey's test for multiple comparisons. $P<0.05$ was the critical criterion for statistical significance.

Results

Radial arm maze (RAM)

B. papyrifera (100 and 150 mg/kg) showed significant reduction in number of days required to make the mice learned in both spatial reference (13.3±0.1, 10.1±0.8) as well as spatial working memory (15.6±0.2, 13.2±0.9). The effect was found to be dose dependent in the former model only. On the contrary, similar doses showed dose dependent reduction in latency to find the food by the learned mice only in spatial working memory (72.3±1.6, 53.9±1.3) when compared to control mice (80.6±2.5). *B. papyrifera* pretreatment did not show any significant ($P>0.05$) change in the number of initial correct entries in either model at any dose level. Also in memory parameters of RAM, difference between *B. papyrifera* 150 mg/kg and piracetam 150 mg/kg wasn't statistically significant ($P>0.05$) (Table 1).

Morris water maze (MWM)

Evaluation of escape latency and swimming speed during training days

Results indicate that *B. papyrifera* administration reduces escape latency during training days in a dose dependent fashion. Also there were differences among experimental groups in the second and fourth days of training. On these days, escape latencies in *B. papyrifera* groups were less than that of control group. This difference was statistically significant in the fourth day of training ($P<0.01$), while there wasn't any statistically significant difference ($P>0.05$) between *B. papyrifera* (150 mg/kg) and piracetam group in none of the four training days (Figure 1). Results also indicate that there was a difference in swimming speed among experimental groups. Post-hoc analysis showed that differences between piracetam group ($P<0.01$), *B. papyrifera* 100 mg/kg ($P<0.05$) and BP 150 mg/kg ($P<0.01$) in comparison with control were significant. Difference in swimming speed between *B. papyrifera* (150 mg/kg) and piracetam (150 mg/kg) wasn't statistically significant ($P>0.05$) (Figure 2).

Table 1. Effect of *B. papyrifera* extract and piracetam on radial maze task performance in mice.

Treatment (mg/kg)	Spatial reference			Spatial working		
	Days to make mice learned	Latency to find food (sec)	Number of initial correct entries	Days to make mice learned	Latency to find food (sec)	Number of initial correct entries
Control	16.1±0.2	55.8±1.2	6.9±0.5	18.2±2.1	80.6±2.5	7.3±0.8
B. papyrifera -50	15.8±0.4	52.6±2.6	6.9±0.1	17.8±1.1	80.1±3.3	7.2±0.4
B. papyrifera -100	13.3±0.1*	40.2±0.9**	6.7±0.3	15.6±0.2**	72.3±1.6*	7.1±0.9
B. papyrifera -150	10.1±0.8**	32.3±1.9**	6.5±0.6	13.2±0.9**	53.9±1.3**	6.8±1.1
Piracetam-150	9.1±0.3**	28.7±1.0**	6.3±0.4	11.5±0.6**	41.5±0.7**	6.7±1.0

Values are expressed as mean±SEM (n= 10).*$P<0.05$, **$P<0.01$ vs. control

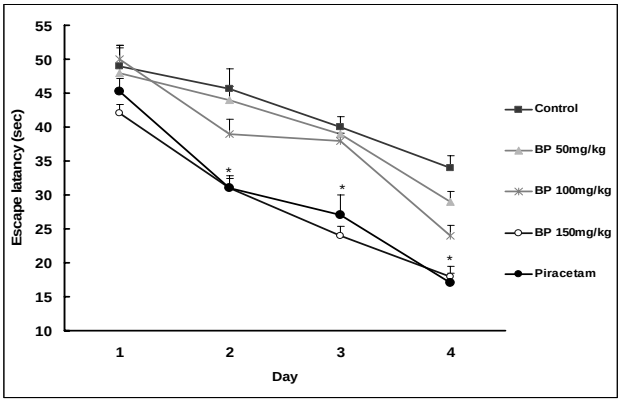

Figure 1. Escape latency in Control, *B. papyrifera* and piracetam groups in the training days. Using Morris water maze in rats. Statistical analysis was performed using one way analysis of variance (ANOVA) followed by Tukly's test for multiple comparisons. Data are shown as means±SEM.* $P< 0.05$ vs. control.

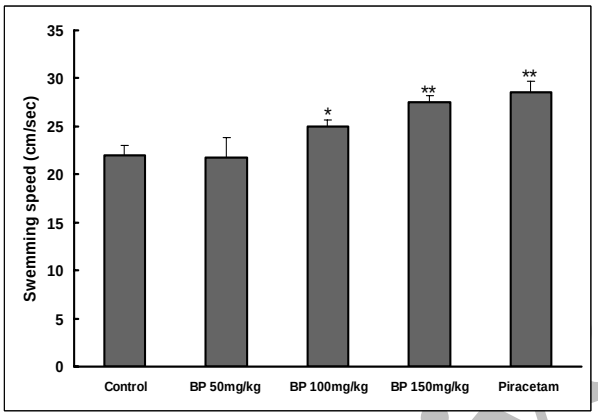

Figure 2. Swimming speed in Control, *B. papyrifera* and piracetam groups in the training days. Using Morris water maze in rats. Statistical analysis was performed using one way analysis of variance (ANOVA) followed by Tukly's test for multiple comparisons. Data are shown as means±SEM. *$P< 0.05$, **$P< 0.01$ vs. control.

Evaluation of percentage of presence in target quarter in probe trial

Percentage of the presence of animals in target quarter (quarter in which platform was located during training days) in probe trial session was investigated. Results show that there was a significant difference among groups. This difference was significant ($P< 0.05$) between control and the other groups (Figure 3).

Preliminary phytochemical analysis

Preliminary phytochemical analysis revealed the presence of alkaloids (Dragendorff's indicator became orange), flavonoids (7, 8 dimethoxyflavone, since the indicator became orange) and saponins (with the ability to produce foam).

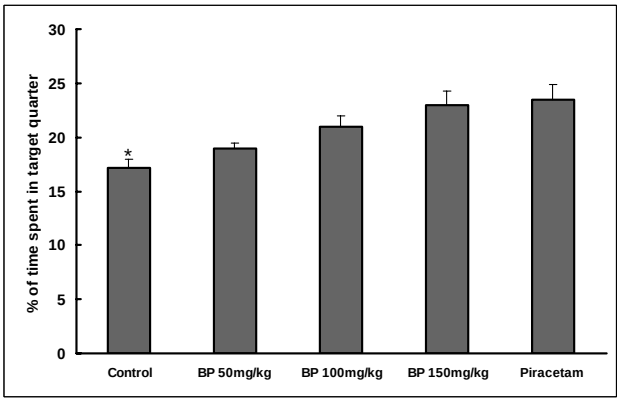

Figure 3. Percentages of time spent in target quarter in probe trial in Control, *B. papyrifera* and piracetam groups. Using Morris water maze in rats. Statistical analysis was performed using one way analysis of variance (ANOVA) followed by Tukly's test for multiple comparisons. Data are shown as means±SEM. *$P< 0.05$ vs. other groups.

Acute toxicity

In Acute toxicity experiment, the behaviour of the treated rats appeared normal. No toxic effect was reported up to 5 times of effective dose of the water extract and there was only one observed death in these groups.

Discussion

Weak memory and impaired learning ability are the most common symptoms of cognitive function loss (22). Nowadays the pharmacotherapy with psychoactive drugs are available, however they are not effective in all cases and exerts numerous side effects especially upon long term administration (16, 23). Series of paradigms for evaluation of memory performance is carried out that work upon different mechanisms (24). Various mazes are used conventionally to assess the learning and memory paradigms in animals (25, 26). RAM performance is an appetitive motivated task and is also useful to assess the spatial reference as well as spatial working memory performance and agents that affect these processes (15). The MWM works on spatial localization or navigation task and is extensively used to study the neurological mechanisms that underlie spatial learning and memory, age-associated changes in spatial navigation and ability of nootropic agents to influence specific cognitive processes (14). Results of this study showed that oral

administration of *B. papyrifera* significantly decreased the number of days required to make the mice learned as per set criteria and time taken to find the food by the learned mice in the RAM model. Also in MWM test, *B. papyrifera* administration during training days, led to decrease in escape latency as well as an increase in the animal swimming speed as compared with the control group. These results confirm the traditional use of *B. papyrifera* for intelligence improving especially for memory enhancement (13). Significant improvement in most of the spatial learning and memory performances is usually considered as the effect of the drug (16, 27, 28) and the dose showing significant improvement in the maximum parameters of memory performance could be considered as the most effective dose. In both MWM and RAM the most effective dose of BP was 150 mg/kg. According to these findings, *B. papyrifera* gum is an agent for facilitation of learning and memory. In addition, the preliminary phytochemical analysis of *B. papyrifera* showed the presence of alkaloids, flavonoids and saponins. These pharmacophores have been shown to possess nootropic activity and thereby support the aforementioned findings (29, 30). The oxidative stresses, generation of free radicals and deprivation of oxygen are common causes for neurodegeneration and related cognitive impairments especially in spatial learning and memory deficit (31, 32). Piracetam is a drug, with a fairly wide effect spectrum. Also, it has been used in the treatment of epilepsy and amnesia (33). Different but complementary effects have been recognized, such as effects on cognitive function, platelet anti-aggregant and antioxidant mechanisms (6, 34, 35). The present study documented facilitation of spatial learning and memory with pretreatment of *B. papyrifera* in a dose dependent manner in RAM and MWM performance. In this study however, *B. papyrifera* at the dose of 150 mg/kg was as effective as piracetam 150 mg/kg. Although the exact *B. papyrifera* mechanism of action is not elucidated, it may be related to piracetam mechanisms of action. It is reported that piracetam as a nootropic (cognition-enhancing) agent, facilitated neurotransmission in the dentate gyrus of rat hippocampal slices and in the *Xenopus* oocyte expression systems, piracetam potentiated currents through a variety of neuronal nicotinic ACh receptors (a3b2, a3b4, a4b2 and a4b4, and a7) to a different extent that have effect on memory (36). These results indicated possible use of the extract as a part of therapy to treat poor learners and patients with impaired spatial memory functions. Moreover, it may be employed as a buffer against neurological disorders (3). Many factors like experimental conditions, employed experimental protocol, modulation of specific neurotransmitters and involved neurochemicals can affect the extract activity on reference and working memory (25, 28). Thus, the exact mechanism of action and responsible phytochemicals will be revealed after detailed biochemical and phytochemical investigations.

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