Avicenna J Med Biochem. 2015 February; 2(2): e24906. DOI: 10.17795/ajmb-24906

Published online 2015 February 2. **Research Article**

Hydro-alcoholic Extract of *Commiphora mukul* Gum Resin May Improve Cognitive Impairments in Diabetic Rats

Iraj Salehi [1]; Zahra Taheraslani [2]; Shirin Moradkhani [3,*]

[1]Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, IR Iran
[2]Department of Physiology, School of Basic Sciences, Hamadan Branch, Islamic Azad University, Hamadan, IR Iran
[3]Department of Pharmacognosy and Pharmaceutical Biotechnology, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, IR Iran

*Corresponding author: Shirin Moradkhani, Department of Pharmacognosy and Pharmaceutical Biotechnology, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, IR Iran. Tel: +98-8138381593, Fax: +98-8138380031, E-mail: shirin.moradkhani@yahoo.com

Received: October 27, 2014; **Revised:** December 26, 2014; **Accepted:** January 3, 2015

Background: Diabetes causes cognitive impairment. Medicinal plants due to different mechanisms, such as antioxidant activities may improve diabetes and relieve its symptoms. *Commiphora mukul* (Burseraceae) has a significant antioxidant activity.
Objectives: This study aimed to examine the effect of hydro- alcoholic extract of *C. mukul* on passive-avoidance learning and memory in streptozotocin (STZ) induced diabetic male rats.
Materials and Methods: Thirty-two adult male Wistar rats were randomly allocated to four groups: normal, diabetic, normal + extract of *C. mukul* and diabetic + extract of *C. mukul* groups with free access to regular rat diet. Diabetes was induced in male rats by single interaperitoneal injection of 60 mg/kg STZ. After the confirmation of diabetes, 300 mg/kg *C. mukul* extract was orally administered to the extract-treated groups. Control groups received normal saline at the same time. Passive-avoidance memory was tested eight weeks after the STZ treatment, and blood glucose and body weight were measured in all groups at the beginning and end of the experiment.
Results: In the present study, diabetes decreased learning and memory. Although the administration of *C. mukul* extract did not affect the step-through latency (STLa) and the number of trials of the diabetic groups during the first acquisition trial, a significant decrease was observed in STLr and also a significant increase in time spent in the dark compartment (TDC) and number of crossing (NOC) in the retention test (after 24 and 48 hours). Although no significant difference was observed in body weight of diabetic + extract of *C. mukul* (DE) and diabetic control (DC) groups, the plasma glucose of DE group was significantly lower in comparison to DC group.
Conclusions: *Commiphora mukul* extract can improve passive-avoidance learning and memory impairments in the STZ-induced diabetic rats. This improvement may be due to the antioxidant, acetylcholinesterase inhibitory activity, anti-inflammatory or power to reduce hyperglycemia and lowering cholesterol and triglyceride properties of this extract. The result of this study is a promising point for new therapeutic alternatives in alleviating cognitive impairments caused by diabetes.

Keywords:Commiphora mukul; Passive Avoidance; Learning; Memory; Diabetes Mellitus

1. Background

Diabetes mellitus is a metabolic disorder of endocrine, which characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. International Diabetes Federation has estimated the incidence of diabetes for year 2030 is 350 million (1).

Therefore, public health concerns about poor academic performance and memory impairment in children and adults with diabetes, respectively. Recent evidences show that the central nervous system is affected by diabetes, which is independent from atherosclerotic disease. In humans, diabetes causes moderate cognitive dysfunctions and patients are at a high risk of dementia and Alzheimer diseases. Cognitive impairments also occur in diabetic rats, which are induced by streptozotocin (STZ). This dysfunction can be as a result of structural and functional deficits in hippocampus and cerebral cortex (2).

The pathogenesis of learning and memory impairments in diabetes has multiple etiologies such as metabolic disorders, chronic inflammation, vascular complications, and the dysfunction of scavenging free radical systems. Up to now, there is no specific and effective treatment for the management of cognitive impairments due to diabetes (3).

Nootropic agents (e.g. vitamins, fatty acids, antioxidants, amino acids, minerals, and phytochemicals) refer to memory enhancers, cognitive enhancers and neuroenhancers that can improve mental functions(4).

According to World Health Organization estimation, 75% of the world's population use traditional remedies and many synthetic drugs are analogues of phytochemicals (5).

Commiphora mukul belongs to Burseraceae family of plant kingdom. It has a resinous secretion known as guggul. Guggul is one of the most valuable remedies in one

of the traditional system of medicine like the ayurvedic medicine. Its usage backs to over 2500 years. Guggul has been used as antidiabetic, antihyperlipidemic, anti-osteoarthritic, anti-inflammatory, antispasmodic, sedative, antiseptic, astringent, carminative, emmenagogue, expectorant, diaphoretic, thyroid stimulant, antiobesity, diuretic, anthelminitic, and demulcent in traditional medicine. It has no well-defined chemical composition due to its very complex nature. Phytochemical investigation of guggul indicates the presence of sugars (fructose, sucrose), amino acids, oil and several steroids. However, only guggulsterone has been purified from the ethyl-acetate extract of resin (6).

Guggulsterone is the active sterol of the plant, as an antagonist of the bile acid farnesoid X receptor, demonstrating the hypolipidemic effect of the resin. In the STZ-induced model of dementia, guggulsterone has shown protective effects which is attributed to cholesterol-lowering antioxidant and antiacetylcholine esterase properties of this steroid. Hence, guggulsterone can be a potential antidimentia drug (4, 7).

2. Objectives

Our literature survey indicated that there is no report on the effect of hydroalcoholic extract of *C. mukul* resin on passive-avoidance learning and memory deficits in the STZ-induced diabetic rats. Therefore, the purpose of the present study was to investigate whether the administration of hydro-alcoholic extract of *C. mukul* resin has any protective effect on cognitive impairments in the STZ-induced diabetic rats.

3. Materials and Methods

3.1. Plant Extraction

Commiphora mukul gum resin was purchased from market in Hamadan, Iran. Then 200 g of resin was macerated in ethanol 80% for 3 days. This process was repeated 3 times. The resulting extract was filtered. The filtered extract was then concentrated to dryness in a rotary evaporator under reduced pressure at a constant temperature of 40 °C. The resulting extract was stored in a refrigerator.

3.2. Animals

Thirty-two male Wistar rats (250 – 280 g) were purchased from animal house, Hamadan University of Medical Sciences. The condition of maintenance was the constant temperature (22 ± 0.5 °C) with 12-hour light and 12-hour dark cycles. All animals had free access to a regular rat diet. The experimental groups were chosen from different cages, randomly with 8 animals per group.

3.3. Experimental Design

The animals were divided into two diabetic and two control groups (n = 8 each). Diabetes was induced by a single intraperitoneal injection of STZ (Sigma-Aldrich, Germany) (60 mg/kg). After three days, fasting blood glucose levels were determined. Blood samples were collected from the tail vein, and plasma glucose was measured using a glucometer. Animals were considered diabetic if plasma glucose levels exceeded 250 mg/dL. As soon as diabetes was confirmed, both diabetic and normal groups received saline or 300 mg/kg of the extract (8) by oral gavage for 60 days. At the end of the experiment, all rats were weighed and blood was collected for plasma glucose measurement.

3.4. Passive Avoidance Learning

A light/dark shuttle-box, the apparatus for quantification of the passive avoidance learning, had illuminated compartments of the light and dark parts with a guillotine door between them. Five seconds after placement of rat in the lighted part, the door was raised and habitually it entered into the dark part. After the rat entrance, it was trapped in dark part and a 1.2-mA constant current shock with 50 Hz frequency in 1.5 seconds was applied. The process of training was repeated until the rat did not cross to dark part and remained in lighted part for 120 seconds. This process was repeated 24 and 48 hours after the acquisition trial as a retention test. The retention performance was quantified by the step-through latency during the retention trial (STLr), time spent in the dark compartment (TDC) and number of crossing (NOC). At 8:00 – 11:00 hours the behavioral tests were performed and the ceiling score was 600 seconds.

3.5. Plasma Glucose Level Measurement

At the end of the experiment, all rats were weighed and decapitated under ketamine HCl (50 mg/kg, i.p.). Measurement of plasma glucose levels was done using a glucometer.

3.6. Statistical Analysis

The data were analyzed by SPSS 21, shown as mean ± SEM and compared by one-way ANOVA, post-hoc test LSD. The P Values of less than 0.05 were considered to be significant.

4. Results

4.1. Effects of Diabetes on the Passive-Avoidance Learning and Memory

One-way ANOVA indicated no significant difference in the STLa and in the number of trials of the diabetic and control groups during the first acquisition trial before the administration of the electrical shock; ($P > 0.05$, Table 1). During the retention test, after 24 and 48 hours the diabetic group had a decreased STLr, and increased TDC and NOC compared to the control group, respectively ($P < 0.001$), Table 1.

Table 1. Effect of *Commiphora mukul* Hydro-alcoholic Extract on Passive-Avoidance Learning and Memory in Rats [a]

Groups	STL_a	No	STL_r (24 h)	TDC (24 h)	NOC (24 h)	STL_r (48h)	TDC (48 h)	NOC (48 h)
NC	11.75 ± 2.73	1.12 ± 0.12	273.73 ± 13.24	6.25 ± 3.23	0.50 ± 0.26	269.67 ± 10.82	18.70 ± 9.63	0.50 ± 0.26
NE	10.87 ± 3.67	1.12 ± 0.12	265.13 ± 17.67	8.63 ± 4.37[b]	0.75 ± 0.41[b]	269.13 ± 15.90	5.88 ± 4.05[b]	1.12 ± 0.44[b]
DC	10.75 ± 2.56	1.37 ± 0.18	165.00 ± 6.62[c]	98.00 ± 11.59[c]	2.63 ± 0.18[c]	149.25 ± 13.87[c]	134.5 ± 14.10[c]	2.63 ± 0.32[c]
DE	9.62 ± 2.56	1.25 ± 0.16	240.68 ± 10.15[b]	18.38 ± 4.25[b]	1.25 ± 0.16[b]	229.50 ± 20.33[b]	19.38 ± 7.59[b]	1.25 ± 0.36[b]

[a] Abbreviations: STLa, step -through latency in the first acquisition trial; No, the number of trials to acquisition; STLr, step-through latency in the retention test; TDC, the time spent in the dark compartment ; NOC, number of crossing in the retention test; NC, normal control; NE, normal + extract of *C. mukul*; DC, diabetic control; DE, diabetic + extract of *C. mukul*.
[b] Significant differences compared to diabetic group: ($P < 0.001$, $P < 0.05$).
[c] significant differences compared to control group: ($P < 0.001$).

Table 2. Body Weight and Plasma Glucose Levels of Different Animal Groups at the Beginning and End of the Study [ab]

Groups	Plasma Glucose, mg/dL		Body Weight, g	
	End	Beginning	End	Beginning
NC	112.87 ± 2.94	104.75 ± 3.16	310.62 ± 6.97	221.37 ± 2.11
DC	517.62 ± 15.54[c]	507.0 ± 11.30[c]	190.37 ± 6.50[c]	225.25 ± 3.07
NE	112.37 ± 1.84[d]	106.87 ± 2.61[d]	321.50 ± 5.72[d]	222.87 ± 4.56
DE	464.25 ± 17.36[c]	477.25 ± 26.77[c]	208.12 ± 6.18[c]	226.25 ± 3.14

[a] Data are Means ± S.E.M.
[b] Abbreviations: NC, normal control; NE, normal + extract of *C. mukul*; DC, diabetic control; DE, diabetic + extract of *C. mukul*.
[c] Significant differences compared to the control group ($P < 0.001$).
[d] significant differences compared to the diabetic group ($P < 0.001$, $P < 0.05$).

4.2. Effects of Commiphora mukul Administration on Passive-Avoidance Learning and Memory in Nondiabetic Rats

There was no significant difference in the STLa and in the number of trials of the control rats treated with extract and untreated control rats during the first acquisition trial (before the administration of the electrical shock; $P > 0.05$, Table 1). Also, during the retention test, after 24 and 48 hours the control rats treated with extract had no significant difference in STLr, TDC, NOC compared to the untreated control rats ($P > 0.05$; Table 1).

4.3. Effects of Commiphora mukul Administration on Passive-Avoidance Learning and Memory in Diabetic Rats

There was no significant difference in the STLa and in the number of trials of the extract-treated diabetic rats and untreated diabetic rats during the first acquisition trial (before the administration of the electrical shock; $P > 0.05$, Table 1). During the retention test, after 24and 48 hours, the extract-treated diabetic rats had an increased STLr and decreased TDC, NOC compared to the untreated diabetic rats, respectively ($P < 0.001$, $P < 0.05$), Table 1.

4.4. Effects of Commiphora mukul Administration on Body Weight and Plasma Glucose

There was a significant increase in blood glucose and also a significant decrease in body weight in diabetic rats as compared to the normal rats. The oral administration of extract of *C. mukul* significantly lowered the blood glucose in comparison with the untreated group of diabetic rats; however, there was no significant increase in body weight, as they were compared with the untreated group of diabetic rats, (Table 2).

In Table 2, the blood glucose levels and body weight of all experimental groups at the beginning and at the end of the study are shown. Plasma glucose levels between all groups at the onset of treatment were significantly different. Eight weeks after the induction of diabetes, behavioral assays were done and then plasma glucose levels and body weight were measured. The body weight of the untreated (190.37 ± 6.50 g) and extract -treated diabetic rats (208.12 ± 6.18 g) were lower than the control rats (310.62 ± 6.97 g). Furthermore, there was no significant difference in the body weight of the extract-treated (321.50 ± 5.72 g) and untreated control (310.62 ± 6.97) animals. Regarding plasma glucose levels, the untreated diabetic animals had significantly ($P < 0.001$) elevated plasma glucose levels (517.62 ± 15.54 mg/dL) compared to the control animals (112.87 ± 2.94 mg/dL). Oral administration of the *C. mukul* extract to diabetic rats decreased the plasma glucose levels of the treated groups (464.25 ± 17.36 mg/dL) compared to the untreated diabetic group (517.62 ± 15.54 mg/dL; $P < 0.05$).

5. Discussion

According to the results of this study, the oral administration of hydro-alcoholic extract of *C. mukul* gum resin

improved passive-avoidance learning and memory of the control rats and alleviated the negative influence of diabetes on learning and memory. Although there was no significant effect in the STLa and in the number of trials of the diabetic groups during the first acquisition trial, a significant decrease in STLr and also a significant increase in TDC, NOC in the retention test (after 24 and 48 h) showed promising results of the present study.

Literature survey revealed that *C. mukul* had a profound effect on the antioxidant defense system; however, there was no report on the effect of *C. mukul* in passive-avoidance learning and memory in diabetic rats. Diabetes is associated with an increased production of reactive oxygen species (ROS), enhanced oxidative stress and changes in the antioxidant capacity (9, 10). Oxidative stress is involved in the pathogenesis of many central nervous system disorders (e.g. neurodegenerative diseases) or in the physiological process of aging (11).

According to the literature, brain is very vulnerable to oxidative stress due to its high-polyunsaturated fatty acids (PUFAs) content, which are particularly susceptible to ROS damage (12, 13).

Apoptosis of nerve cells as a result of increased Thiobarbituric acid reactive substances (TBARS) (lipid peroxidation productions) in frontal cortex and hippocampus, induces the dysfunction of learning and memory due to the structural and functional changes in biological membranes induced by lipid peroxidation (14).

Impairment of learning and memory in the diabetic groups may be related to the increased oxidative stress in diabetic animal's brain, but *C. mukul* as an antioxidant may reduce the oxidative stress, and lead to the better behavioral activity of the animals in extract-treated diabetic groups. Clinical and experimental studies suggest that hyperglycemia and/or insulin deficiency itself may be responsible for impaired cognitive function in type-1diabetes (15).

Moreover, antioxidants, antihyper-glycemics and insulin sensitizing agents can reduce cognitive dysfunction in diabetes (16). The underlying mechanism of its action may be attributed to its antioxidant, anti-inflammatory or acetylcholinesterase (AChE) inhibitory properties. In vitro evaluation of *C. mukul* gum resin extract revealed that it has a profound effect on the antioxidant defense system (10) and can affect parameters of oxidative stress glutathione and malondialdehyde (GSH and MDA). *Commiphora mukul*, with profound antioxidant potential and having the ability to trigger cellular antioxidants, can be exploited for its use against a number of disorders including cardiovascular diseases, inflammation, and cancer (17).

Commiphora mukul has been reported to contain flavonoids, terpenes, and phytosterols (18). Flavonoids are potent antioxidants at very low concentrations. The chemopreventive properties of flavonoids are generally believed to reflect their ability to scavenge the endogenus ROS.

By inhibiting or stimulating various signaling pathways, flavonoids at low concentration could affect cellular function (19, 20). Acetylcholinesterase expression is pivotal during apoptosis. Indeed, the AChE inhibitors partially protect cells from apoptosis. During the type 1 diabetes mellitus development, an accumulation of AChE in the pancreatic islets induces apoptotic βcells. Decrease in hyperglycemia and incidence of diabetes, and restoration of plasma insulin levels and plasma creatinine clearance are the consequences of treatment with AChE inhibitors.

Induction and accumulation of AChE in pancreatic islets and the protective effects of AChE inhibitors on the onset and development of type 1 diabetes indicate a close relationship between AChE and type 1 diabetes (21). AChE inhibitors enhance cholinergic function in the brain when loss or decline in memory and cognitive impairment has occurred (22, 23). *Commiphora mukul* can increase whole brain AChE enzyme inhibitory activity (24). Polyphenols have shown AChE inhibitory effect (25) and considering that *C. mukul* contains flavonoids (18), another possible mechanism of *C. mukul* effect on passive avoidance learning can be involved in the AChE inhibitory potential of plant. Besides flavonoids, *C. mukul* is rich in guggulsterone. On the other hand, antioxidant and anti-inflammatory effects are relevant to each other (26). Hence, guggulsterone , a phytosterol with potent anti-inflammatory activity can be responsible for some of beneficial effects of *C. mukul* (27). Also, the extract affected plasma glucose.

The improvement of cognitive function observed in the diabetic animals in this study may be partly due to the ability of *C. mukul* to attenuate hyperglycemia. In both human and animal models, guggul lowered both serum low-density lipoprotein (LDL) cholesterol and triglyceride levels, due to antagonistic effect of guggul on the bile acid receptor farnesoid X-receptor. Biochemical and epidemiological studies demonstrated a link between cholesterol, amyloid precursor protein processing and Alzheimer's disease. Cholesterol lowering drugs decreased neuronal cholesterol levels, which in turn inhibit the beta amyloid-forming amyloidogenic pathway, possibly by removing amyloid precursor protein from cholesterol and sphingolipid-enriched membrane micro domains. These results indicate that the administration of cholesterol-lowering drugs is associated with decreased prevalence of Alzheimer's disease (7).

In conclusion, the findings of this study indicate that *C. mukul* can improve cognitive impairment in diabetic rats. Cellular and animal studies as well as clinical trials are required to support its role as useful preparation in alternative medicine.

Acknowledgements

The authors are grateful to Neuroscience Research Center, Hamadan University of Medical Sciences, Hamadan, Iran, for its financial supports.

Funding/Support

This research was supported by a grant of the Neuroscience Research Center, Hamadan University of Medical Sciences, Hamadan, Iran.

References

1. Ramesh B, Karuna R, Sreenivasa Reddy S, Sudhakara G, Saralakumari D. Ethanolic extract of Commiphora mukul gum resin attenuates streptozotocin-induced alterations in carbohydrate and lipid metabolism in rats. *Exp Clin Sci*
2. *Int online J Adv Sci.* 2013:556–68.
3. Heng LJ, Yang RH, Jia D. Diabetes impairs learning performance through affecting membrane excitability of hippocampal pyramidal neurons. *Behav Brain Res.* 2011;**224**(2):250–8.
4. Zhao CH, Liu HQ, Cao R, Ji AL, Zhang L, Wang F, et al. Effects of dietary fish oil on learning function and apoptosis of hippocampal pyramidal neurons in streptozotocin-diabetic rats. *Brain Res.* 2012;**1457**:33–43.
5. Joshi PC. A review on natural memory enhancers (Nootropics). *Unique J Engin Adv Sci.* 2013;**1**(1):8–18.
6. Cornick CL, Strongitharm BH, Sassano G, Rawlins C, Mayes AE, Joseph AN, et al. Identification of a novel agonist of peroxisome proliferator-activated receptors alpha and gamma that may contribute to the anti-diabetic activity of guggulipid in Lep(ob)/Lep(ob) mice. *J Nutr Biochem.* 2009;**20**(10):806–15.
7. Bellamkonda R, Rasineni K, Singareddy SR, Kasetti RB, Pasurla R, Chippada AR, et al. Antihyperglycemic and antioxidant activities of alcoholic extract of Commiphora mukul gum resin in streptozotocin induced diabetic rats. *Pathophysiology.* 2011;**18**(4):255–61.
8. Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: a review. *Alzheimers Res Ther.* 2012;**4**(3):22.
9. Masten SA. *Gum guggul and some of its steroidal constituents: review of toxicological literature.* Research Triangle Park, North Carolina, USA: Document prepared for National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health, US Department of Health and Human Services; 2005.
10. Xie W, Du L. High-cholesterol diets impair short-term retention of memory in alloxan-induced diabetic mice, but not acquisition of memory nor retention of memory in prediabetic mice. *Life Sci.* 2005;**77**(5):481–95.
11. In-vitro antioxidant activity of the ethyl acetate extract of gum guggul (Commiphora mukul). In: Dubey D, Prashant K, Jain SK editors. . *Biological Forum-An Int J.* 2009 pp. 32–5.
12. Halliwell B, Gutteridge JMC. Oxygen radicals and the nervous system. *Trends in Neurosci.* 1985;**8**:22–6.
13. Cui K, Luo X, Xu K, Ven Murthy MR. Role of oxidative stress in neurodegeneration: recent developments in assay methods for oxidative stress and nutraceutical antioxidants. *Prog Neuropsychopharmacol Biol Psychiatry.* 2004;**28**(5):771–99.
14. Halliwell B. Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging.* 2001;**18**(9):685–716.
15. Palmeira CM, Oliveira CR. Partitioning and membrane disordering effects of dopamine antagonists: influence of lipid peroxidation, temperature, and drug concentration. *Arch Biochem Biophys.* 1992;**295**(1):161–71.
16. Zare K, Tabatabaei SRF, Shahriari A, Jafari RA. Effect of Butter and Sesame Oils on Avoidance Memory of Diabetic Rats. *Energy (ME/Kg).* 2011;**3010**(3653):3552.
17. Bhutada P, Mundhada Y, Bansod K, Tawari S, Patil S, Dixit P, et al. Protection of cholinergic and antioxidant system contributes to the effect of berberine ameliorating memory dysfunction in rat model of streptozotocin-induced diabetes. *Behav Brain Res.* 2011;**220**(1):30–41.
18. Preethi KC, Kuttan G, Kuttan R. Antioxidant Potential of an Extract of Calendula officinalis. Flowers in Vitro. and in Vivo. *Pharm biol,.* 2006;**44**(9):691–7.
19. Sultana N, Jahan S. Studies on the constituents of Commiphora mukul. *Zeitschrift für Naturforschung. B, A J ChemSci.* 2005;**60**(11):1202–6.
20. Kundu JK, Surh YJ. Breaking the relay in deregulated cellular signal transduction as a rationale for chemoprevention with anti-inflammatory phytochemicals. *Mutat Res.* 2005;**591**(1-2):123–46.
21. Chandran PK, Kuttan R. Effect of Calendula officinalis Flower Extract on Acute Phase Proteins, Antioxidant Defense Mechanism and Granuloma Formation During Thermal Burns. *J Clin Biochem Nutr.* 2008;**43**(2):58–64.
22. Zhang B, Yang L, Yu L, Lin B, Hou Y, Wu J, et al. Acetylcholinesterase is associated with apoptosis in beta cells and contributes to insulin-dependent diabetes mellitus pathogenesis. *Acta Biochim Biophys Sin (Shanghai).* 2012;**44**(3):207–16.
23. Mesulam M. The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learn Mem.* 2004;**11**(1):43–9.
24. Fodale V, Quattrone D, Trecroci C, Caminiti V, Santamaria LB. Alzheimer's disease and anaesthesia: implications for the central cholinergic system. *Br J Anaesth.* 2006;**97**(4):445–52.
25. Pandey R, Taranalli A, Saravanan E, Ganguly K. Commiphora Mukul: Evaluation Of Its Nootropic Effects In Rats. *J Cell Tissue Res Vol.* 2009;**9**(1):1697–702.
26. Kim HK, Kim M, Kim S, Kim M, Chung JH. Effects of green tea polyphenol on cognitive and acetylcholinesterase activities. *Biosci Biotechnol Biochem.* 2004;**68**(9):1977–9.
27. Kim SS, Lim J, Bang Y, Gal J, Lee SU, Cho YC, et al. Licochalcone E activates Nrf2/antioxidant response element signaling pathway in both neuronal and microglial cells: therapeutic relevance to neurodegenerative disease. *J Nutr Biochem.* 2012;**23**(10):1314–23.
28. Gebhard C, Stampfli SF, Gebhard CE, Akhmedov A, Breitenstein A, Camici GG, et al. Guggulsterone, an anti-inflammatory phytosterol, inhibits tissue factor and arterial thrombosis. *Basic Res Cardiol.* 2009;**104**(3):285–94.