

Received: 2011.03.13
Accepted: 2011.08.17
Published: 2012.01.01

Preventive effect of *Teucrium polium* on learning and memory deficits in diabetic rats

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Parisa Hasanein^{1ADEFG}, Siamak Shahidi^{2BCFG}

¹ Department of Biology, School of Basic Sciences, Bu-Ali Sina University, Hamedan, Iran

² Department of Physiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

Source of support: Departmental sources

Summary

Background:

Cognitive impairment occurs in diabetes mellitus. *Teucrium polium* L. (Lamiaceae) has been used in folk medicine to improve mental performance. Here we hypothesized that chronic treatment with an aqueous extract of *Teucrium polium* (100, 200 and 400 mg/kg, p.o.) would have an effect on passive avoidance learning (PAL) and memory in control and streptozocin-induced diabetic rats.

Material/Methods:

Treatments were begun at the onset of hyperglycemia, and PAL was assessed 30 days later. A retention test was performed 24 h (hours) after training. After PAL and memory assessment, animals were weighed and blood samples were drawn for plasma glucose measurement.

Results:

Diabetes caused impairment in acquisition of PAL and retrieval of memory. *Teucrium polium* treatment (200 and 400 mg/kg) improved learning and memory in control rats and reversed learning and memory deficits in diabetic rats. The 100 mg/kg dose did not affect cognitive function. *Teucrium polium* treatment partially improved the reduced body weight and hyperglycemia of treated diabetic rats, although the differences were not significant compared to non-treated diabetic rats.

Conclusions:

These results show that *Teucrium polium* prevented the deleterious effects of diabetes on PAL and memory. Antioxidant, anticholinesterase and hypoglycemic effects of *Teucrium* may be involved in the obtained effects. Therefore, *Teucrium polium* appears to be a promising candidate for memory improvement in diabetes, but this needs confirmation by future clinical studies.

key words:

diabetes mellitus • *Teucrium polium* • learning • memory • rats

Full-text PDF:

<http://www.medscimonit.com/fulltxt.php?ICID=882201>

Word count:

2693

Tables:

1

Figures:

1

References:

43

Author's address:

Parisa Hasanein, Bu-Ali Sina University, School of Basic Sciences, Department of Biology, 65178-33391 Hamedan, Iran, e-mail: p.hasanein@basu.ac.ir

BACKGROUND

Diabetes mellitus, one of the most serious health problems worldwide, is associated with neurological complications in both the peripheral and central nervous systems [1,2]. Evidence indicates that diabetes causes learning and memory deficits [3–5], and moderate impairment of learning and memory has been observed in adults with diabetes mellitus [6–8]. Cognitive impairment has also been reported to occur in streptozotocin-induced diabetes, which is a well-characterized experimental model of type I diabetes mellitus [9–12].

Recently, focus has shifted to the use of plant extracts for the treatment of diabetes mellitus and its complications. The WHO has estimated that approximately 80% of the worldwide population relies on traditional medicine for their primary health care needs, and most of this therapy involves the use of plant extracts [13].

Teucrium polium L. (Lamiaceae) is one of the most popular herbal medicines in the world and has been used for over 2000 years in traditional medicine due to its exceptional pharmacological properties. *Teucrium polium* is mainly used in folk medicine to improve mental performance [14–17]. Recently, it has been reported that *Teucrium polium* extract has anti-amnesic properties in a mouse model of scopolamine-induced amnesia [18]. Therefore, *Teucrium polium* may be an herbal alternative for memory improvement, and it will be worthwhile to explore its potential for the management of cognitive deficits. In light of these reports, we examined whether the aqueous extract of *Teucrium polium* could protect against learning and memory deficits in diabetic rats. Therefore, the aim of this study was to evaluate the effects of long-term administration of *Teucrium polium* (100, 200 and 400 mg/kg, p.o.) on passive avoidance learning (PAL) and memory performance in healthy and diabetic rats.

MATERIAL AND METHODS

Animals

Sixty-four locally-sourced male Wistar rats (250–280 g) were used in the present experiments. All animals were maintained at a constant temperature (22±0.5°C) with 12 h light: 12 h dark cycle. They had free access to laboratory chow and tap water. Each experimental group consisted of 8 animals that were chosen randomly from different cages, and each was used only once.

Chemicals

The following drugs were used in the present study: streptozotocin (STZ) was obtained from Pharmacia and Upjohn (USA) and dissolved in 1 ml normal saline immediately before use. Ketamine HCL was purchased from Rotexmedica (Trittau, Germany).

Plant extraction

The dried aerial parts of *Teucrium polium* were purchased from herbalists in Kerman and were authenticated by Dr. A. Musavai, Center for Research on Natural Resources and

Livestock (Ministry of Agricultural Jihad, Hamedan, Iran). Dried plant material (25 g) was stirred in 250 ml of distilled water for 15 min (minutes) at 95°C, followed by rapid filtration through a crude cellulose filter. The average w/w yield was 11.5%. The resulting filtrate was freeze-dried and used for the experiments. *Teucrium polium* extract was fed to rats orally at doses of 100, 200 and 400 mg/kg, once a day for 30 consecutive days.

Experimental design

The animals were divided into 4 diabetic and 4 control groups (n=8 each). Diabetes was induced by a single i.p. injection of STZ (60 mg/kg). Three days later, fasting blood glucose levels were determined. Blood samples were collected from the tail vein, and plasma glucose was measured using a kit (through enzymatic “glucose oxidase”; Zistshimi, Tehran, Iran) and a spectrophotometer (UV3100, Shimadzu, Tokyo, Japan). Animals were considered diabetic if plasma glucose levels exceeded 250 mg/dl. As soon as diabetes was confirmed, the diabetic groups received saline or 100, 200 and 400 mg/kg of the extract by oral gavage for 30 days. The doses of the extract used here were based on previously published studies [19–21]. The control groups received saline or extract at the same doses as the diabetic groups by oral gavage for 30 days. After the treatment period, the different animal groups were tested using a standard experimental paradigm of learning and memory. At the end of experiment, all rats were weighed and blood was collected for plasma glucose measurement. The operator was unaware of the specific treatment groups to which each animal belonged. Animals were handled in accordance with the criteria outlined in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication 86–23; revised 1985; <http://www.oacu.od.nih.gov/regs/guide/guidex.htm>). All protocols were also approved by the Institutional Ethics Committee of Bu-Ali Sina University.

Passive avoidance learning (PAL) test (step-through test)

The apparatus and procedure were basically the same as in our previous studies [22,23]. Briefly, the step-through passive avoidance apparatus consisted of a lighted chamber (20×20×30 cm) made of transparent plastic and a dark chamber made of dark opaque plastic (20×20×30 cm). The floors of both chambers were made of stainless steel rods (3 mm diameter) spaced 1 cm apart. The floor of the dark chamber could be electrified using a shock generator. A rectangular opening (6×8 cm) was located between the two chambers and could be closed by an opaque guillotine door.

Training

We habituated the rats to the apparatus as follows: the rats were placed in the lighted compartment of the apparatus facing away from the door, and 5 s (seconds) later the guillotine door was raised. Rats have a natural preference for dark environments. Upon the entrance of the rat to the dark compartment, the door was closed, and after 30 s the rat was removed from the dark compartment and placed in its home cage. This habituation trial was repeated 30 min later. The first acquisition trial started 30 min after the second habituation trial.

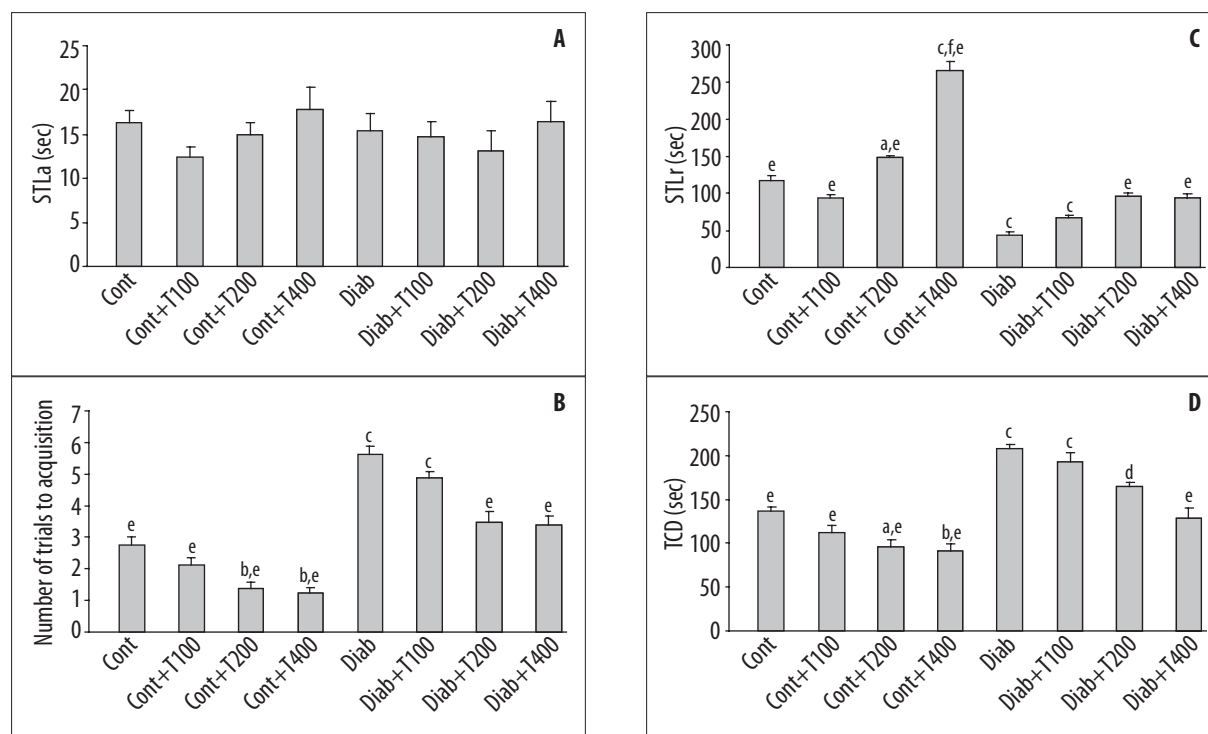


Figure 1. Effects of long-term administration of *Teucrium polium* extract on the PAL test. The effect of long-term oral administration of extract on the step-through latency (STLa) in the first acquisition trial (A), the number of trials to acquisition (B), step through latency (STLr) in the retention test (C) and the time spent in the dark compartment during the retention test (TDC) (D) between different control (Cont) and diabetic (Diab) groups (n=8). ^a P<0.05, ^b P< 0.01 and ^c P< 0.001 compared to control group. ^d P<0.01 and ^e P<0.001 compared to diabetic group. ^f P<0.001 difference in STLr between 200 and 400 mg/kg extract-treated control rats. Each column and bar represents mean \pm S.E.M.

The latency to enter the dark compartment (step-through latency during acquisition, STLa) was recorded when the animal had placed all 4 paws in the dark compartment. After the animal had spontaneously entered the dark compartment, the guillotine door was lowered and a mild electrical shock (0.5 mA) was applied for 3 s. After 30 s, the rat was removed from the dark compartment and returned to its home cage. Then after 2 min, the procedure was repeated. The rat received a foot shock each time it re-entered and had placed all 4 paws in the dark compartment. Training was terminated when the rat remained in the light compartment for 120 consecutive seconds. The number of trials to acquisition (entries into the dark chamber) was recorded.

Retention test

The retention test was performed 24 h after the PAL acquisition trial. The rat was placed in the lighted chamber as during PAL training. Five seconds later, the guillotine door was raised, and the step-through latency during the retention trial (STLr) and the time spent in the dark compartment (TDC) were recorded up to 300 s. If the rat did not enter the dark compartment within 300 s, the retention test was terminated and a ceiling score of 300 s was assigned.

Measurement of plasma glucose levels

At the end of experiment, all rats were decapitated under ketamine HCl anesthesia (50 mg/kg, i.p.) and blood

samples were drawn. Plasma glucose levels were measured using a kit and a spectrophotometer, as explained above.

Statistical analysis

All data are expressed as mean \pm S.E.M. Differences between groups were statistically tested by one-way analysis of variance (ANOVA) with Tukey post-hoc test. Probability values less than 0.05 were considered significant.

RESULTS

Effects of diabetes on the PAL and memory

One-way ANOVA indicated that there was no significant difference in the STLa of the diabetic and control groups during the first acquisition trial (before the administration of the electrical shock; $P>0.05$, Figure 1A). There was a significant difference ($P<0.001$) in the number of trials before acquisition between the diabetic (5.62 ± 0.26) and control groups (2.75 ± 0.25 ; Figure 1B). During the retention test, the diabetic group had a decreased STLr (43.5 ± 4.5) and increased TDC (207.7 ± 4.9) compared to the control group (116.6 ± 6.4 , 137.2 ± 4.3 , respectively) (both $P<0.001$; Figure 1C, D).

Effects of *Teucrium polium* administration on PAL and memory in non-diabetic rats on PAL and memory

There were no significant differences in the STLa during the first acquisition trial among any of the groups ($P>0.05$,

Table 1. Body weight and plasma glucose levels of different animal groups at the beginning and end of the study.

Plasma glucose(mg/dl)		Body weight(g)		Groups
End	Beginning	End	Beginning	
98.3±4	104.6±4.1	311±5	255±3	Control
100.6±7.9	97±5.5	320±7	268±3	Cont+Tp100
87.6±5.2	82±2.9	316±6	271±4	Cont+ Tp200
92±6.2	90±5.4	318±8	276±2	Cont+ Tp400
394.7±5.6 ^a	86±2.6	193±6 ^a	272±3	Diab
259.7±9.8 ^{a,e}	106±7	243±7 ^a	266±4	Diab+ Tp100
149.6±4 ^{a,e}	91±8.2	263±8 ^b	272±3	Diab+ Tp200
137.7±7.4 ^{d,e}	101±6	278±6 ^c	258±2	Diab+ Tp400

Animal groups included: control rats, control rats treated with 100 mg/kg *Teucrium polium* (Tp) (Cont +Tp100), control rats treated with 200 mg/kg Tp (Cont + Tp200), control rats treated with 400 mg/kg Tp (Cont +Tp400), diabetic rats (Diab), diabetic rats treated with 100 mg/kg Tp (Diab + Tp100), diabetic rats treated with 200 mg/kg Tp (Diab + Tp200), and diabetic rats treated with 400 mg/kg Tp (Diab + Tp400). The symbols indicate significant differences compared to the control group (^a P=0.001, ^b P=0.01, ^c P=0.047 and ^d P=0.002, ^e P<0.001, ANOVA, Tukey's test for post-hoc comparisons).

Figure 1A). Administration of 100 mg/kg *Teucrium polium* to control rats did not affect on the number of trials to acquisition, STLR or TDC (Figure 1B–D). The number of trials to acquisition in the 200 and 400 mg/kg *Teucrium polium*-treated control groups were fewer than in the untreated control group (both P<0.01; Figure 1B). However, there was no difference in the number of trials to acquisition between the 2 treated groups. In the retention test, administration of 200 and 400 mg/kg *Teucrium polium* to the control group caused an increased STLR (147.5±3.6 and 264.6±13.3, respectively) compared to the untreated control group (116.6±6.4; P<0.05 and P<0.001, respectively; Figure 1C). Furthermore, there was a significant difference in the STLR between the 200 and 400 mg/kg extract-treated control animals (P<0.001; Figure 1C). The TDC of 200 and 400 mg/kg extract-treated control rats (96.8±7.9 and 91.2±8.1, respectively) was significantly less than in untreated control rats (137.2±4.3; P<0.05 and P<0.01, respectively; Figure 1D).

Effects of *Teucrium polium* administration to diabetic rats on PAL and memory

In the diabetic groups, administration of 100 mg/kg *Teucrium polium* did not significantly affect the number of trials to acquisition, STLR or TDC compared to untreated diabetic rats (Figure 1B–D). However, administration of 200 and 400 mg/kg *Teucrium polium* to diabetic animals produced a significant difference in the number of trials to acquisition (both P<0.001), STLR (both P<0.001) and TDC (P<0.01, P<0.001, respectively) compared to untreated diabetic animals (Figure 1B–D). There was no significant difference between extract-treated diabetic rats and untreated control rats in these parameters (Figure 1B–D).

Effects of *Teucrium polium* administration on body weight and plasma glucose

The body weight and blood glucose levels of different animal groups at the beginning and at the end of the experiment

are shown in Table 1. There was no significant difference in body weight or plasma glucose between any of the groups before the onset of diabetes. Body weight and plasma glucose levels were measured at the end of behavioral assays (30 days after the onset of hyperglycemia). At the end of assays, the body weight of the untreated (193±6) and extract-treated (100, 200 and 400 mg/kg) diabetic rats (243±7, 263±8 and 278±6, respectively) were significantly (P<0.001, P<0.001, P<0.01 and P<0.05, respectively) lower than control rats (311±5). Furthermore, there was no significant difference in the body weight of extract-treated (100, 200 and 400 mg/kg) and untreated control animals. Regarding plasma glucose levels, untreated diabetic animals had significantly (P<0.001) elevated plasma glucose levels (394.7±5.6) compared to control animals (98.3±4). Administration of 100, 200 and 400 mg/kg *Teucrium polium* to diabetic rats significantly decreased the plasma glucose levels of the treated groups (259.7±9.8, 149.6±4 and 137.7±7.4, respectively) compared to the untreated diabetic group (394.7±5.6; all P<0.001). However, there were still significant differences in the plasma glucose levels between extract-treated diabetic animals (100, 200 and 400 mg/kg) and untreated control animals (P<0.001, P<0.001 and P<0.01, respectively; Table 1).

DISCUSSION

The results of the present study show that treatment with 200 and 400 mg/kg *Teucrium polium* for 30 days from the onset of diabetes improved PAL and memory of control rats and alleviated the negative influence of diabetes on learning and memory. The decrease in the number of trials to acquisition in the PAL task is evidence of an improvement in memory acquisition. The increase in STLR and decrease in TDC during the retention test demonstrates facilitatory effects on memory retention [4,9,24].

The benefits of Iranian medicinal plants, including *Teucrium polium*, have been systematically reviewed [25,26]. *Teucrium polium* has been approved in modern medicine for its anti-inflammatory and anti-oxidative effects [19,27]. Interestingly,

Teucrium in folk medicine has been used to improve mental performance, but until now there have not been many reports of *in vivo* anti-amnesic effects of this herb. Our present results showing a significant improvement in rat learning and memory in the PAL task after treatment with *Teucrium polium* are consistent with a recent published study showing that *Teucrium polium* extract enhances the retrieval of memory in mice [18].

In the present experiments, the number of trials to acquisition during the PAL task was increased in diabetic rats, which is indicative of learning impairment. In the retention test, the STLr was decreased and TDC was increased, which demonstrates memory retention deficits induced by diabetes. Learning and memory deficits induced by diabetes mellitus have been previously reported in animals and humans [4,6,8,9,11,12]. Our current experiments expand on these reports and demonstrate the potential for *Teucrium polium* to protect against memory impairment in diabetes. The results are quite promising. Administration of *Teucrium polium* clearly prevented the learning and memory impairments caused by diabetes. Indeed, administration of 200 and 400 mg/kg *Teucrium polium* to diabetic animals reversed the increased number of trials to acquisition, indicative of a preventive effect of the treatment on acquisition deficits. In the retention trial, decreased STLr and increased TDC of diabetic rats were also reversed by *Teucrium polium* treatment.

Interestingly, there have been many studies reporting that *Teucrium polium* extract has antioxidant properties [28–30]. Its high antioxidant activity could be considered to depend on the phenolic compounds detected in this herb, including hydroxybenzoic acid derivatives, caffeic acid, and ferulic acid, in addition to the flavonoid derivatives, luteolin and quercetin [31]. It has also been shown that *Teucrium polium* extract has significant antioxidant activity *in vivo* and that the antioxidant activity of the extract is comparable to that of one of the strongest antioxidants, alpha-tocopherol [21]. Oxidative stress is not only involved in the pathogenesis of diabetes but also plays a role in diabetic complications such as memory deficits [4,32]. Additionally, it has been suggested that oxidative stress is central to the development of diabetic complications. This suggestion has been supported by the demonstration of increased levels of indicators of oxidative stress in diabetic individuals who are experiencing complications [33]. As oxidative stress is thought to play a crucial role in the development of memory impairment in diabetes mellitus [4,32,34,35], the antioxidant properties of *Teucrium polium* extract may be responsible for the observed memory enhancing effects. Furthermore, it has been reported that intracerebroventricular (i.c.v.) injection of streptozotocin at a subdiabetogenic dose in rats may increase anticholinesterase activity, and this increase may lead to diminished cholinergic transmission due to a decrease in central acetylcholine level [32,36–39]. This ultimately may result in cognitive impairment in i.c.v. streptozotocin-treated rats [32]. Interestingly, *Teucrium polium* extract showed strong acetylcholinesterase inhibition in the anticholinesterase assay [18]. α -pinene, one of the major contributors to the anticholinesterase property of *Teucrium polium*, has been well-studied for its strong anti-acetylcholinesterase effects [18]. As central cholinergic pathways play a prominent role in learning and memory processes, the anticholinesterase effects of *Teucrium polium* may be involved in the nootropic effects observed during the present experiments.

Furthermore, prolonged hyperglycemia is a primary cause of most complications of diabetes. Indeed, chronic hyperglycemia is thought to lead to cognitive impairments in diabetes [12,40]. Our study shows that administration of *Teucrium polium* extract did not affect body weight and plasma glucose in treated control animals. However, extract-treated diabetic rats showed a minor increase in body weight and decrease in plasma glucose levels, which is in accordance with the reported hypoglycemic effect of *Teucrium polium* [41,42]. Therefore, the restoration of cognitive function observed in the diabetic animals in this study may be partly due to the ability of *Teucrium polium* to attenuate hyperglycemia.

There have been no reported effects of *Teucrium polium* on motor function in doses equal to the ones used in this study [18]. In addition, as STLr in the first acquisition trial was not different between animal groups, and as we also did not observe any abnormal motor behavioral responses during the experiments, the nootropic properties of *Teucrium polium* may not be attributed to possible effects on locomotion.

CONCLUSIONS

This study demonstrates that *Teucrium polium* may protect against memory impairment in diabetic rats. While questions remain regarding the medicinal value of herbal supplements, based on cellular and animal studies as well as human clinical trials, the literature supports a role for these preparations as useful alternatives [43]. We plan to conduct further studies in future to confirm the protective effect of *Teucrium polium* observed in this study.

REFERENCES:

- Gispén WH, Biessels GJ: Cognition and synaptic plasticity in diabetes mellitus. *Trends in Neurosci*, 2000; 23: 542–49
- McCall AL: The impact of diabetes on the CNS. *Diabetes*, 1992; 41: 557–70
- Artola A, Kamal A, Ramakers GM et al: Diabetes mellitus concomitantly facilitates the induction of long-term depression and inhibits that of long-term potentiation in hippocampus. *Eur J Neurosci*, 2005; 22: 169–78
- Kucukatay V, Ağar A, Gumuslu S et al: Effect of sulfur dioxide on active and passive avoidance in experimental diabetes mellitus: Relation to oxidant stress and antioxidant enzymes. *Int J Neurosci*, 2007; 117: 1091–107
- Kucukatay V, Hacıoğlu G, Ozkaya G et al: The effect of diabetes mellitus on active avoidance learning in rats: the role of nitric oxide. *Med Sci Monit*, 2009; 15(3): BR88–93
- Reaven GM, Thompson LW, Nahum D et al: Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care*, 1990; 13: 16–21
- Ryan CM: Neurobehavioral complications of type I diabetes. Examination of possible risk factors. *Diabetes Care*, 1988; 11: 86–93
- Tun PA, Nathan DM, Perlmutter LC: Cognitive and affective disorders in elderly diabetics. *Clin Geriatr Med*, 1990; 6: 731–46
- Baydas G, Nedzvetskii VS, Nerush PA et al: Altered expression of NCAM in hippocampus and cortex may underlie memory and learning deficits in rats with streptozotocin-induced diabetes mellitus. *Life Sci*, 2003; 73: 1907–16
- Lupien SB, Bluhm EJ, Ishii DN: Systemic insulin-like growth factor-I administration prevents cognitive impairment in diabetic rats, and brain IGF regulates learning/memory in normal adult rats. *J Neurosci Res*, 2003; 74: 512–23
- Patil CS, Singh VP, Kulkarni SK: Modulatory effect of sildenafil in diabetes and electroconvulsive shock-induced cognitive dysfunction in rats. *Pharmacol Rep*, 2006; 58: 373–80

12. Tuzcu M, Baydas G: Effect of melatonin and vitamin E on diabetes-induced learning and memory impairment in rats. *Eur J Pharmacol*, 2006; 537: 106–10
13. Craig WJ: Health-promoting properties of common herbs. *Am J Clin Nutr*, 1999; 70: S491–99
14. Hasani-Ranjbar S, Nayebi N, Larijani B et al: A systematic review of the efficacy and safety of Teucrium species; From anti-oxidant to antidiabetic effects. *Int J Pharmacol*, 2010; 6: 315–25
15. Howes MJR, Perry NSL, Houghton PJ: Plants with traditional uses and activities relevant to the management of Alzheimer's disease and other cognitive disorders. *Phytother Res*, 2003; 17: 1–18
16. Perry N, Court G, Bidet N et al: Cholinergic activities of European herbs and potential for dementia therapy. *J Geriatr Psychiatry*, 1996; 11: 1063–69
17. Tuncer H: Utilization of Wild Plants as Medicine, vol. II. In: The Ministry of Food and Agriculture eds. 1978, Ankara, Atak Printhouse
18. Orhan I, Aslan M: Appraisal of scopolamine-induced anti-amnesic effect in mice and *in vitro* antiacetylcholinesterase and antioxidant activities of some traditionally used *Lamiaceae* plants. *J Ethnopharmacol*, 2009; 122: 327–32
19. Abdolghaffari AH, Baghaei A, Moayer F et al: On the benefit of Teucrium in murine colitis through improvement of toxic inflammatory mediators. *Hum Exp Toxicol*, 2010; 29: 287–95
20. Baluchnejadmojarad T, Roghani M, Roghani-Dehkordi F: Antinociceptive effect of Teucrium polium leaf extract in the diabetic rat formalin test. *J Ethnopharmacol*, 2005; 97: 207–10
21. Hasani P, Yasa N, Vosough-Ghanbari S et al: *In vivo* antioxidant potential of Teucrium polium, as compared to alpha-tocopherol. *Acta Pharm*, 2007; 57: 123–29
22. Lashgari R, Motamedi F, Zahedi Asl S et al: Behavioral and electrophysiological studies of chronic oral administration of L-type calcium channel blocker verapamil on learning and memory in rats. *Behav Brain Res*, 2006; 171: 324–28
23. Shahidi S, Motamedi F, Bakeshloo SA et al: The effect of reversible inactivation of the supramammillary nucleus on passive avoidance learning in rats. *Behav Brain Res*, 2004; 152: 81–87
24. Shahidi S, Komaki A, Mahmoodi M et al: Ascorbic acid supplementation could affect passive avoidance learning and memory in rat. *Brain Res Bull*, 2008; 76: 109–13
25. Hasani-Ranjbar S, Larijani B, Abdollahi M: A systematic review of Iranian medicinal plants useful in diabetes mellitus. *Arch Med Sci*, 2008; 3: 285–92
26. Hasani-Ranjbar S, Larijani B, Abdollahi M: A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. *Inflamm Allergy Drug Targets*, 2009; 8: 2–10
27. Abdollahi M, Karimpour H, Monsef-Esfehani HR: Antinociceptive effects of Teucrium polium L total extract and essential oil in mouse writhing test. *Pharmacol Res*, 2003; 48: 31–35
28. Kadifkova-Panovska T, Kulevanova S, Stefova M: *In vitro* antioxidant activity of some Teucrium species (*Lamiaceae*). *Acta Pharm*, 2005; 55: 207–14
29. Ljubuncic P, Azaizeh H, Portnaya I et al: Antioxidant activity and cytotoxicity of eight plants used in traditional Arab medicine in Israel. *J Ethnopharmacol*, 2005; 99: 43–47
30. Suboh SM, Bilito YY, Aburjai TA: Protective effects of selected medicinal plants against protein degradation, lipid peroxidation and deformability loss of oxidatively stressed human erythrocytes. *Phytother Res*, 2004; 18: 280–84
31. Proestos C, Sereli D, Komaitis M: Determination of phenolic compounds in aromatic plants by RP-HPLC and GC-MS. *Food Chem*, 2006; 95: 44–52
32. Tiwari V, Kuhad A, Bishnoi M et al: Chronic treatment with tocotrienol, an isoform of vitamin E, prevents intracerebroventricular streptozotocin-induced cognitive impairment and oxidative-nitrosative stress in rats. *Pharmacol Biochem Behav*, 2009; 93: 183–89
33. Rahimi R, Nikfar S, Larijani B et al: A review on the role of antioxidants in the management of diabetes and its complications. *Biomed Pharmacother*, 2005; 59: 365–73
34. Baynes JW: Role of oxidative stress in development of complications in diabetes. *Diabetes*, 1991; 40: 405–12
35. Kakkar R, Kalra J, Mantha S et al: Lipid peroxidation and activity of antioxidant enzymes in diabetic rats. *Mol Cell Biochem*, 1995; 151: 113–19
36. Blokland A, Jolles J: Spatial learning deficit and reduced hippocampal ChAT activity in rats after an ICV injection of streptozotocin. *Pharmacol Biochem Behav*, 1993; 44: 491–94
37. Sharma M, Gupta YK: Effect of chronic treatment of melatonin on learning, memory and oxidative deficiencies induced by intracerebroventricular streptozotocin in rats. *Pharmacol Biochem Behav*, 2001a; 70: 325–31
38. Sharma M, Gupta YK: Intracerebroventricular injection of streptozotocin in rats produces both oxidative stress in the brain and cognitive impairment. *Life Sci*, 2001b; 68: 1021–29
39. Sonkusare S, Srinivasan K, Kaul C et al: Effect of donepezil and lercanidipine on memory impairment induced by intracerebroventricular streptozotocin in rats. *Life Sci*, 2005; 77: 1–14
40. Biessels GJ, Kerssen A, de Haan EH et al: Cognitive dysfunction and diabetes: Implications for primary care. *Prim Care Diabetes*, 2007; 1: 187–93
41. Gharaibeh MN, Elayan HH, Salhab AS: Hypoglycemic effects of Teucrium polium. *J Ethnopharmacol*, 1988; 24: 93–99
42. Shahraki MR, Arab MR, Mirimokaddam E et al: The effect of Teucrium polium (*Calpoureh*) on liver function, serum lipids and glucose in diabetic male rats. *Iran Biomed J*, 2007; 11: 65–68
43. Weeks BS: Formulations of dietary supplements and herbal extracts for relaxation and anxiolytic action: Relarian. *Med Sci Monit*, 2009; 15(11): RA256–62