

1-1-2011

## Piracetam reverses haloperidol-induced catalepsy in mice

OMAR ABDEL SALAM

SOMAIA NADA

Follow this and additional works at: <https://journals.tubitak.gov.tr/medical>



Part of the [Medical Sciences Commons](#)

---

### Recommended Citation

SALAM, OMAR ABDEL and NADA, SOMAIA (2011) "Piracetam reverses haloperidol-induced catalepsy in mice," *Turkish Journal of Medical Sciences*: Vol. 41: No. 4, Article 17. <https://doi.org/10.3906/sag-1006-870>

Available at: <https://journals.tubitak.gov.tr/medical/vol41/iss4/17>

This Article is brought to you for free and open access by TÜBİTAK Academic Journals. It has been accepted for inclusion in Turkish Journal of Medical Sciences by an authorized editor of TÜBİTAK Academic Journals. For more information, please contact [academic.publications@tubitak.gov.tr](mailto:academic.publications@tubitak.gov.tr).

## Piracetam reverses haloperidol-induced catalepsy in mice

Omar Abdel SALAM<sup>1</sup>, Somaia NADA<sup>2</sup>

**Aim:** To investigate the memory-enhancing drugs piracetam, vinpocetine, and ginkgo biloba for their ability to reduce catalepsy in mice treated with haloperidol. Haloperidol is a classic neuroleptic drug that induces motor abnormalities and cognitive impairment due to a blockade of dopamine D2 receptors in the striatum.

**Materials and methods:** Catalepsy was induced by intraperitoneal haloperidol (2 mg/kg) administration. The drugs being tested were either administered intraperitoneally (IP) along with the dosage of haloperidol or 30 min prior to the introduction of the haloperidol. Catalepsy was measured using the bar test.

**Results:** The administration of haloperidol (2 mg/kg, IP) resulted in significant catalepsy. Piracetam (in dosages of 50, 100, and 300 mg/kg) given IP at the time of haloperidol administration reduced the duration of catalepsy by 24.4%, 32.3%, and 48.2%, respectively. Piracetam given as a 30-min pretreatment reduced the duration of catalepsy by 59.5%, 72.3%, and 78.2%, respectively. Vinpocetine coadministered IP with haloperidol did not modify catalepsy, but given as a 30-min pretreatment, the drug increased catalepsy duration by 53.5%, 53.6%, and 65.1%, respectively. Ginkgo biloba coadministered IP with haloperidol at 25, 50, or 150 mg/kg increased catalepsy duration by 13.6%-17.1%. Ginkgo biloba given 30 min prior to haloperidol increased catalepsy duration by 29.1%, 35.1%, and 37.2%, respectively.

**Conclusion:** The present study indicates that the nootropic drug piracetam reduces haloperidol-induced catalepsy in mice.

**Key words:** Catalepsy, haloperidol, piracetam, vinpocetine, ginkgo biloba, mice

### Introduction

Typical antipsychotics used in schizophrenia treatment, such as haloperidol, produce extrapyramidal side effects, which are attributed to a blockade of D2 in the striatum (1). Catalepsy is a state of postural immobility (akinesia) with muscular rigidity. Catalepsy induced by haloperidol is considered a rodent model of the Parkinson's-like side effects caused by typical antipsychotics in humans (2). Antipsychotics can also induce deficits in working memory (3,4) and, accordingly, drugs that improve learning and memory are often prescribed to counteract the cognitive impairment.

Piracetam is a pyrrolidine derivative (2-oxo-1-pyrrolidine acetamide) that has been shown to facilitate learning and prevent the development of amnesia under different experimental conditions (5). In clinical practice, the drug has been shown to enhance recovery from aphasia after stroke (6), and to improve cognitive function in the elderly (7) and after coronary artery bypass (8). It also improved degenerative cerebellar ataxia (9) and prevented alcohol withdrawal delirium (10).

Vinpocetine (vinpocetine-ethyl apovincaminat) is a synthetic derivative of the alkaloid vincamine, an extract of periwinkle (*Vinca minor*), and is widely used to improve the cognitive

Received: 04.06.2010 – Accepted: 14.09.2010

<sup>1</sup> Department of Toxicology and Narcotics, National Research Centre, Cairo - EGYPT

<sup>2</sup> Department of Pharmacology, National Research Centre, Cairo - EGYPT

**Correspondence:** Omar M.E. Abdel SALAM, Department of Toxicology and Narcotics, National Research Centre, Cairo - EGYPT  
E-mail: omasalam@hotmail.com

function of patients with cerebrovascular disease. This effect is a result of its ability to increase cerebral blood flow, which in turn increases the regional cerebral glucose uptake (11). It also significantly decreased the risk of transient ischemic attacks and strokes in patients with chronic cerebrovascular insufficiency (12). The drug displayed memory-protective and memory-enhancing properties (13,14). Vinpocetine is a phosphodiesterase 1 inhibitor (15) and a blocker of voltage-gated Na<sup>+</sup> channels (16), which are thought to be especially relevant to its anticonvulsant and neuroprotective effects. Vinpocetine also inhibited lipid peroxidation stimulated by ascorbate/Fe<sup>2+</sup> in rat brain synaptosomes (17).

Standardized extracts from the leaves of ginkgo biloba are widely used to improve cognition and memory in cases of cerebral insufficiency (18,19). Extracts of ginkgo biloba contain 24% ginkgo-flavone glycosides and 6% terpenoids (ginkgolides, bilobalide). The beneficial effects of ginkgo biloba have been ascribed to its antioxidant and free radical scavenging activities (20), as well as its antiinflammatory (21), vasodilatory (22), and rheological (23) properties. Moreover, ginkgolides, especially ginkgolides B and C, are potent platelet-activating factor antagonists (24).

Apart from being used to improve cognitive functions in the elderly and in different disease processes, the aforementioned nootropic drugs might also affect motor circuits in the brain and could therefore be used in the treatment of movement disorders or with conditions that have adverse motor influences. For example, piracetam has been used in the cortical myoclonus, where it resulted in a significant improvement in motor performance (25). It improved gait in patients with cerebellar ataxia (9) and appeared to be effective in reducing the symptoms of tardive dyskinesia in schizophrenic patients on antipsychotic treatment (26). Vinpocetine is a blocker of voltage-gated sodium channels. Such channels are responsible for action potential generation and propagation, and an increased activity of these channels accompanies disease states such as epilepsy, chronic pain, neurodegenerative diseases, and spasticity (27). Vinpocetine has been reported to decrease spontaneous locomotor activity in rats (28). Ginkgo biloba delayed the deterioration of motor

functions in rats with chronic cerebral insufficiency (29). Furthermore, these drugs also displayed a capacity for altering neurotransmitter levels in the brain and dopamine activity in the striatum (30-33), which is relevant to the cataleptic state.

The aim of this study was therefore to investigate the effect of the memory-enhancing drugs piracetam, vinpocetine, and ginkgo biloba on motor symptoms in an animal model of haloperidol-induced Parkinson's disease.

## Materials and methods

### Animals

Swiss male albino mice with a body weight of 20-22 g were used in this study. Standard laboratory food and water were provided ad libitum. Animal procedures were performed in accordance with the Ethics Committee of the National Research Centre and followed the recommendations of the National Institute of Health's Guide for Care and Use of Laboratory Animals (34). Equal groups were used in all experiments, with 6 mice in each group. All drug dosages used in the study were based upon the human dose converted to meet the physical parameters of the rats, as detailed in the Paget and Barnes conversion tables (35).

### Haloperidol-induced catalepsy

Catalepsy, defined as a reduced ability to initiate movement and a failure to achieve correct posture, was measured by the bar test. Mice were positioned so that their hindquarters were on the bench and their forelimbs rested on a 1-cm diameter horizontal bar that was 4 cm above the bench. Mice were judged to be cataleptic if they maintained this position for 30 s or more. The length of time for which the mouse maintained this position was recorded with a stopwatch with a maximum duration of 180 s. This procedure was performed 30 min after the administration of haloperidol (2 mg/kg, IP). The test drugs, i.e. piracetam (100, 150, or 300 mg/kg, IP), vinpocetine (1, 2, or 4 mg/kg), and ginkgo biloba (25, 50, or 150 mg/kg), were given either at the time of the haloperidol administration or 30 min prior to the haloperidol administration. Control animals received 0.9% saline (the vehicle).

## Statistical analyses

Data were expressed as mean  $\pm$  SE. Differences between treatment groups were determined using one-way ANOVA tests followed by multiple comparison by Duncan's multiple range test. A probability value less than 0.05 was considered statistically significant.

## Results

At a dosage of 2 mg/kg, the IP administration of haloperidol produced a significant cataleptic response. The duration of haloperidol-induced catalepsy was significantly reduced by the simultaneous administration of 50, 100, and 300 mg/kg dosages of piracetam, with the reduction figures being 24.4%, 32.3%, and 48.2% ( $P < 0.05$ ), respectively. Piracetam given 30 min prior to haloperidol further reduced the duration of catalepsy by 59.5%, 72.3%, and 78.2% ( $P < 0.05$ ), respectively (Figure 1). Findings showed that the duration of catalepsy was significantly shorter when piracetam was given 30 min prior to

the administration of haloperidol than when the same dosages were given to the mice at the time of haloperidol administration ( $P < 0.05$ ). Vinpocetine (in doses of 1, 2, or 4 mg/kg) had no significant effect on haloperidol catalepsy when given at the same time as the injection of haloperidol. In contrast, the same dosages of vinpocetine administered 30 min before the haloperidol injection significantly increased the duration of catalepsy, by 53.5%, 53.6%, and 65.1% ( $P < 0.05$ ), respectively (Figure 2). The duration of catalepsy was significantly higher when vinpocetine was given 30 min before haloperidol as compared with the results seen in mice given vinpocetine at the same time as the haloperidol administration ( $P < 0.05$ ). The administration of 25, 50, or 150 mg/kg of ginkgo biloba at the time of the haloperidol injection increased catalepsy duration by only 13.6%-17.1% ( $P > 0.05$ ). In contrast, ginkgo biloba given 30 min prior to haloperidol resulted in a significant increase in the duration of the catalepsy response, with data indicating an increase of 29.1%, 35.1%, and 37.2% ( $P < 0.05$ ), respectively (Figure 3). The duration of

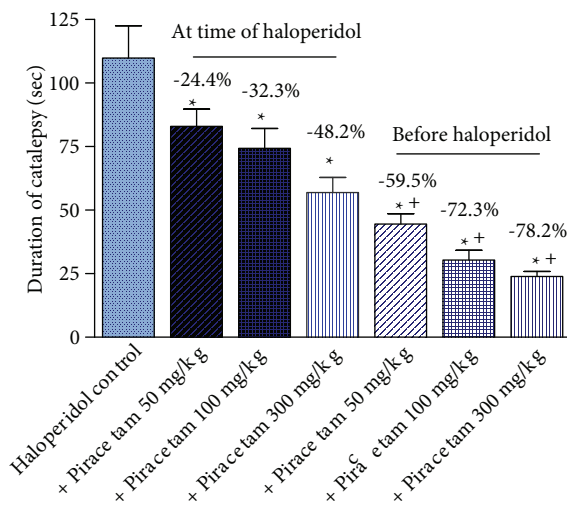


Figure 1. Effect of piracetam on haloperidol-induced (2 mg/kg, IP) catalepsy in mice. Piracetam was given IP either at the time of the haloperidol administration or 30 min prior to that injection. Data represent mean values  $\pm$  SE of 6 mice per group and the percentage change (%) in comparison with the control animals. Statistical differences between the test groups and the control group are indicated by asterisks (\*). The plus sign (+) indicates a significant change from the corresponding treatment group given piracetam at the time of the haloperidol administration.

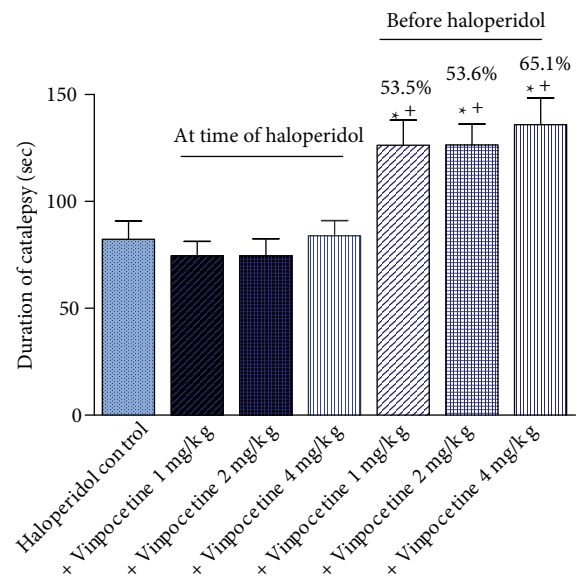


Figure 2. Effect of vinpocetine on haloperidol-induced (2 mg/kg, IP) catalepsy in mice. Vinpocetine was given IP either at the time of the haloperidol administration or 30 min prior to that injection. Data represent mean values  $\pm$  SE of 6 mice per group and the percentage change (%) in comparison with the control animals. Statistical differences between the test groups and the control group are indicated by asterisks (\*). The plus sign (+) indicates a significant change from the corresponding treatment group given vinpocetine at the time of the haloperidol administration.

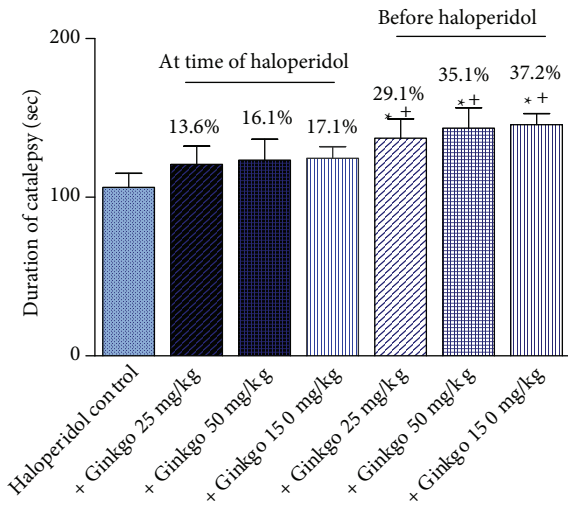


Figure 3. Effect of ginkgo biloba on haloperidol-induced (2 mg/kg, IP) catalepsy in mice. Ginkgo biloba was given IP either at the time of the haloperidol administration or 30 min prior to that injection. Data represent mean values  $\pm$  SE of 6 mice per group and the percentage change (%) in comparison with the control animals. Statistical differences between the test groups and the control group are indicated by asterisks (\*). The plus sign (+) indicates a significant change from the corresponding treatment group given ginkgo biloba at the time of the haloperidol administration.

catalepsy was significantly higher when ginkgo biloba was given 30 min before haloperidol, as compared with mice given ginkgo biloba at the same time as the administration of haloperidol ( $P < 0.05$ ).

## Discussion

The present study provided evidence that catalepsy induced by the antipsychotic drug haloperidol is reduced by the administration of the nootropic drug piracetam and increased by vinpocetine and ginkgo biloba. Typical antipsychotics such as haloperidol, a dopamine D2 receptor antagonist, produce extrapyramidal side effects, which are attributed to a blockade of D2 in the striatum (1). Rats treated with haloperidol show akinesia and rigidity (i.e. catalepsy), effects that are mediated by a blockade of striatal D2 receptors (2). Akinetic catalepsy induced in rats by haloperidol can model human Parkinson's disease. Haloperidol remains effective in inducing catalepsy and striatal Fos/Jun expression in the D1 mutants, and these behavioral and neural effects can be blocked

by D2 dopamine receptor agonists (36). Catalepsy occurs when more than 80% of D2 receptors are occupied by the drug (37). Catalepsy is also driven by the excitatory adenosine and glutamatergic inputs acting on adenosine A2A and N-methyl-D-aspartate (NMDA) receptors in the striatum. This is because NMDA receptor antagonists (38), the nonselective adenosine receptor antagonist caffeine, selective A1, and selective A2A antagonists decreased haloperidol-induced catalepsy in rats (38,39). Catalepsy is also reduced by alpha2 receptor antagonists (alpha2C or alpha2A) (40) or 5-HT1A agonists (41), as well as by metabotropic glutamate receptor 4 agonists (42). Despite having a striatal D2 receptor occupancy similar to classical agents, atypical antipsychotics are less likely to cause extrapyramidal side effects because of their ability to activate 5-HT1A receptors (43).

Piracetam is a drug used to enhance memory and cognitive performance in the elderly or after cerebrovascular accidents (6) by increasing blood flow and affecting membrane fluidity (44) and glucose transport into the cells (45). Piracetam, however, is not without effects on intracortical neurotransmitters. Piracetam restored the number of active GABA-A receptors in rats made anxiolytic and depressed by prolonged hypokinesia (46). It also inhibited the effect of flumazenil and therefore may be shown to act on the benzodiazepine site of the GABA-benzodiazepine receptor complex (47). Drug-inhibited monoamine uptake (dopamine, noradrenaline, serotonin) in cortical and striatal synaptosomes (30) increased K<sup>+</sup>-induced dopamine release from rat striatum in aged rats (31). Thus, piracetam is capable of modifying the dopaminergic activity of the rat striatum, thereby stimulating the neuromediator release (31). Studies also suggested the involvement of the dopaminergic system in the excitatory effects of piracetam (100 mg/kg) on foot shock-induced aggressive behavior in mice, which was blocked by treatment with haloperidol (48). The effect of piracetam on dopaminergic transmission might be of particular relevance to the inhibition of haloperidol-induced catalepsy observed in the present study. Because catalepsy is thought to be a good predictor of extrapyramidal symptoms in humans, treatment with piracetam might decrease the occurrence or severity of extrapyramidal symptoms induced in humans by the use of antipsychotics. Other

researchers have reported that piracetam caused an increase of haloperidol-induced catalepsy in rats, but those findings reflect studies that tested a dose considerably higher than those used in the present study (1000 mg/kg) (49); studies that examined a piracetam dosage of 500 mg/kg showed markedly inhibited haloperidol catalepsy (50).

In the present study, vinpocetine increased catalepsy when administered prior to haloperidol. Other studies have indicated that vinpocetine (5-100 mg/kg PO) did not antagonize reserpine-induced catalepsy, and it did not impair rotarod performance or produce ataxia in mice (28). There is limited information on the effect of vinpocetine on dopaminergic neurotransmission. In striatal slices, vinpocetine reduced the efflux of dopamine and acetylcholine evoked by glutamate, quisqualate, and NMDA (51), and it inhibited the release of dopamine evoked by veratridine reversal of the dopamine transporter (32). These effects could explain the present study's observed increase in catalepsy duration after the introduction of vinpocetine. Other studies found no inhibitory activity for vinpocetine and its major metabolite, apovincaminic acid, in monoamine receptor binding assays or in synaptosomal uptake assays performed *in vitro* (52). Vinpocetine inhibits the permeability of voltage-sensitive presynaptic Na<sup>+</sup> channels, which selectively inhibits the transporter-mediated release of all neurotransmitters (32).

Some studies have suggested that, in light of its antioxidant properties, ginkgo biloba might prove valuable in the treatment of PD. One of its diterpenes, ginkgolide B, inhibited apoptosis induced by 6-hydroxydopamine by decreasing the intracellular calcium concentration (53). In a mouse model of Parkinson's disease caused by the administration

of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a compound that causes nigrostriatal dopaminergic degeneration, ginkgo biloba attenuated the toxin-induced loss of striatal dopamine levels and tyrosine hydroxylase immunostaining in the striatum and substantia nigra pars compacta. This neuroprotective effect of ginkgo biloba was associated with the inhibition of lipid peroxidation and the reduction of superoxide radical production (54). Extracts of ginkgo biloba leaves have been found to influence dopaminergic neurotransmission in the brain. Ginkgo biloba increased the extracellular concentration of dopamine in the prefrontal cortex of rats and upregulated the subgroup of dopamine receptors in the frontal cortex (55). The extract also increased the level of serotonin (5-HT) in the hippocampus and 5-HIAA (5-HT metabolite) in the prefrontal cortex (56). In other studies, norepinephrine, serotonin, and dopamine uptake transporters and MAO activity were inhibited by ginkgo biloba *in vitro* (33). Ginkgo biloba inhibited NMDA-evoked currents and Na<sup>+</sup> channels in cultured cortical cells (57). In the present study, however, haloperidol-induced catalepsy was increased by the administration of ginkgo biloba (25, 50, and 150 mg/kg). Other researchers have also found that doses of 40 and 80 mg/kg of ginkgo biloba extract significantly enhanced haloperidol- and L-nitroarginine-induced catalepsy in mice (58). The mechanism(s) behind this effect of ginkgo is or are not clear and this issue awaits further studies.

In conclusion, the present paper provides evidence that piracetam is able to improve haloperidol-induced catalepsy in mice. In contrast, the administration of vinpocetine or ginkgo biloba was associated with a worsening of catalepsy.

## References

- Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. PET-analysis of central D-2 and D2-dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. *Archl Gen Psychiatry* 1992; 49: 538-44.
- Hoffman DC, Donovan H. Catalepsy as a rodent model for detecting antipsychotic drugs with extrapyramidal side effect liability. *Psychopharmacology* 1995; 120: 128-33.
- Legangneux E, McEwen J, Wesnes K, Berougnan L, Miget N, Canal M et al. The acute effects of amisulpride (50 mg and 200 mg) and haloperidol (2 mg) on cognitive function in healthy elderly volunteers. *Journal of Psychopharmacology* 2000; 14: 164-71.
- Harrison BE, Therrien B. Effect of antipsychotic medication use on memory in patients with Alzheimer's disease: Assessing the potential risk for accelerated recent autobiographical memory loss. *J Gerontol Nurs* 2007; 33: 11-20.

5. Shorvon S. Pyrrolidone derivatives. *Lancet* 2001; 358: 1885-92.
6. Kessler J, Thiel A, Karbe H, Heiss WD. Piracetam improves activated blood flow and facilitates rehabilitation of poststroke aphasic patients. *Stroke* 2000; 31: 2112-6.
7. Waegemans T, Wilsher CR, Danniau A, Ferris SH, Kurz A, Winblad B. Clinical efficacy of piracetam in cognitive impairment: a meta-analysis. *Dement Geriatr Cogn Disord* 2002; 13: 217-24.
8. Holinski S, Claus B, Alaaraj N, Dohmen PM, Kirilova K, Neumann K et al. Cerebroprotective effect of piracetam in patients undergoing coronary bypass surgery. *Med Sci Monit* 2008; 14: PI53-7.
9. Ince GD, Agan K, Afsar N, Borucu D, Us O. The effect of piracetam on ataxia: clinical observations in a group of autosomal dominant cerebellar ataxia patients. *J Clin Pharm Ther* 2008; 33: 175-8.
10. Kalmar S. Adjuvant therapy with parenteral piracetam in alcohol withdrawal delirium. *Orv Hetil* 2003; 144: 927-30.
11. Vas A, Gulyas B, Szabo Z, Bonoczki P, Csiba L, Kiss B et al. Clinical and non-clinical investigations using positron emission tomography, near infrared spectroscopy and transcranial Doppler methods on the neuroprotective drug vinpocetine: a summary of evidences. *J Neurol Sci* 2002; 203-4: 259-62.
12. Valikovics A. Investigation of the effect of vinpocetine on cerebral blood flow and cognitive functions. *Ideggyogy Sz* 2007; 60: 301-10.
13. DeNoble VJ, Repetti SJ, Gelpke LW, Wood LM, Keim KL. Vinpocetine: nootropic effects on scopolamine-induced and hypoxia-induced retrieval deficits of a step-through passive avoidance response in rats. *Pharmacol Biochem Behav* 1986; 24: 1123-8.
14. Bhatti JZ, Hindmarch I. Vinpocetine effects on cognitive impairments produced by flunitrazepam. *Int Clin Psychopharmacol* 1987; 2: 325-31.
15. Van Staveren WCG, Markerink Ittersum M, Steinbusch HW, de Vente J. The effects of phosphodiesterase inhibition on cyclic GMP and cyclic AMP accumulation in the hippocampus of the rat. *Brain Res* 2001; 888: 275-86.
16. Sitges M, Galvan E, Nekrassov V. Vinpocetine blockade of sodium channels inhibits the rise in sodium and calcium induced by 4-aminopyridine in synaptosomes. *Neurochem Int* 2005; 46: 533-40.
17. Santos MS, Duarte AI, Moreira PI, Oliveira CR. Synaptosomal response to oxidative stress: Effect of vinpocetine. *Free Radic Res* 2000; 32: 57-66.
18. DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. *Curr Drug Targets* 2000; 1: 25-58.
19. Oken BS, Strozach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol* 1998; 55: 1409-15.
20. Schindowski K, Leutner S, Kressmann S, Eckert A, Müller WE. Age-related increase of oxidative stress-induced apoptosis in mice prevention by Ginkgo biloba extract (EGb761). *J Neural Transm* 2001; 108: 969-78.
21. Abdel-Salam OME, Baiuomy AR, El-Batran S, Arbid MS. Evaluation of the anti-inflammatory, anti-nociceptive and gastric effects of ginkgo biloba in the rat. *Pharmacol Res* 2004; 49: 133-42.
22. Chung HS, Harris A, Kristinsson JK, Ciulla TA, Kagemann C, Ritch R. Ginkgo biloba extract increases ocular blood flow velocity. *J Ocul Pharmacol Ther* 1999; 15: 233-40.
23. Jung F, Mrowietz C, Kiesewetter H, Wenzel E. Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers. *Arzneimittelforschung* 1990; 40: 589-93.
24. Korth R, Nunez D, Bidault J, Benveniste J. Comparison of three paf-acether receptor antagonist ginkgolides. *Eur J Pharmacol* 1988; 152: 101-10.
25. Fedi M, Reutens D, Dubeau F, Andermann E, D'Agostino D, Andermann E. Long-term efficacy and safety of piracetam in the treatment of progressive myoclonus epilepsy. *Arch Neurol* 2001; 58: 781-6.
26. Libov I, Miodownik C, Bersudsky Y, Dwolatzky T, Lerner V. Efficacy of piracetam in the treatment of tardive dyskinesia in schizophrenic patients: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2007; 68: 1031-7.
27. Tarnawa I, Bölcskei H, Kocsis P. Blockers of voltage-gated sodium channels for the treatment of central nervous system diseases. *Recent Patents on CNS Drug Discovery* 2007; 2: 57-78.
28. Keim KL, Hall PC. General neuropharmacology of vinpocetine: A putative cerebral activator. *Drug Development Research* 2004; 11: 107-15.
29. Lin CC, Cheng WL, Hsu SH, Chang CM. The effects of Ginkgo biloba extracts on the memory and motor functions of rats with chronic cerebral insufficiency. *Neuropsychobiology* 2003; 47: 47-51.
30. Stancheva SL, Alova LG. Biogenic monoamine uptake by rat brain synaptosomes during aging. Effects of nootropic drugs. *Gen Pharmacol* 1994; 25: 981-7.
31. Budygin EA, Gainetdinov RR, Titov DA, Kovalev GI. The effect of a low dose of piracetam on the activity of the dopaminergic system in the rat striatum. *Eksp Klin Farmakol* 1996; 59: 6-8.
32. Trejo F, Nekrassov V, Sitges M. Characterization of vinpocetine effects on DA and DOPAC release in striatal isolated nerve endings. *Brain Res* 2001; 909: 59-67.
33. Fehske CJ, Leuner K, Müller WE. Ginkgo biloba extract (EGb761) influences monoaminergic neurotransmission via inhibition of NE uptake, but not MAO activity after chronic treatment. *Pharmacol Res* 2009; 60: 68-73.
34. National Institute of Health. Guide for the care and use of laboratory animals, publication no. 85-23. Washington, DC: National Academies Press; 1985.

35. Paget GE, Barnes JM. Toxicity tests. In: Laurence DR, Bacharach AL, editors. *Evaluation of drug activities pharmacometrics*. London and New York: Academic Press; 1964. p.1-135.
36. Moratalla R, Xu M, Tonegawa S, Graybiel AM. Cellular responses to psychomotor stimulant and neuroleptic drugs are abnormal in mice lacking the D1 dopamine receptor. *Proc Natl Acad Sci USA* 1996; 93: 14928-33.
37. Wadenberg ML, Soliman A, VanderSpek SC, Kapur S. Dopamine D2 receptor occupancy is a common mechanism underlying animal models of antipsychotics and their clinical effects. *Neuropsychopharmacology* 2001; 25: 633-41.
38. Góngora-Alfaro JL, Moo-Puc RE, Villanueva-Toledo JR, Alvarez-Cervera FJ, Bata-García JL, Heredia-López FJ et al. Long-lasting resistance to haloperidol-induced catalepsy in male rats chronically treated with caffeine. *Neurosci Lett* 2009; 463: 210-4.
39. Varty GB, Hodgson RA, Pond AJ, Grzelak ME, Parker EM, Hunter JC. The effects of adenosine A2A receptor antagonists on haloperidol-induced movement disorders in primates. *Psychopharmacology* 2008; 200: 393-401.
40. Imaki J, Mae Y, Shimizu S, Ohno Y. Therapeutic potential of alpha2 adrenoceptor antagonism for antipsychotic-induced extrapyramidal motor disorders. *Neurosci Lett* 2009; 454: 143-7.
41. Prinssen EP, Colpaert FC, Koek W. 5-HT1A receptor activation and anti-cataleptic effects: high-efficacy agonists maximally inhibit haloperidol-induced catalepsy. *Eur J Pharmacol* 2002; 453: 217-21.
42. Niswender CM, Johnson KA, Weaver CD, Jones CK, Xiang Z, Luo Q et al. Discovery, characterization, and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4. *Mol Pharmacol* 2008; 74: 1345-58.
43. Nowakowska E, Kus K, Krzyzanski W, Czubak A. Influence of haloperidol and clozapine on some behavioral effects in rats. *Arzneimittelforschung* 2006; 56: 807-13.
44. Müller WE, Koch S, Scheuer K, Rostock A, Bartsch R. Effects of piracetam on membrane fluidity in the aged mouse, rat, and human brain. *Biochem Pharmacol* 1997; 53: 135-40.
45. Heiss WD, Hebold I, Klinkhammer P, Ziffling P, Szelies B, Pawlik G et al. Effect of piracetam on cerebral glucose metabolism in Alzheimer's disease as measured by positron emission tomography. *J Cereb Blood Flow Metab* 1988; 8: 613-7.
46. Akopian VP, Balian LS, Avetisian NA. The effect of hypokinesia on depression and on the central GABA-A receptor complexes in the rat brain. *Eksp Klin Farmakol* 2006; 69: 10-3.
47. Moldavkin GM, Voronina TA, Neznamov GG, Maletova OK, Eliava NV. Participation of GABA-benzodiazepine receptor complex in the anxiolytic effect of piracetam. *Eksp Klin Farmakol* 2006; 69: 7-9.
48. Pant KK, Nath C. Dopaminergic involvement in the effects of piracetam on foot shock induced aggression in mice. *Indian J Med Res* 1993; 98: 155-9.
49. Rägo LK, Allikmets LH, Zarkovsky AM. Effects of piracetam on the central dopaminergic transmission. *Naunyn Schmiedebergs Arch Pharmacol* 1981; 318: 36-7.
50. Gainetdinov RR, Raevskii KS. Substances increasing the extracellular content of dopamine in the striatum prevent the development of haloperidol catalepsy in rats. *Bull Exp Biol Med* 1996; 121: 399-401.
51. Kiss B, Cai NS, Erdő SL. Vinpocetine preferentially antagonizes quisqualate/AMPA receptor responses: evidence from release and ligand binding studies. *Eur J Pharmacol* 1991; 209: 109-12.
52. Lee DKH, Geiger G. Effect of vinpocetine on monoamine receptor binding and synaptosomal uptake in the rat brain. *Drug Development Research* 2004; 14: 281-3.
53. Meng H, Li C, Feng L, Cheng B, Wu F, Wang X et al. Effects of Ginkgolide B on 6-OHDA-induced apoptosis and calcium overload in cultured PC12. *Int J Dev Neurosci* 2007; 25: 509-14.
54. Rojas P, Serrano-García N, Mares-Sámamo JJ, Medina-Campos ON, Pedraza-Chaverri J, Ogren SO. EGB761 protects against nigrostriatal dopaminergic neurotoxicity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in mice: role of oxidative stress. *Eur J Neurosci* 2008; 28: 41-50.
55. Su SY, Hsieh CL, Wu SL, Cheng WY, Li CC, Lo HY et al. Transcriptomic analysis of EGB 761-regulated neuroactive receptor pathway in vivo. *J Ethnopharmacol* 2009; 123: 68-73.
56. Blecharz-Klin K, Piechal A, Joniec I, Pyrzanowska J, Widy-Tyszkiewicz E. Pharmacological and biochemical effects of Ginkgo biloba extract on learning, memory consolidation and motor activity in old rats. *Acta Neurobiol Exp (Wars)* 2009; 69: 217-31.
57. Szasz BK, Lenkey N, Barth AM, Mike A, Somogyvari Z, Farkas O et al. Converging effects of Ginkgo biloba extract at the level of transmitter release, NMDA and sodium currents and dendritic spikes. *Planta Med* 2008; 74: 1235-9.
58. Fontana L, Souza AS, Del Bel EA, Oliveira RM. Ginkgo biloba leaf extract (EGB 761) enhances catalepsy induced by haloperidol and L-nitroarginine in mice. *Braz J Med Biol Res* 2005; 38: 1649-54.