



Research Article

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AMELIORATION OF HALOPERIDOL-INDUCED OROFACIAL DYSKINESIA AND CATALEPSY BY ELLAGIC ACID IN RATS

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Received on: 13/01/16 Revised on: 31/01/16 Accepted on: 09/02/16

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DOI: 10.7897/2277-4343.07292

ABSTRACT

The aim of the present study was to investigate the effect of ellagic acid on haloperidol-induced orofacial dyskinesia and catalepsy in Wistar male albino rats and to explore the possible underlying mechanisms for these effects. Haloperidol (1 mg/kg, ip) was administered on 21 successive days to induce orofacial dyskinesia in rats. Ellagic acid (10, 20 and 40 mg/kg, po) was administered for 21 successive days to separate groups of haloperidol treated rats. Haloperidol significantly induced orofacial dyskinesia in rats as indicated by increase in vacuous chewing movements and tongue protrusions. It also increased duration of catalepsy and decreased locomotor activity of rats. Ellagic acid significantly reversed haloperidol-induced vacuous chewing movements, tongue protrusions, catalepsy and hypolocomotion in rats and significantly ameliorated haloperidol-induced decrease in brain dopamine and serotonin levels. Ellagic acid significantly attenuated haloperidol-induced orofacial dyskinesia and catalepsy, probably through increase in brain dopamine and serotonin levels. Thus, ellagic acid may be explored further for its potential in the management of neuroleptic-induced tardive dyskinesia and Parkinsonism.

Key words: Ellagic acid, Haloperidol, Orofacial dyskinesia, Catalepsy

INTRODUCTION

Tardive dyskinesia is a neurological syndrome resulting from chronic administration of neuroleptics, such as haloperidol; and characterized by repetitive involuntary movements involving bucco-lingual region. Occurrence of tardive dyskinesia is about 20-50 % in patients who are on prolonged antipsychotic medications¹. Haloperidol, a typical neuroleptic widely used for treatment of schizophrenia, is associated with many neurological and extrapyramidal side effects mainly parkinsonism and tardive dyskinesia². Tardive dyskinesia may be due to increase in oxidative stress and dopamine supersensitivity. Haloperidol is metabolized by an oxidase which generates large quantities of oxyradicals and a toxic pyridinium-like metabolite³ and induces oxidative stress⁴. Chronic blockade of dopamine D₂ receptors by neuroleptics in nigrostriatal neurones of the brain leads to increase in dopamine turnover in basal ganglia and this may lead to overproduction of free radicals such as dopamine quinone and hydrogen peroxide through the activity of MAO. Tardive dyskinesia is due to a neurotoxic effect of these free radical byproducts from catecholamine metabolism in the basal ganglia⁵. The dopamine supersensitivity hypothesis proposes that antipsychotic drug treatment causes hypersensitization of dopamine D₂ receptors, via increased density in all dopaminergic pathways. This disturbs dopamine levels in brain regions responsible for motor symptoms, resulting in motor dysfunction. Classical neuroleptics such as haloperidol remain bound to dopamine D₂ receptors and accumulate in brain tissue⁶. This leads to increased density of dopamine D₂ receptors and increased uptake of dopamine, especially after withdrawal of antipsychotics, which results in tardive dyskinesia. Various neurotransmitter (dopaminergic, serotonergic, noradrenergic and GABAergic) systems abnormalities have been implicated in the pathophysiology of tardive dyskinesia⁷.

Bioactive compounds possessing antioxidant activity such as quercetin⁸, gallic acid⁹, etc. have been shown to be effective in reversing neuroleptic-induced orofacial dyskinesia in laboratory animals. Vitamin E and melatonin have antioxidant property and been reported to reverse symptoms of tardive dyskinesia in clinical studies^{10, 11}. Thus, substances possessing antioxidant activity may be explored for prevention and treatment of neuroleptic-induced tardive dyskinesia¹².

Ellagic acid is a naturally occurring polyphenolic compound, present in a number of plants such as *Embllica officinalis*¹³, *Punica granatum*¹⁴ etc. Ellagic acid has been reported to possess neuroprotective¹⁵, antidepressant¹⁶, anti-epileptic¹⁷, anti-Alzheimer¹⁸, anti-amyloid¹⁹, anti-parkinsonian²⁰, anti-anxiety²¹ and antioxidant²² activities. Recently, we have reported protective effect of ellagic acid against reserpine-induced orofacial dyskinesia and catalepsy in rats²³. But the effect of ellagic acid on haloperidol-induced orofacial dyskinesia and catalepsy has not been reported in the literature. So this study was designed to explore the effect of ellagic acid on haloperidol-induced orofacial dyskinesia, catalepsy and hypolocomotion in rats.

MATERIALS AND METHODS

Experimental animals

Wistar male albino rats, weighing 100-150 g and 2-3 months age were purchased from Disease Free Small Animal House, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (Haryana, India). Only male rats were used in present study, since estrogens present in female rats have been reported to possess neuroprotective property which may mask development of orofacial dyskinesia²⁴. The animals were housed under standard laboratory conditions with 12 hour light-dark cycle. They had free access to food and water. The animals were

acclimatized to laboratory conditions prior to experimentation. The experiments were carried out between 9:00 and 16:00 h. The experimental protocol was approved by Institutional Animal Ethics Committee [Item no. 4 of the minutes of 26th meeting of IAEC (Endst. No. IAEC/193-201; dated 09-5-2014)]. The animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India.

Drugs and chemicals

Haloperidol (Serenace®, RPG Life Sciences Ltd, Mumbai, India), ellagic acid and dopamine hydrochloride (Hi-Media Laboratories Pvt. Ltd., Mumbai, India), serotonin creatinine sulfate monohydrate (Sigma-Aldrich, USA) were used in the present study. All other reagents used were of analytical grade. Haloperidol injection was diluted with distilled water and administered intraperitoneally. Ellagic acid was suspended in 0.1% w/v gum acacia and administered orally. All the drugs were administered in a volume of 0.5 ml per 100 g of body weight of rats.

Selection of doses

Doses of various drugs were selected on the basis of literature, i.e., 1 mg/kg haloperidol²⁵, 10, 20 and 40 mg/kg ellagic acid^{17, 26}.

Induction of orofacial dyskinesia

Haloperidol (1 mg/kg, ip) was administered for 21 successive days to induce orofacial dyskinesia. All behavioral assessments were done weekly and last quantification was done after 24 hour of last dose of haloperidol²⁵.

Experimental protocol

The animals were distributed into the following groups, each group having 6 animals:

Groups 1 to 5 (n = 6 each): Vehicle (0.1% gum acacia), haloperidol (1 mg/kg, ip), ellagic acid (10, 20, 40 mg/kg, po) + haloperidol (1 mg/kg, ip), respectively.

Haloperidol was administered for 21 successive days for induction of oral dyskinesia. Ellagic acid was administered orally for 21 successive days. Haloperidol was administered after 50 min of ellagic acid administration daily for 21 successive days. Vacuous chewing movements (VCMs) and tongue protrusions were recorded weekly i.e. on 7th and 14th day before ellagic acid administration and on 22nd day (24 h after last dose administration of haloperidol). After recording of VCMs and tongue protrusions in animals of group 1 to 5, they were subjected to behavioral assessment for catalepsy. Animals from group 1 to 5 after behavioral assessment for catalepsy were tested in actophotometer for recording of locomotor activity.

Behavioral models

Haloperidol-induced VCMs and tongue protrusions

On test day, rats were individually placed in a small observation cage (20×20×19 cm³) for assessment of orofacial dyskinesia. Animals were given 10 min to get used to observation cage before behavioral assessments. To quantify the occurrence of orofacial dyskinesia, mirrors were placed under the floor and behind the back wall of the observation cage to permit observations when animal faced away from the observer. The behavioral parameters (VCMs and tongue protrusion) of oral dyskinesia were measured continuously for a period of 5 min. VCMs are defined as single mouth openings in the vertical plane not directed towards physical material. VCMs or tongue protrusion were not taken into account during a period of grooming. Counting was stopped whenever the rat began

grooming, and restarted when grooming stopped. In all the experiments, the scorer was unaware of the treatment given to the animals⁸.

Haloperidol-induced catalepsy

The catalepsy was assessed using 3 and 9 cm wooden blocks²⁷. The following scores were assigned to the rats: rats move normally when placed on table, score 0; rats move normally when touched/pushed, score 0.5; front paws of rat were placed on 3 cm block and if it fails to correct the posture in 10 s, a score of 0.5 was assigned to each paw (total 1). If the rat fails to correct the posture within 10 s, when placed on 9 cm block, score for each paw was 1 (total 2); thus for a single rat maximum score assigned was 3.5.

Measurement of locomotor activity

The horizontal locomotor activities of control and test animals were measured for a period of 10 min²⁷ using Medicraft Photoactometer, Model No. 600-6D (INCO, Ambala, India). The locomotor activity was expressed in terms of total photo beam counts/10 min per animal.

Biochemical estimations

Dissection and homogenization

After behavioral testing, on day 22, rats were sacrificed by cervical dislocation and forebrain⁸ was dissected out. Dopamine and serotonin levels were estimated by the method of Schlumpf et al.²⁸ with slight modifications. The forebrain was weighed and homogenized in 3 ml HCl- Butanol (0.85 ml 37% HCl in 1 liter n-butanol) in a cool environment for 1 min. The sample was then centrifuged at 0° C for 10 min at 2000 g using refrigerated centrifuge (Remi instrument, C-30 plus, Mumbai, India). 0.8 ml of supernatant phase was removed and added to a centrifuge tube containing 2 ml of heptane and 0.25 ml 0.1 M HCl. After 10 min of vigorous shaking, the tube was centrifuged under same conditions as in order to separate two phases. Upper organic phase was discarded and the aqueous phase was used for dopamine and serotonin assay.

Estimation of brain dopamine levels

To 1 ml of the HCl phase, 0.25 ml 0.4 M HCl and 0.5 ml EDTA/sodium acetate buffer (pH 6.9) were added, followed by 0.5 ml iodine solution (0.1 M in ethanol) for oxidation. The reaction was stopped after 2 min by the addition of 0.5 ml sodium sulphite in 5 M sodium hydroxide (0.5 g Na₂SO₃ in 2 ml H₂O + 18 ml 5 M NaOH). 10 M Acetic acid (0.5 ml) was added 1.5 min later. The solution was then heated to 100°C for 6 min. When the samples again reach room temperature, fluorescence was read (330 to 375 nm) using Systronic photofluorometer (Model 152, Ahmedabad, Gujarat). Compared the tissue values (fluorescence of tissue extract minus fluorescence of tissue blank) with an internal reagent standard (fluorescence of internal reagent standard minus fluorescence of internal reagent blank). Tissue blanks for the assay were prepared by adding the reagents of the oxidation step in reverse order (sodium sulphite before iodine). Internal reagent standards were obtained by adding 500 ng of dopamine hydrochloride in 0.125 ml distilled water and 2.5 ml HCl-Butanol, which was then carried through the entire extraction procedure. For the internal reagent blank, 0.125 ml water was added to 2.5 ml HCl-butanol²⁸.

Estimation of brain serotonin levels

1.25 ml of o-phthalaldehyde reagent (20 mg% in conc. HCl) was added to 1 ml of the aqueous phase (mentioned above under dissection and homogenization). The fluorophore was developed by heating to 100°C for 10 min. After the samples reached equilibrium with the ambient temperature, fluorescence or

intensity readings at 360-470 nm were taken using Systronic photofluorometer (Model 152, Ahmedabad, Gujarat). Compared the tissue values (fluorescence of tissue extract minus fluorescence of tissue blank) with an internal reagent standard (fluorescence of internal reagent standard minus fluorescence of internal reagent blank). For serotonin tissue blank, 0.025 conc. HCl without o-phthalaldehyde was added. Internal reagent standard was obtained by adding 500 ng of serotonin creatinine sulfate monohydrate in 0.125 ml distilled water and 2.5 ml HCl-Butanol, which was then carried through the entire extraction

procedure. For the internal reagent blank, 0.125 ml distilled water was added to 2.5 ml HCl-butanol²⁸.

Statistical analysis

All the results were expressed as mean ± SEM. Data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test using Graph Pad Instat. *p* < 0.05 was considered as statistically significant.

Table 1: Effect of ellagic acid on haloperidol-induced changes in brain dopamine and serotonin levels

Drug Treatment (mg/kg)	Dopamine levels (pg/mg) (mean ± SEM)	Serotonin levels (pg/mg) (mean ± SEM)
Vehicle (0.1% gum acacia)	919.86 ± 95.21	1718.75 ± 124.55
Haloperidol (1)	518.67 ± 40.53 ^a	952.33 ± 79.17 ^a
Ellagic Acid (10) + Haloperidol (1)	906.33 ± 52.08 ^b	1526.71 ± 119.79 ^b
Ellagic Acid (20) + Haloperidol (1)	938.34 ± 93.77 ^b	1826.54 ± 104.5 ^c
Ellagic Acid (40) + Haloperidol (1)	1018.69 ± 54.21 ^c	1504.35 ± 72.74 ^b
<i>F</i> (4, 25)	7.632	10.856
<i>p</i> value	<0.05	<0.05

n = 6 each group. Data were analysed by using one-way ANOVA followed by Tukey's multiple comparison test. ^a *p* < 0.01 as compared to vehicle treated control, ^b *p* < 0.01, and ^c *p* < 0.001 as compared to haloperidol treated group.

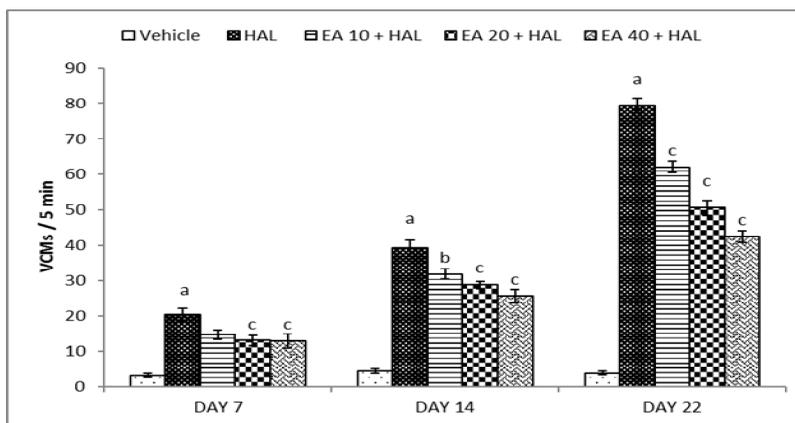


Figure 1: Effect of ellagic acid on haloperidol-induced vacuous chewing movements in rats

n = 6 each group. Values are expressed as the mean ± SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test.

F (4, 25), Day 7=17.17; Day 14=70.73; Day 22=266.55. *p* < 0.05. ^a *p* < 0.001, as compared to vehicle treated control, ^b *p* < 0.05 and ^c *p* < 0.001 respectively as compared to haloperidol treated group. HAL stands for haloperidol; EA stands for ellagic acid.

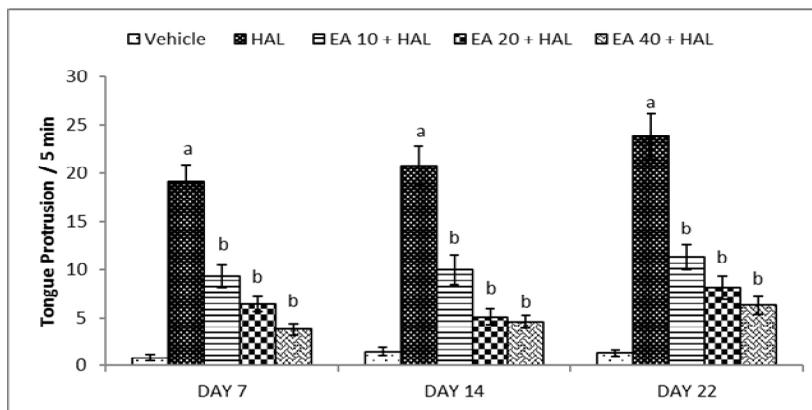


Figure 2: Effect of ellagic acid on haloperidol-induced tongue protrusions in rats

n = 6 each group. Values are expressed as the mean ± SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test.

F (4, 25), Day 7=45.89; Day 14=37.94; Day 22=38.47. *p* < 0.05. ^a *p* < 0.001 as compared to vehicle treated control, ^b *p* < 0.001 as compared to haloperidol treated group. HAL stands for haloperidol; EA stands for ellagic acid.

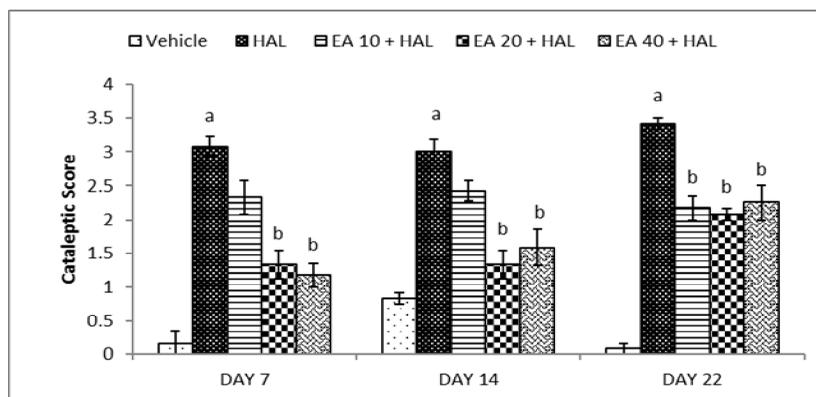


Figure 3: Effect of ellagic acid on haloperidol-induced catalepsy in rats

n= 6 each group. Values are expressed as the mean \pm SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test.

$F(4, 25)$, Day 7=34.17; Day 14=34.53; Day 22=65. $p < 0.05$. ^a $p < 0.001$ as compared to vehicle treated control, ^b $p < 0.001$ as compared to haloperidol treated group. HAL stands for haloperidol; EA stands for ellagic acid.

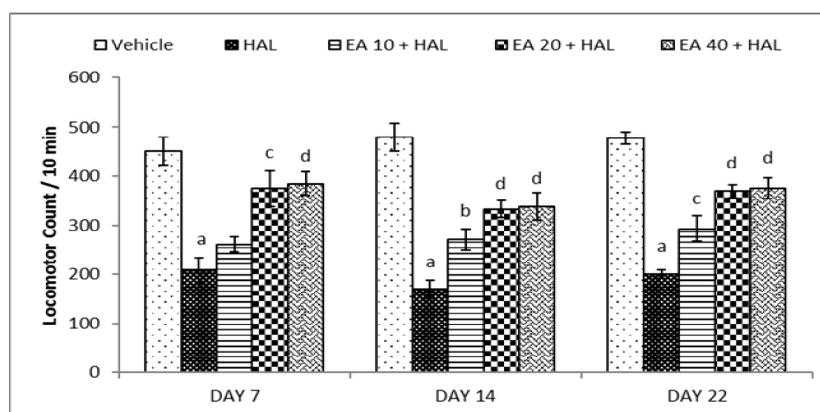


Figure 4: Effect of ellagic acid on locomotor activity of rats using actophotometer

n= 6 each group. Values are expressed as the mean \pm SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test.

$F(4, 25)$, Day 7=13.69; Day 14=24.08; Day 22=34.53. $p < 0.05$. ^a $p < 0.001$ as compared to vehicle treated control, ^b $p < 0.05$, ^c $p < 0.01$ and ^d $p < 0.001$ as compared to haloperidol treated group. HAL stands for haloperidol; EA stands for ellagic acid.

RESULTS

Effect of ellagic acid on haloperidol-induced VCMs and tongue protrusion

Haloperidol (1 mg/kg, ip) treatment significantly increased VCMs and tongue protrusion in rats on day 7, 14 and 22 as compared to respective vehicle treated control. Ellagic acid (20 and 40 mg/kg, po) significantly reversed haloperidol-induced VCMs and tongue protrusion on day 7, 14 and 22 as compared to respective haloperidol treated animals. The lowest dose of ellagic acid (10 mg/kg) did not significantly reverse haloperidol-induced VCMs on 7th day, but significantly reversed haloperidol-induced VCMs on 14th day and 22nd day. Ellagic acid (10 mg/kg) significantly decreased haloperidol-induced tongue protrusion on 7th, 14th and 22nd days (Figure 1 and 2).

Effect of ellagic acid on haloperidol-induced catalepsy in rats

Haloperidol (1 mg/kg, ip) treatment significantly increased cataleptic scores of rats on day 7, 14 and 22 as compared to respective vehicle treated control. Ellagic acid (20 and 40 mg/kg, po) administered for 21 successive days significantly reversed haloperidol-induced catalepsy. But the lowest dose (10

mg/kg) of ellagic acid significantly reversed haloperidol-induced catalepsy on day 22 only (Figure 3).

Effect of ellagic acid on haloperidol-induced decrease in locomotor activity of rats

Haloperidol (1 mg/kg, ip) treatment significantly decreased the locomotor activity of rats on day 7, 14 and 22 as compared to respective vehicle treated control. Ellagic acid (20 and 40 mg/kg, po) significantly reversed haloperidol-induced decrease in locomotor activity of rats after 7, 14 and 21 days of treatment. The lowest dose (10 mg/kg) of ellagic acid did not show significant increase in locomotor count on 7th and 14th days, but significantly reversed haloperidol-induced decrease in locomotor activity of rats after 21 days of treatment (Figure 4).

Effect of ellagic acid on haloperidol-induced changes in brain dopamine and serotonin levels

Haloperidol significantly decreased dopamine and serotonin levels in rat brain. Whereas, ellagic acid (all the 3 doses) significantly reversed haloperidol-induced decrease in brain dopamine and serotonin levels (Table 1).

DISCUSSION

In the present study, chronic administration of ellagic acid significantly inhibited haloperidol-induced orofacial dyskinesia and catalepsy as compared to vehicle-treated control. Haloperidol-induced orofacial dyskinesia model is widely employed model in rodents to predict anti-tardive dyskinesia potential of drugs^{8, 29}. Haloperidol (1 mg/kg, ip) produced significant increase in VCMs and tongue protrusions in rats, indicating induction of orofacial dyskinesia. Haloperidol also significantly produced catalepsy in rats. Catalepsy in animals shares similarities with Parkinson's disease in humans. Antipsychotic drugs induce catalepsy by decreased dopamine transmission at dopamine D₂ receptors^{30, 31}. Ellagic acid administered for 21 successive days significantly reversed haloperidol-induced catalepsy in rats.

The dopamine system has also been regarded crucial in controlling motor activity³². In the present study, haloperidol significantly decreased locomotor activity of rats. Dopamine receptor supersensitivity might be responsible for decrease in locomotor activity by haloperidol²⁵. Ellagic acid administered for 21 successive days significantly reversed haloperidol induced-decrease in locomotor activity.

Chronic administration of haloperidol also significantly decreased dopamine and serotonin levels in forebrain as compared to vehicle treated control, which is also supported by the literature²⁹. Ellagic acid administered for 21 successive days significantly restored the decreased levels of brain dopamine and serotonin. Chronic haloperidol administration produces dopamine supersensitivity which may increase the number of dormant receptors and this result in decrease in levels of dopamine in brain extracellular spaces. Accumulation of haloperidol metabolites in brain resulting after chronic haloperidol administration, may lead to the death of dopaminergic neurons. Also, quinone species formation is responsible for decrease in dopamine levels. It is well reported that after chronic administration of haloperidol, there is increase in dopamine and nor-adrenaline receptor density^{6, 7}. Ellagic acid has been reported to possess antioxidant activity^{16, 22}, which might prevent formation of quinone species and death of dopaminergic neurons. The serotonergic system plays a role in inhibitory modulation of activity of dopaminergic neurons³³. The decrease in serotonin levels in rat brain after chronic administration of haloperidol is in line with the literature^{25, 29}. Ellagic acid dose dependently prevented this depletion of serotonin in brain.

Typical neuroleptics including haloperidol, mostly act by blocking dopamine D₂ receptors and result in increased dopamine turnover. This may conceivably result in increased hydrogen peroxide production and other toxic metabolites of dopamine, resulting in increased oxidative stress. So, the compounds possessing potent antioxidant and neuroprotective properties could be possible candidates for treating this hyperkinetic disorder⁸. Since ellagic acid has been reported to possess antioxidant activity^{16, 18, 34} which might also be responsible for its anti-tardive dyskinesia effect.

CONCLUSION

In conclusion, ellagic acid significantly reversed haloperidol-induced tardive dyskinesia and catalepsy in rats probably through increase in brain dopamine and serotonin levels; and also through its antioxidant activity. Therefore, ellagic acid may

be explored further for its potential in the management of neuroleptic-induced tardive dyskinesia and Parkinsonism.

Abbreviations

VCMs – Vacuous chewing movements; po – per oral; ip – intraperitoneal

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Cite this article as:

Dinesh Dhingra*, Nidhi Gahalain. Amelioration of haloperidol-induced orofacial dyskinesia and catalepsy by ellagic acid in rats. *Int. J. Res. Ayurveda Pharm.* Mar - Apr 2016;7(Suppl 2):222-227 <http://dx.doi.org/10.7897/2277-4343.07292>

Source of support: Nil, Conflict of interest: None Declared

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