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Research Article
Protective Effect of Ellagic Acid Against Reserpine-Induced Orofacial Dyskinesia and Oxidative Stress in Rats

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Abstract
The aim of the present study was to evaluate effect of ellagic acid, a polyphenol bioactive compound, on reserpine-induced orofacial dyskinesia in Wistar male albino rats and to explore the possible underlying mechanisms for this effect. Reserpine (1 mg kg^{-1}, i.p.) was administered on every alternate day for a period of 5 days (day 1, 3 and 5) to induce orofacial dyskinesia in rats. Ellagic acid (10, 20 and 40 mg kg^{-1}, po) was administered for 15 successive days (from 6th-20th day) to separate groups of reserpine treated rats. Reserpine increased vacuous chewing movements, indicating induction of orofacial dyskinesia. It also decreased locomotor activity of rats. Ellagic acid significantly reversed reserpine-induced vacuous chewing movements and hypolocomotion in rats and significantly ameliorated reserpine-induced oxidative stress, as indicated by decrease in brain lipid peroxidation and increase in brain reduced glutathione, catalase and superoxide dismutase activities. Ellagic acid significantly attenuated reserpine-induced orofacial dyskinesia, probably through alleviation of oxidative stress. Thus, ellagic acid may be explored further for its potential in management of tardive dyskinesia.

Key words: Antioxidant, tardive dyskinesia, vacuous chewing movements, oxidative stress, reserpine, ellagic acid

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Tardive dyskinesia is a syndrome characterized by late-onset hyperkinetic involuntary movements, most commonly affecting the orofacial region and is due to long-term treatment with classical neuroleptics[1]. Vacuous Chewing Movements (VCMs) have been used as potential surrogate model of orofacial dyskinesia. Reserpine treatment is a putative animal model of orofacial dyskinesia. Repeated treatment with reserpine (1 mg kg^{-1}, ip) on every alternate day for a period of 5 days produced vacuous chewing movements in rats. Oxidative stress may be involved in the development of VCMs. Reserpine causes depletion of vesicular dopamine stores, which can increase dopamine levels and consequently, its metabolism via monoamine oxidase. The exacerbation of dopamine metabolism in basal ganglia can lead to overproduction of free radicals such as highly reactive hydroxyl radicals and auto-oxidation of dopamine into dopamine quinones (which are free radicals themselves) and superoxide anions which cause neurotoxicity[2-4].

Bioactive compounds possessing antioxidant activity such as quercetin[3], gallic acid[5], alpha lipoic acid[6], rutin[7], 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[8,9]. Among plants, *Ginkgo biloba* has been reported to be effective clinically in reversing symptoms of tardive dyskinesia in schizophrenia patients and improvement may be mediated through the well-known antioxidant activity of this extract[10]. Thus, substances possessing antioxidant activity may be explored for prevention and treatment of neuroleptic-induced tardive dyskinesia[11].

Ellagic acid is a natural polyphenol compound and present in a number of plants such as *Punica granatum*[12], *Emblica officinalis*[13] and so on. It has been reported to possess antiepileptic[14], antidepressant[15], anxiolytic[16], antioxidant[17] and anti-amyloid[18]activities. Since ellagic acid has antioxidant and neuroprotective activities and oxidative stress is reported to be involved in the development of VCMs, so the present study was designed to evaluate the effect of ellagic acid on reserpine-induced orofacial dyskinesia and brain oxidative stress in rats.

MATERIALS AND METHODS

Experimental animals: Wistar male albino rats, weighing 100-200 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). Since estrogens have been reported to neuroprotective and may mask development of tardive dyskinesia[19], so we excluded female rats and used only male rats for the present study. The animals were housed under standard laboratory conditions with 12 h 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 and 16 h. The experimental protocol was approved by Institutional Animal Ethics Committee. 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: Reserpine, ellagic acid and glacial acetic acid (Hi-Media Laboratories Pvt. Ltd., Mumbai, India) were used in the present study. Reserpine was dissolved in 0.1% acetic acid and then diluted in distilled water[3]. Ellagic acid was suspended in 0.1% 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^{-1} reserpine[3], 10, 20 and 40 mg kg^{-1} ellagic acid[14,20].

Behavioral models

Reserpine-induced orofacial dyskinesia: Reserpine (1 mg kg^{-1}, ip) was administered on day 1, 3 and 5 (on alternate days) for a period of five days, to induce oral dyskinesia in rats. The VCMs were recorded 24 h after the last dose of reserpine[3]. To quantify the occurrence of oral dyskinesia, rats were placed individually in observation cages ($20 \times 20 \times 19$ cm^3), which have mirrors fixed under the floor and behind the back wall of the cage. The animals were acclimatized for 10 min to the observation chamber before behavioral assessment. The VCMs are operationally defined as single mouth openings in the vertical plane not directed towards physical material. If VCMs occurred during a period of grooming, they were not taken into account. The VCMs were measured continuously for a period of 10 min, using hand operated counters.

Measurement of locomotor activity: To rule out the effects of various drug treatments on locomotor activity, horizontal locomotor activities of control and test animals were recorded for a period of 10 min[21] using photoactometer (INCO, Ambala, India). The photoactometer consisted of a square activity cage

(30×30×25 cm^3) with wire mesh floor, in which the animal moves. Six lights and six photocells placed in the outer periphery of the bottom in such a way that a single rat can block only one beam. Technically its principle is that a photocell is activated when the rays of light falling on the photocells are cut off by animals crossing the beam of light. As the photocell is activated, a count is recorded. The photocells are connected to an electronic automatic counting device which counts the number of "cut offs".

Biochemical estimations: Animals were sacrificed by decapitation immediately after behavioral testing. Their brains were removed, rinsed with isotonic saline and weighed. A 10% (w/v) tissue homogenate was prepared in 0.1 M phosphate buffer (pH 7.4). The homogenate was divided into three fractions. First fraction (10% w/v homogenate) was used for estimation of malondialdehyde, reduced glutathione and total protein. The second fraction (10% w/v homogenate) was centrifuged (Remi instruments, Mumbai, India) at 1000 g for 20 min at 4°C and the supernatant (post-mitochondrial supernatant) was used for estimation of catalase. The third fraction (10% w/v homogenate) was centrifuged at 12000 g for 60 min at 4°C and this supernatant (post-mitochondrial supernatant) was used for estimation of superoxide dismutase[3].

Estimation of reduced glutathione: Reduced GSH in the brain tissue was estimated by the method of Ellman[22]. The homogenate was mixed with 10% w/v trichloroacetic acid in ratio of 1:1 and centrifuged at 4°C for 10 min at 5000 rpm using refrigerated centrifuge (Remi instruments, Mumbai, India). The supernatant obtained (0.5 mL) was mixed with 2 mL of 0.3 M disodium hydrogen phosphate buffer (pH 8.4) and 0.4 mL of double distilled water. Then 0.25 mL of 0.001 M freshly prepared DTNB [5, 5'-dithiobis (2-nitrobenzoic acid)] dissolved in 1% w/v sodium citrate was added. The reaction mixture was incubated for 10 min and absorbance of yellow colored complex was recorded at 412 nm using UV-visible spectrophotometer (Genesys 10S, Thermo Scientific, Singapore).

Estimation of lipid peroxidation: Malondialdehyde levels, an index of lipid peroxidation were estimated according to the method of Ohkawa *et al.*[23]. In brief, the reaction mixture was prepared by mixing 0.2 mL homogenate with 0.2 mL of 8.1% sodium dodecylsulfate, 1.5 mL of 20% acetic acid (pH 3.5), 1.5 mL of 0.8% thiobarbituric acid and 0.6 mL of distilled water. The mixture was incubated at 95°C in water bath for 1 h. After cooling with tap water, 1.0 mL of distilled water and a mixture of butanol: pyridine (15:1 v/v) was added. Then mixture was shaken and centrifuged at 4000 rpm for 10 min (Remi instruments, Mumbai, India). The absorbance of upper organic layer was measured at 532 nm using UV-visible spectrophotometer (Genesys 10S, Thermo Scientific, Singapore).

Estimation of total protein: The total protein concentration was estimated in brain homogenate by biuret method,[24] using total protein kit (Crest Biosystems, Coral Clinical Systems, Goa, India).

Estimation of catalase activity: The catalase activity was estimated using method of Aebi[25]. In brief, the post mitochondrial supernatant (50 µL) was added to a 3.0 mL cuvette that contained 1.95 mL of 50 mM phosphate buffer (pH 7.0). 1.0 mL of 30 mM hydrogen peroxide was added and changes in absorbance were recorded at 240 nm for 30 sec at 15 sec intervals using UV-visible spectrophotometer (Genesys 10S, Thermo Scientific, Singapore).

Measurement of superoxide dismutase activity (SOD): The SOD was estimated according to the methods of Kono[26]. In brief, the reaction mixture containing solution A (50 mM Na_2CO_3, 0.1 M EDTA, pH = 10.0), solution B (96 µM nitroblue tetrazolium in solution A) and solution C (0.6% Triton X-100 in solution A) were incubated at 37°C for 10 min. Reaction was started by introducing 100 µL of solution D (20 mM hydroxylamine hydrochloride, pH = 6.0). This was followed by addition of 10 µL aliquot of post mitochondrial supernatant to the reaction mixture and 50% inhibition in the rate of nitroblue tetrazolium reduction by SOD present in the enzyme source was measured using UV-visible spectrophotometer (Genesys 10S, Thermo Scientific, Singapore). The rate of nitroblue tetrazolium reduction by O_2^- anion generated due to photo-activation of hydroxylamine hydrochloride was measured at λ_{max} = 560 nm in the absence of post mitochondrial supernatant. A unit of SOD activity was defined by 50% inhibition of nitroblue tetrazolium. The SOD activity was expressed in U mg^{-1} protein.

Experimental protocol: The animals were distributed into the following groups:

- **Group 1-5 (n = 8 each):** Vehicle (0.1% gum acacia), reserpine (1 mg kg^{-1}, ip), ellagic acid (10, 20, 40 mg kg^{-1}, po) +reserpine (1 mg kg^{-1}, ip), respectively

Reserpine was administered on alternate days (day 1, 3, 5) for a period of five days. Ellagic acid was administered for 15 successive days (from 6th-20th day). Vacuous chewing movements were recorded 1 h after administration of the drugs on 20th day.

- **Group 6-10 (n = 6 each):** Details of the groups are same as mentioned under groups 1-5, except locomotor activity was recorded

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. The $p<0.05$ was considered as statistically significant.

RESULTS

Effect of ellagic acid on reserpine-induced Vacuous Chewing Movements (VCMs): Reserpine (1 mg kg^{-1}, ip) administered on alternate days (day 1, 3 and 5) for a period of 5 days significantly ($p<0.001$) increased VCMs in rats as compared to vehicle treated group. Ellagic acid (10, 20 and 40 mg kg^{-1}, po) administered for 15 successive days significantly and dose-dependently reduced reserpine-induced VCMs (Fig. 1).

Effect of ellagic acid on reserpine-induced hypolocomotion: Reserpine (1 mg kg^{-1}, ip) significantly ($p<0.001$) decreased the locomotor activity in rats as compared to vehicle treated control. Ellagic acid (10, 20 and 40 mg kg^{-1}, po) significantly reversed reserpine-induced hypolocomotion of rats (Fig. 2).

Effect on ellagic acid on brain lipid peroxidation, reduced glutathione levels, catalase and superoxide dismutase activities: Reserpine significantly increased brain malondialdehyde levels, decreased reduced glutathione levels and decreased activities of catalase and superoxide dismutase as compared to vehicle treated control. Ellagic acid (10, 20 and 40 mg kg^{-1}, po) significantly decreased brain malondialdehyde levels. Low dose (10 mg kg^{-1}) and middle dose (20 mg kg^{-1}) of ellagic acid significantly increased reduced glutathione and superoxide dismutase activities. But only the middle dose (20 mg kg^{-1}) of ellagic acid significantly increased catalase activity (Table 1).

DISCUSSION

In the present study, ellagic acid administered for 15 successive days significantly inhibited reserpine-induced VCMs and hypolocomotion. Reserpine is well reported for inducing VCMs in rats[2,3]. The present study also showed that reserpine administration produced a significant increase in brain lipid peroxidation and significant decrease in GSH levels, SOD and catalase activities, supporting the involvement of oxidative stress in reserpine-induced orofacial dyskinesia. Reserpine binds strongly to adrenergic vesicles in central and peripheral adrenergic neurons. It remains bound there for a prolonged period. This binding inhibits the vesicular catecholamine transporter that facilitates the vesicular storage. Therefore, nerve ending lose their capacity to concentrate and store norepinephrine and dopamine. Catecholamines leak into the cytoplasm, where they are metabolized through the interneuronal monoamine oxidase, leading to the formation of 3, 4-dihydroxyphenyacetic acid and hydrogen peroxide. In presence of ferrous ion, hydrogen

Table 1: Effect of ellagic acid on reserpine-induced alternations in brain malondialdehyde levels, reduced glutathione, catalase and superoxide dismutase activities of rats

Treatments	Dose (kg^{-1})	Malondialdehyde (nmoles/min/mg protein)	GSH (nmoles of GSH/mg protein)	Catalase (μmoles/min/mg protein)	SOD (% inhibition) (units/min/g fresh weight)
Vehicle (0.1% gum acacia)	5 mL	0.15±0.04	2.73±0.46	41.60±4.11	60.68±4.98
Reserpine	1 mg	3.72±0.19*	0.81±0.27†	12.65±2.12*	17.09±6.84*
Reserpine+ ellagic acid	1 mg 10 mg	2.16±0.06‡	2.98±0.76§	29.88±4.26	40.10±1.25§
Reserpine+ ellagic acid	1 mg 20 mg	2.43±0.15‡	4.24±1.47‡	52.08±7.07‡	48.07±1.55‡
Reserpine+ ellagic acid	1 mg 40 mg	1.08±0.09‡	2.22±0.14	21.420±2.08	23.68±2.63
F(4, 25)		126.03	10.18	13.11	19.13

n = 6 in each group, values are expressed as the Mean±SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test, *$p<0.001$ and †$p<0.05$ as compared to vehicle treated control, ‡$p<0.001$ and §$p<0.01$ as compared to reserpine treated group

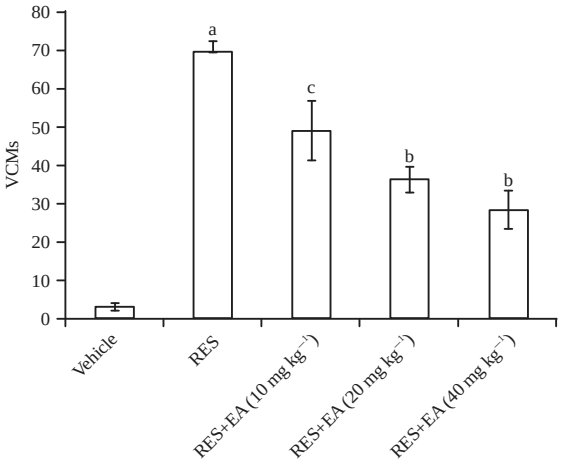

Fig. 1: Effect of ellagic acid on reserpine-induced vacuous chewing movements in rats, n = 8 in each group, Values are expressed as the Mean±SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test. F (4, 35) = 28.46, p<0.0001, [a]p<0.001 as compared to vehicle treated control, [b]p<0.001 and [c]p<0.05 as compared to reserpine treated group, RES: Reserpine, EA: Ellagic acid

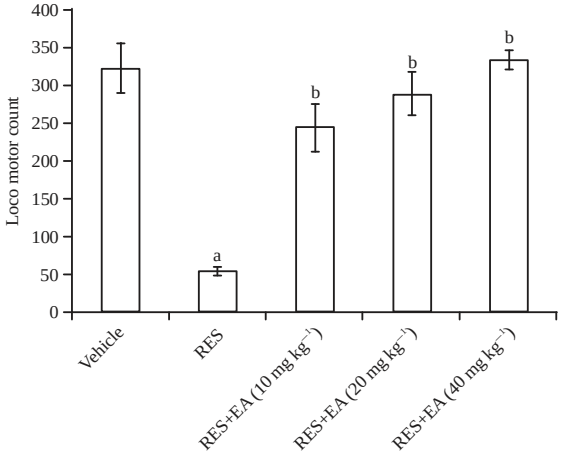

Fig. 2: Effect of ellagic acid on locomotor activity of rats, n = 6 in each group. Values are expressed as the Mean±SEM. Data were analyzed by using one-way ANOVA followed by Tukey's multiple comparison test, F (4, 25) = 21.48, p = 0.017. [a]p<0.001 as compared to vehicle treated control, [b]p<0.001 as compared to reserpine treated group, RES: Reserpine, EA: Ellagic acid

peroxide undergoes spontaneous conversion to form a hydroxyl free radical, which causes oxidative stress and degeneration of neurons[27]. Clinical studies have shown increased levels of lipid peroxidation products in blood and cerebrospinal fluid of tardive dyskinesia as compared to non-tardive dyskinesia patients[28].

Ellagic acid administered for 15 successive days significantly alleviated brain oxidative stress, as indicated by significant decrease in lipid peroxidation, significant increase in GSH levels and antioxidant enzymes (catalase and SOD) activities in reserpine-treated rats. This is also supported by an earlier study where ellagic acid significantly attenuated brain oxidative stress in rats[17]. Involvement of dopamine and noradrenaline has been reported in the control of motor activity[29]. Reserpine induces orofacial dyskinesia in animals by depleting dopamine[2,3]. In the present study, reserpine significantly decreased locomotor activity. Ellagic acid significantly reversed reserpine-induced hypolocomotion, indicating improved exploration, which is in accordance with the earlier study[30].

CONCLUSION

Ellagic acid significantly reversed reserpine-induced orofacial dyskinesia and hypolocomotion, probably due to restoration of the levels of brain SOD, catalase and GSH and inhibition of lipid peroxidation. Thus, ellagic acid may be investigated further for its potential in the management of tardive dyskinesia.

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