Original Article

Schinus terebinthifolius administration prevented behavioral and biochemical alterations in a rotenone model of Parkinson's disease

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ABSTRACT

Parkinson's disease is a neurodegenerative disorder characterized by motor impairment, cognitive decline and psychiatric symptoms. *Schinus terebinthifolius* Raddi, Anacardiaceae, had been studied for its anti-inflammatory and antioxidant properties, and in this study, the stem bark was evaluated for the neuroprotective effects on behavioral and biochemical alterations induced by administrations of rotenone in rats. Behavioral evaluations were performed using open-field and rotarod. The *in vitro* and *in vivo* antioxidant activities were determined by the DPPH radical scavenging activity and lipid peroxidation method respectively. The administration of rotenone (3 mg/kg, *s.c.*) produced hypolocomotion, increase of immobility and muscle incoordination, while the treatment with *S. terebinthifolius* stem bark extract (150, 300 and 600 mg/kg *p.o.*) for seven days prevented rotenone-induced dysfunctional behavior. Biochemical analysis of the substantia nigra, striatum and cortex revealed that rotenone administration significantly increased lipid peroxidation, which was inhibited by treatment with all doses of *S. terebinthifolius*. The results suggested neuroprotective effect of *S. terebinthifolius* possibly mediated through its antioxidant activity, indicating a potential therapeutic benefit of this species in the treatment of Parkinson's disease.

Introduction

The increase of elderly population has led to an increasing incidence of neurodegenerative diseases worldwide, leading, thus, to the interest in studies for prevention and treatment of these pathologies. Natural constituents derived from plants are important to investigate, since studies have shown that these compounds exhibited a range of biological activities, with therapeutic potential, for instance antioxidant and anti-inflammatory effects.

Parkinson's disease (PD) is one if the major neurodegenerative disorder in the entire world and is characterized by progressive degeneration of dopamine-containing neurons that project from substantia nigra pars compacta to the striatum. Besides, motor impairment (bradykinesia, rigidity, tremor at rest and disturbances in balance), cognitive decline and psychiatric symptoms (like depression) are the cardinal symptoms of the pathology (Dutta and Mohanakumar, 2015; Fernandez, 2015). Main mechanisms have been proposed to explain the events culminating in neuronal death in PD, which are associated with oxidative stress, mitochondrial dysfunction, neuroinflammation and environmental exposures, like pesticides, contributing for the appearance of behavioral and biochemical alterations (Dauer and Przedborski, 2003; Renaud et al., 2015). Several animal models have been used to mimetize and elucidate the pathogenesis of PD, in special rotenone, MPTP and 6-hydroxydopamine (Dauer and Przedborski, 2003; Blesa et al., 2012).

Rotenone (*Derris* sp., Fabaceae) has been a potent hydrophobic pesticide and its environmental exposure mimics the clinical and pathological features of PD, such as behavioral, biochemical and pathological changes, providing a reproducible animal model for PD (Betarbet et al., 2000). It provoked neurodegeneration via multiple mechanisms, mainly by inhibition of complex I, increase of oxidative stress and induction of apoptosis (Zaitone et al., 2012; von Wrangel et al., 2015).

Schinus terebinthifolius Raddi, Anacardiaceae, is a native plant of South America (Corrêa, 1974). In Brazil it is popularly called Aroeira

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or Cabuí. In folk medicine, it has been used for the treatment of ulcers, respiratory problems, wounds and arthritis (Morton, 1978) and as an antiseptic, antiinflammatory and haemostatic (Medeiros et al., 2007). Many of its properties or healing effects attributed by folk medicine are associated to the presence of polyphenols in the plant, which give the plant its antioxidant properties (Medeiros et al., 2007; Abdou et al., 2015). The aim of this study was to investigate the possible neuroprotective effects of *S. terebinthifolius* in the behavior activity and on the oxidative stress induced by rotenone as experimental model of Parkinson's disease in rats.

Materials and methods

Plant material

Stem bark of *Schinus terebinthifolius* Raddi, Anacardiaceae, were collected in the remains of the Atlantic rainforest located in the municipality of Cabo de Santo Agostinho, Pernambuco, Brazil between February and April 2013 (8°20′33″ S and 34°56′59″ W). A voucher specimen was authenticated in the Department of Botany of the Federal University of Pernambuco by the curator M. Barbosa and was deposited at Geraldo Mariz Herbarium under record n°. 8758. Extraction was performed by maceration and air dried, and 500 g of pulverized *S. terebinthifolius* bark was added to 1.0 l of ethanol 70% at room temperature, for 7 days, and was occasionally shaken. In the laboratory, the crude ethanolic extract was evaporated to dryness under reduced pressure for the total elimination of alcohol, followed by lyophilization, yielding approximately 35 g of dry residue. The lyophilized extract of *S. terebinthifolius* was kept at room temperature until use and suspended in distilled water.

High performance liquid chromatography (HPLC) analysis

The main phytochemical markers (gallic acid, ellagic acid, catechin and epicatechin) in *S. terebinthifolius* samples were analyzed by way by way of liquid chromatography-diode array detection (LC-DAD) analysis using a Shimadzu system (LC-20AT) equipped with a photo diode array detector (SPD-M20A). The chromatographic separation was performed using a Gemini RP-18 column 5 μm particle size and 250 mm × 4.60 mm i.d. (Phenomenex), protected by a guard column of the same material. A gradient elution was performed by varying the proportion of Solvent A (0.5% acetic acid in distilled water, v/v) and solvent B (methanol) at a flow rate of 0.8 ml/min following gradient program: 20–40% B (10 min), 40–60% B (10 min), 60% B (10 min), 60–40% B (10 min), and 40–20% B (10 min). The dried extracts and standards were dissolved in methanol:water (20/80, v/v) and filtered through a membrane of 0.45 μm (Millipore®, USA) prior to injection of 20 μl. The peaks of each marking on dry substance were identified by comparing retention times and UV spectra of DAD.

Animals

Adult male Wistar rats (*Rattus norvegicus* var. *albinus*), age 3 months and weighing between 250 and 300 g, were obtained from the Department of Physiology and Pharmacology at the Federal University of Pernambuco, Brazil. The animals were maintained in standard environmental conditions (22 ± 2 °C, 12:12 h dark/light cycle). Commercial food (Presence®, Purina, Brazil) and water were available *ad libitum*. All protocols were approved by the Animal Experimentation Ethics Committee of the Federal University of Pernambuco, under license n°. 23076.050131/2013-82 in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Drugs

Butylated hydroxytoluene (BHT), 2,2-diphenyl-1-picrylhydrazyl (DPPH), malondialdehyde (MDA), thiobarbituric acid (TBA), epinephrine, 1,1,3,3-tetrametoxipropane (TMP), Tween 80, DMSO and rotenone, were purchased from Sigma–Aldrich® (St. Louis, MO, USA). Rotenone was dissolved in sunflower oil one day before beginning treatment. On subsequent days, solutions remained in the refrigerator (4 °C). Sunflower oil was obtained in local market.

Experimental groups

The animals were randomly divided into five experimental groups (*n* = 10). Rats from Group 1 received water by gavage (1 ml/kg) and 1 h later a subcutaneous (*s.c.*) administration of the vehicle (90%, w/v sunflower oil, +10% w/v DMSO) for seven days. Group 2 also received water by gavage and rotenone (3 mg/kg, *s.c.*) diluted in vehicle after 1 h during seven days. Groups 3, 4 and 5 received by gavage 150, 300 or 600 mg/kg of *S. terebinthifolius*, respectively, suspended in water, and 1 h later were given them rotenone (3 mg/kg, *s.c.*) also during seven days. 24 h after the last day of treatment, the rats were evaluated with behavioral tests and biochemical assays (Linard-Medeiros et al., 2015).

Open field test

The open field test was carried out to Broadhurst (1957) and Bernardi and Palermo-Neto (1979). To quantify exploratory and general locomotor activity, each rat was placed into the center of an open-field arena (a circular wooden box with a diameter of 100 cm and 40 cm high, with floor divided into 19 regions). Rats were assessed individually for 5 min, while four parameters were analyzed: (i) latency to start the movement (time to leave the inner circle, in s), (ii) locomotion frequency (number of square crossed with four paws), (iii) rearing frequency (number of times the animal stood on their hind paws) and (iv) immobility time (lack of movement during testing, in s). The apparatus was cleaned with a 5% ethanol solution before behavioral testing to eliminate possible bias due to odors left by previous rat.

Rotarod activity test

In order to quantify motor deficiency, the rotarod test was used at a fixed speed, according to Monville et al. (2006). To perform this test, the animal was placed with all four paws on a bar with a diameter of 7 cm and set 25 cm above the floor. The bar rotated at a speed of 25 rpm. Before being submitted to the different treatments, the rats were trained in two sessions of 180 s each for habituation. Animals were placed on the rotating bar and the time spent on the rotating bar was recorded. A cut-off time of 180 s was maintained throughout the experiment. The average results were recorded as time of fall.

Biochemical analysis

After behavioral observations, animals were immediately anesthetized, euthanized by decapitation and their brains removed. Bilateral substantia nigra, striatum and cortex were dissected, weighed and homogenized in a Potter–Elvehjem type homogenizer with a tissue homogenate 1× phosphate buffered saline (10% w/v, PBS) to which was added butylated hydroxytoluene (0.004% w/v, BHT) for preventing oxidation of the samples. The homogenate was centrifuged at 10,000 × *g* for 30 min at 4 °C and an aliquot of supernatant was separated for biochemical analysis. Each individual experiment was carried out in triplicate and repeated two or three times.

DPPH radical scavenging activity in vitro

Antioxidant radical scavenging activity was evaluated using DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals (Brand-Williams et al., 1995). 1 ml of DPPH solution (30 mM, in 95% ethanol) was incubated with 2.5 ml of varying concentrations of *S. terebinthifolius* extract (2.5–250 μg/ml). The reaction mixture was shaken well and incubated for 30 min at room temperature, and the absorbance of the resulting solution was read at 515 nm against a blank. The radical scavenging activity was measured as an absorbance decrease of DPPH and was calculated using the following equation: (Absorbance of control − Absorbance of test) × 100/Absorbance of control. The synthetic antioxidant butylated hydroxytoluene (BHT) was included in experiments as a positive control. The EC_{50} value for each sample (tree replicates), was calculated from a calibration curve obtained for the percentage of radical scavenging activity *versus* concentration of the sample required to reduce the absorbance of the negative control (DPPH solution) by 50%. The BHT curve antioxidant was $y = 15.695 \ln(x) + 16.477$ ($R^2 = 0.9544$). The *S. terebinthifolius* extract curve was $y = 18.322 \ln(x) - 24.936$ ($R^2 = 0.9026$).

Measurement of lipid peroxidation in vivo

The quantitative measurement of lipid peroxidation in the substantia nigra, striatum and cortex was performed according to the method described by Buege and Aust (1978). The amount of malondialdehyde (MDA) of lipid peroxidation was measured by reaction with thiobarbituric acid. Briefly, aliquots (500 μl) of supernatant were placed in test tubes and added to 1 ml of TBA reagent: 0.38% (w/w) TBA, 250 ml of 1 N hydrochloric acid, 15% (w/w) of trichloroacetic acid and 20 ml of 2% (w/v) ethanolic BHT. The solution was shaken and heated to 100 °C for 15 min, followed by cooling in an ice bath. Then, 1.5 ml of *n*-butanol was added. The mixture was shaken and centrifuged to 3000 × *g* for 20 min. After centrifugation, the upper layer was collected and assessed with a spectrophotometer (CARY 3E UV–Visible Spectrophotometer Varian, Inc. Brazil) at 532 nm. Results of TBARS of substantia nigra, striatum and cortex were expressed as nmol MDA/mg protein using a standard curve generated with different concentrations of 1,1,3,3-tetramethoxypropane solution.

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). The difference between groups was analyzed by one-way analysis of variance (ANOVA) followed by *post hoc* Newman–Keuls test. The comparisons were carried out by GraphPad Prism® 5.0 and significant at $p \leq 0.05$.

Results

High performance liquid chromatography (HPLC) analysis

From the comparison of retention times with extract standards previously injected into the HPLC, it was possible to confirm that, *S. terebinthifolius* sample demonstrated the presence of phenolic acids (gallic acid, 4.66 min; ellagic acid, 7.51 min) and also flavonoids (catechin, 10.24 min; epicatechin 19.05 min) (Fig. 1).

Effects of S. terebinthifolius *on behavioral tests*

Rotenone administration (3 mg/kg, *s.c.*) during 7 days significantly reduced the frequencies of locomotion and rearing and increased the time of immobility and latency to start the movement in the open field test. Pre-treatment with the stem bark
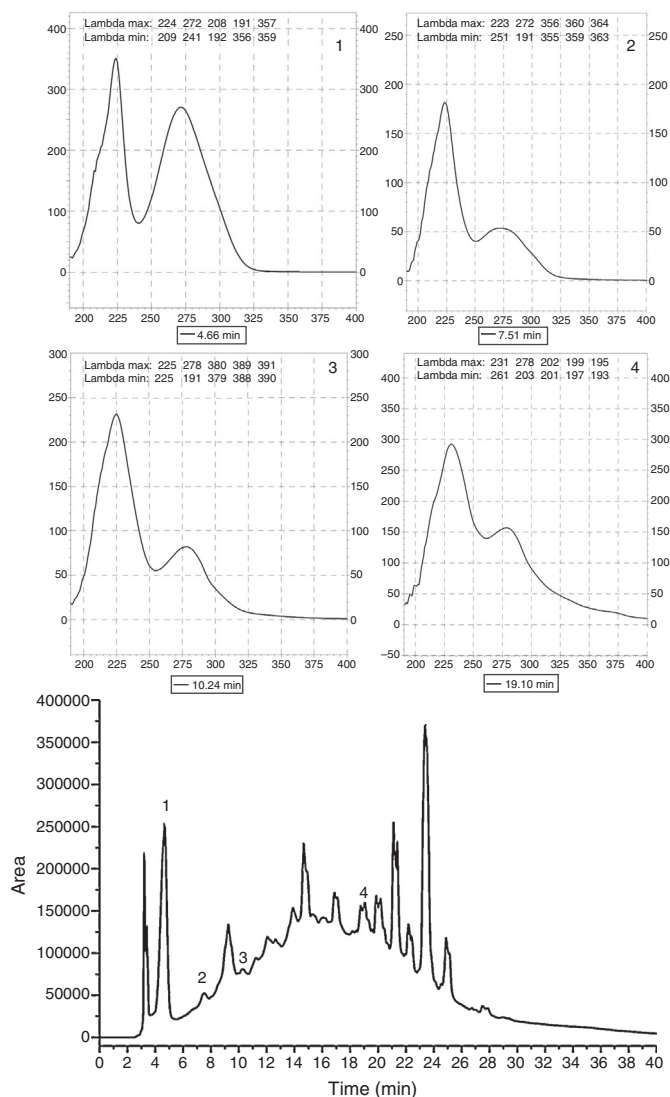

Fig. 1. Chromatogram of *Schinus terebinthifolius* stem bark detected at 278 nm. Peaks: gallic acid (Rt = 4.66), catechin (7.51), epicatechin (10.24) and ellagic acid (Rt = 19.05) obtained by HPLC method.

(150, 300 and 600 mg/kg) significantly improved locomotor activity and rearing and decreased the time of immobility and latency to start the movement when compared to rotenone animals. However, the lower dose of the extract (150 mg/kg) was unable to prevent the rotenone-induced locomotor deficits in the open field test (Fig. 2a–d).

On rotarod test, rotenone administration (3 mg/kg, *s.c.*) induced a significant decrease in the time of permanency of the animals compared with control rats during the observation in the apparatus. Daily pre-treatment of 300 and 600 mg/kg doses was able to increase the time of permanency in comparison to rotenone group. However, the lower dose of the extract was unable to prevent the rotentone-induced locomotor deficits in the open field test (Fig. 3).

Reduction of 2,2-diphenyl-1-picrylhydrazyl radical in vitro

Significant DPPH radical scavenging activity was evident in all concentrations tested of *S. terebinthifolius* stem bark (1–250 μ/ml). The extract was able to reduce the stable free radical DPPH to the yellow-colored 1,1-diphenyl-2-picrylhydrazyl with an EC_{50} 12.176 ± 0.077 μg/ml. Under similar conditions, the
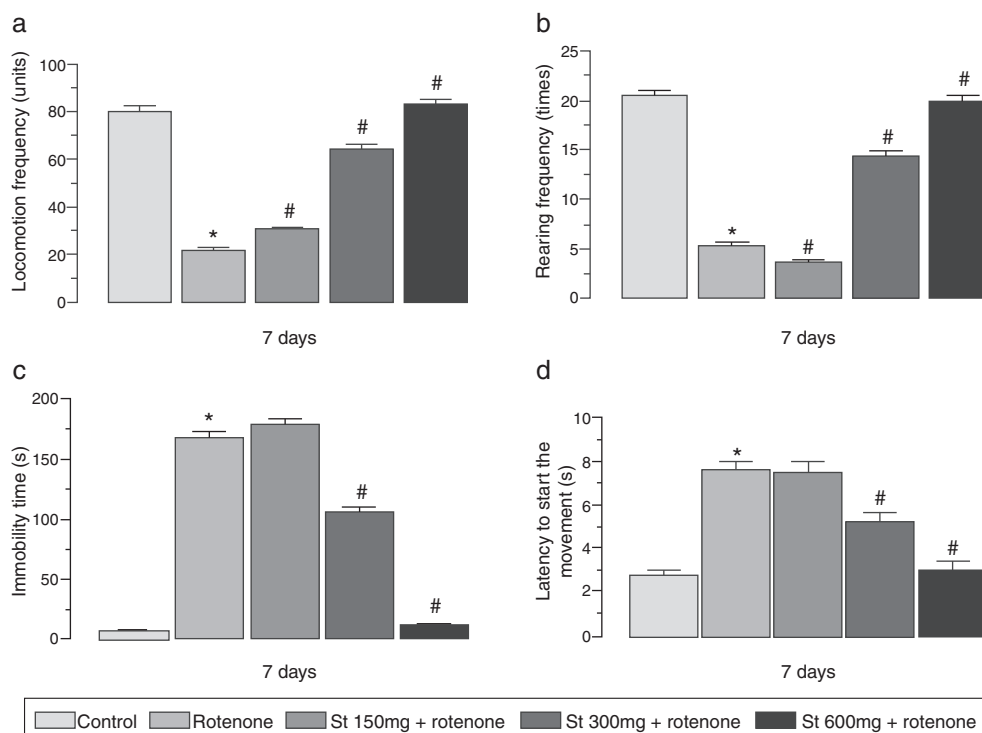
Fig. 2. Effect of *Schinus terebinthifolius* (St, 150, 300 and 600 mg/kg, *p.o.*) on open field test in rats before rotenone (3 mg/kg, *s.c.*) administration. (a) Total ambulatory activity, (b) rearing frequency, (c) immobility time and (d) latency to start de movement. The values are expressed as mean ± S.E.M. (*n* = 10/group). One-way ANOVA followed by Newman–Keuls test (*$p \leq 0.05$ *vs.* control group and #$p \leq 0.05$ *vs.* rotenone group).
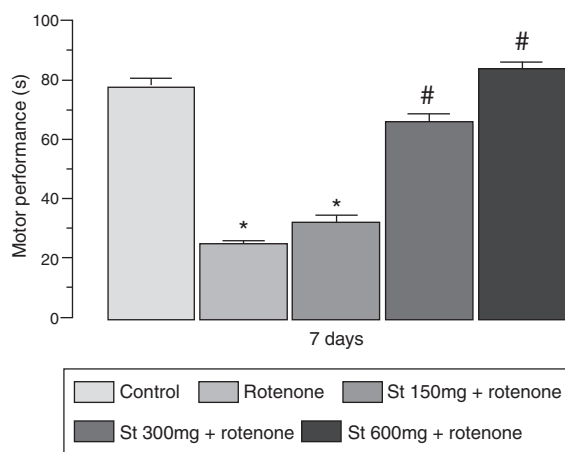

Fig. 3. Effect of *Schinus terebinthifolius* (St, 150, 300 and 600 mg/kg, *p.o.*) on rotarod test in rats before rotenone (3 mg/kg, *s.c.*) administration. The values are expressed as mean ± S.E.M. (*n* = 10/group). One-way ANOVA followed by Newman–Keuls test (*$p \leq 0.05$ *vs.* control group and #$p \leq 0.05$ *vs.* rotenone group).

synthetic antioxidant BHT showed EC$_{50}$ 25.768 ± 0.147 µg/ml. This activity was about 2.1 times smaller when compared to *S. terebinthifolius*.

Measurement of lipid peroxidation *in vivo (TBARS)*

Rotenone administration (3 mg/kg) during 7 days provoked an increase on oxidative stress as indicated by the significant increase of MDA concentrations in substantia nigra, striatum and cortex when compared to control group. However, the pre-treatment with all doses of *S. terebinthifolius* was able to inhibit the lipid peroxidation in comparison to rotenone animals (Fig. 4a–c).

Discussion

This report showed the neuroprotective effect of *S. terebinthifolius* in Parkinson's disease using the model of rotenone subcutaneous administration during 7 days. All doses of *S. terebinthifolius* (150, 300 and 600 mg/kg) significantly prevented motor deficits in the open field and rotarod tests, and mainly, was able to inhibit the oxidative stress induced by systemic rotenone administration observed in *in vivo* TBARS method. It was also demonstrated the *in vitro* antioxidant effect of *S. terebinthifolius*, as well its mainly compounds in HPLC method. The antioxidant activity of the extract was also measured in the DPPH radical assay, which primarily evaluates proton radical-scavenging ability.

Rotenone is a potent inhibitor of complex I (NADH: ubiquinoneoxidoreductase) of the mitochondrial electron transport chain. In rats, this toxin causes a syndrome that replicates both neuropathological findings and behavioral symptoms of Parkinson's disease. Application of low doses of rotenone *in vitro* and *in vivo* have been shown to affect many of the mechanisms involved in the pathogenesis of Parkinson's disease, such as altered calcium signaling, induction of oxidative stress and apoptosis, loss of tyrosine hydroxlase, proteasomal dysfunction, nigral iron accumulation and the formation of fibrillar cytoplasmic inclusions that contain ubiquitin and α-synuclein (von Wrangel et al., 2015). Sherer et al. (2003) also showed that the exposure to low doses of rotenone (2–3 mg/kg/day) caused highly selective nigrostriatal dopaminergic lesion. A common feature of all toxin-induced models of Parkinson's disease is their ability to produce an oxidative stress and to cause cell death in dopamine neuronal populations that reflect what is seen in Parkinson's disease (Blesa et al., 2012). Markers of oxidative stress are typically found in brain biopsies, peripheral cells, and biological fluids derived from patients with Parkinson's disease, indicating that indeed oxidative stress is a key factor in pathogenesis. Malondialdehyde (MDA) is a specific marker of lipid peroxidation, which is
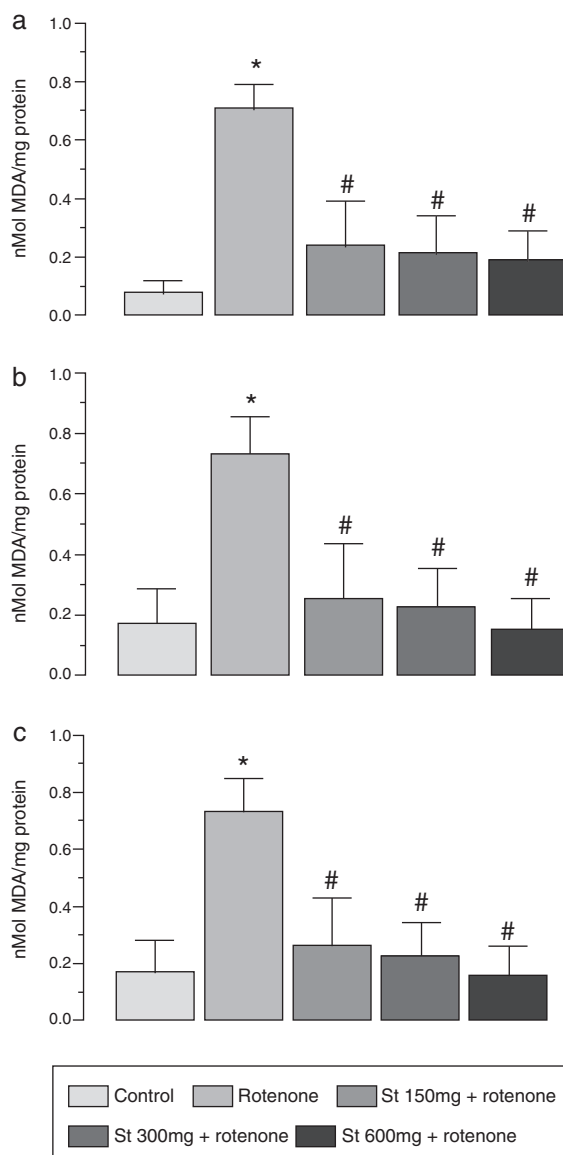
Fig. 4. Effect of *Schinus terebinthifolius* (St, 150, 300 and 600 mg/kg, *p.o.*) on lipid peroxidation levels in rats before rotenone (3 mg/kg, *s.c.*) administration. (a) Substantia nigra, (b) striatum and (c) cortex of brain rats. The values are expressed as mean ± S.E.M. (n = 10/group). One-way ANOVA followed by Newman–Keuls test (*$^*p \leq 0.05$ vs. control group and $^\#p \leq 0.05$ vs. rotenone group).

largely a result of the peroxidation of polyunsaturated fatty acids with more than two double bonds (Sanders and Greenamyre, 2013).

In our study, administration of rotenone promoted increased levels of MDA in substantia nigra, striatum and cortex, suggesting an increased lipid peroxidation and, thus, oxidative stress. In this way, there was an increase in brain MDA levels (an indicator of lipid peroxidation due to free radicals) which was inhibited by the administration of stem bark of all doses of *S. terebinthifolius*, suggesting its antioxidant action. Indeed, recently Costa et al. (2015) shown that extract from different tissues of *S. terebinthifolius* present antioxidant activity by DPPH radical assay. Abdou et al. (2015) investigated the curative and protective effects of *S. terbenthifolius* ethanolic extract (350 mg/kg, *p.o.*) against CCl_4-induced acute hepatotoxicity in rats and shown that the administration significantly reinstated the antioxidant capacity. Oxidative stress due to an increase in free radical generation or an impaired endogenous antioxidant mechanism is an important factor that had been implicated in various neurodegenerative diseases (Sanders and Greenamyre, 2013; Solanki et al., 2015).

The brain is highly susceptible to free radical damage because of its high utilization of oxygen and the presence of a relatively low concentration of antioxidant enzymes and free radical scavengers. There is a growing interest in establishing therapeutic and dietary strategies to combat oxidative stress induced damage to the central nervous system (Gao et al., 2012; Virmani et al., 2013). Studies in humans and animals have suggested that flavonoids, a large group of polyphenolic compounds found in fruits and vegetables are capable of counteracting neuronal injury, thereby delaying the progression of neurodegenerative diseases, motivating researches efforts to identify the mechanisms of neuronal death as well to discover new compounds to control them (Dutta and Mohanakumar, 2015; Chen et al., 2015; Solanki et al., 2015; Renaud et al., 2015).

The major compounds of stem bark of *S. terebinthifolius* Raddi are flavonoids (cathechin and epicatechin) and phenolics acids (gallic acid and ellagic acid). Catechins are powerful antioxidants and free radical scavengers *in vitro* assays and *in vivo* models (Srividhya et al., 2009; Solanki et al., 2015). It has been found that catechins have much higher antioxidant activity in comparison to vitamins C and E *in vitro*. The chemical structures have been contributed to this effect to chelate metal ions, prevent the generation of free radicals, allow the displacement of electrons and provide high reactivity to eliminate the free radicals (Mandel et al., 2006; Khan and Mukhtar, 2007; Senthil, 2008). Furthermore, the catechins and epicatechins were also able to indirectly modulate expression of some protective enzymes antioxidants (Hidgon and Frei, 2003; Weinreb et al., 2004). The chronic treatment with catechins prevented the decline in the activity of SOD and GSH enzymes in the serum of old mice, preventing also significantly increased TBARS in the hippocampus of these animals (Abd El Mohsen et al., 2002; Mandel et al., 2006). Otherwise, gallic acid and ellagic acid are hydrolyzed tannins of natural products found in abundance in grapes, tea, fruit and wine (Singh et al., 2004). These acids were able to reduce the production of ROS and superoxide, such as hydrogen peroxide, hydroxyl radicals and hypochlorous acid; also due to their antimutagenic and anticarcinogenic activities (Kim, 2007). In the cognitive impairment induced by another animal model of Parkinson's disease in animals, 6-OHDA, the treatment with gallic acid significantly reduced the level of TBARS in the rat brains (Kim, 2007).

In conclusion, the results of this study confirm that the subcutaneous administration of rotenone in rats induces neurobehavioral and biochemical changes mimicking those observed in Parkinson's disease. Treatment of rats with *S. terebinthifolius* produced significant neuroprotection probably mediated through its antioxidant activity. Taken together, our data suggested neuroprotective effects of *S. terebinthifolius* Raddi, probably mediated through its antioxidant activity. Thus, the present work brought out new insights for the treatment of neurodegenerative diseases and highlighted the pharmacological properties for Parkinson's disease and other neurodegenerative pathologies.

Author's contributions

Conflicts of interest

Acknowledgements

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