


**Research Article**
**Treatment of rotenone induced neurodegeneration by taurine and hesperidin**

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**Abstract:** Taurine (2-aminoethane sulphonic acid) is a sulphonic acid which is derived from cysteine and is widely distributed in animal tissues. It is one of the most abundant amino acid in mammals and plays several crucial roles including modulation of calcium signaling, osmoregulation and membrane stabilization. Hesperidin occurs in the cells in crystalline, feather-like aggregates or sphaerocrytalline masses and it exhibits pharmacological and biological properties such as anti-inflammatory, anticarcinogenic, inhibit bone loss, lowering of lipid, hypoglycaemic and antioxidant activities. The current study was performed to evaluate the effect of taurine and hesperidin on neurodegeneration resulted from rotenone administration by a dose of 1.5 mg/kg b.wt three times per week for two months. Also we summarize recent findings emphasizing the role of catecholamines neurotransmitters, Tyrosine hydroxylase and oxidative stress in neurodegenerative disease model. These rats received taurine and hesperidin through gastric intubation daily for one month after rotenone administration. The results revealed that taurine and hesperidin treatment significantly ameliorated the decreased levels of the catecholamines neurotransmitters and Tyrosine hydroxylase which were decreased as after rotenone injection. Moreover, taurine and hesperidin treatment ameliorated lipid peroxidation and catalase levels.

**Keywords:** Rotenone, Taurine, Hesperidin, Neurodegeneration, Catecholamines, Oxidative Stress.

**Introduction**

Taurine (2-amino-ethanesulfonic acid) is a  $\beta$ -amino acid and is the most abundant amino acid in mammals, being widely distributed in the central nervous system (CNS) occupying the second place after glutamate in relation of its concentration which differs depending on the brain activity regions and animal species studied and presenting different functions which have been studied for their potential in neurology as a trophic factor in brain development, in calcium transport regulation, in the eardrum integrity, as neuromodulator, neurotransmitter, osmoregulator and for its neuroprotective action (Wu and Prentice, 2010).

Hesperidin (Hsp) is a flavanone glycoside (flavonoid C<sub>28</sub>H<sub>34</sub>O<sub>15</sub>) found abundantly in citrus fruits (Walaa *et al*, 2014). Hesperidin occurs in the cells in crystalline, feather-like aggregates or sphaerocrytalline masses (Priya and Vijayalakshmi, 2016). Hsp, a flavonoid that is particularly abundant in oranges and lemons, exerts antioxidant, antihypertensive, anticarcinogenic, antiviral and anti-inflammatory effects (Parhiz *et al*, 2015). In addition, it can cross the blood-brain barrier (BBB) and can protect the neurons against various types of insult associated with neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's disease (HD) (Santa *et al*, 2016).

Rotenone (ROT) is a lipophilic, naturally occurring compound and mainly derived from the roots and stems of *Lonchocarpus* and *Derris species*. ROT acts as a strong inhibitor of the mitochondrial respiratory chain (MRC) complex I (Sabrina *et al*, 2017).

The aim of this study was to evaluate the treatment effect of taurine and hesperidin against rotenone induced neurodegeneration.

**Materials and Methods**
**Experimental animals:**

White male albino rats (*Rattus norvegicus*) weighing between 100 g and 120 g were used as experimental animals in the present investigation. They were obtained from the animal house of National Research Institute, El-Giza, Egypt. They were kept under observation for about 10 days before the onset of the experiment to exclude any intercurrent infection. The chosen animals were housed in plastic cages with good aerated covers at normal atmospheric temperature (25±5°C) as well as under good ventilation and received water and standard balanced diet. All the procedures were performed in accordance with the Institutional Animal Ethics Committee in Beni-Suef University recommendations.

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**Chemicals:**

Rotenone (ROT), Taurine (Tau), Hesperidin (Hsp), Dimethyl sulfoxide (DMSO) and Carboxy methyl cellulose (CMC) were purchased from Sigma Chemical Company, St. Louis, MO, USA. The dose selection for each compound was based on previously published studies.

**Doses and treatment:**

The dose of rotenone used in this study was 1.5 mg/kg.b.wt. dissolved in 1ml DMSO+ 4ml saline (Abdelkader *et al*, 2014). It was administered three times per week for two months by subcutaneous injection. Taurine and hesperidin were administered by gastric intubation in a dose of 100 mg / kg.b.wt. dissolved in distilled water (Ezekiel *et al*, 2015) and 50 mg/kg.b.wt. dissolved in 1% CMC (Balakrishnan and Menon, 2007) respectively, daily for one month after rotenone administration.

**Experimental design:**

The number of rats used in the present study is 36 rats. They were allocated into 6 groups; designed as follow:

**Group 1:** The control group, it was given the vehicle of the administered substances for three months.

**Group 2:** The taurine treated group.

**Group 3:** The hesperidin treated group.

**Group 4:** The rotenone injected group.

**Group 5:** The rotenone + taurine group, the rats of this group were administered with taurine daily for one month after two months of rotenone injection.

**Group 6:** The rotenone + hesperidin group, the rats of this group were administered with hesperidin daily for one month after two months of rotenone injection.

At the end of three months, six animals of each group were sacrificed under mild diethyl ether anesthesia. Brain from each animal was rapidly excised after dissection. 0.5g from brain was homogenized in 5ml 0.9% sterilized NaCl (10% w/v) using teflon homogenizer (Glas-Col, Terre Haute, USA) for biochemical analysis.

**Biochemical analyses:**

Epinephrine (E) and Norepinephrine (NE) contents were measured fluorometrically. Tyrosine hydroxylase (TH) was measured by using western blotting assay. In the midbrain, lipid peroxidation

was determined by the method of Ohkawa *et al*, (1979) and catalase activity was determined by the method of Aebi, (1984).

**Statistical analysis:**

The Statistical Package for the Social Sciences (IBM SPSS for WINDOWS7, version 20; SPSS Inc, Chicago) was used for the statistical analysis of the results. Comparative analysis was conducted by using the general linear models procedure (IBM SPSS).  $p > 0.05$  were considered statistically non-significant, while  $p < 0.05$  were considered statistically significant.

**Results**

Data summarized in Table 1 and figures 1, 2, 3 and 4 indicating the effect of rotenone administration and treatment with taurine and hesperidin on midbrain epinephrine, norepinephrine and tyrosine hydroxylase in striatum. Our results revealed that the administration of rotenone produced marked impairment demonstrated by significant decrease in these parameters as compared to normal rats, while oral administration of taurine and hesperidin significantly increased these decreased levels of brain epinephrine, norepinephrine and tyrosine hydroxylase when compared with the rotenone administered rats recording noticeable significant amelioration as compared to the control ones.

Table 2 and figures 5 and 6 showing the effect of the tested taurine and hesperidin on the midbrain oxidative stress markers and antioxidant defense system in the midbrain of rotenone-administered rats. Lipid peroxidation (LPO) was significantly increased as a result of rotenone administration while treatment of rotenone-administered rats with taurine and hesperidin significantly decreased these elevated values and becomes near to those of control values. On the other hands, rats injected with rotenone exhibited a significant decrease in values of catalase activity as compared to control ones. While, the treatment with taurine and hesperidin produced a significant increase of this antioxidant enzyme activity as compared to the corresponding rotenone administered group pointing to a marked amelioration.

**Table 1:** Effect of taurine and hesperidin on epinephrine, norepinephrine and tyrosine hydroxylase levels in rotenone-administered rats.

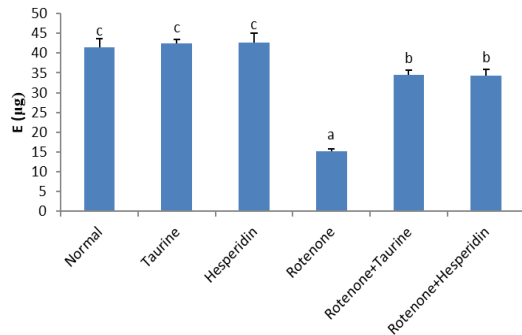
| Groups              | E ( $\mu$ g)                  | NE ( $\mu$ g)                   | TH                            |
|---------------------|-------------------------------|---------------------------------|-------------------------------|
| Normal              | 41.50 $\pm$ 2.08 <sup>c</sup> | 634.85 $\pm$ 4.87 <sup>d</sup>  | 1.03 $\pm$ 0.003 <sup>e</sup> |
| Taurine             | 42.38 $\pm$ 1.04 <sup>c</sup> | 649.85 $\pm$ 6.12 <sup>d</sup>  | 1.02 $\pm$ 0.01 <sup>c</sup>  |
| Hesperidin          | 42.70 $\pm$ 2.33 <sup>c</sup> | 639.10 $\pm$ 14.55 <sup>d</sup> | 1.04 $\pm$ 0.01 <sup>c</sup>  |
| Rotenone            | 15.20 $\pm$ 0.53 <sup>a</sup> | 212.25 $\pm$ 3.23 <sup>a</sup>  | 0.29 $\pm$ 0.02 <sup>a</sup>  |
| Rotenone+Taurine    | 34.47 $\pm$ 1.18 <sup>b</sup> | 511.87 $\pm$ 7.96 <sup>c</sup>  | 0.85 $\pm$ 0.01 <sup>b</sup>  |
| Rotenone+Hesperidin | 34.26 $\pm$ 1.61 <sup>b</sup> | 468.07 $\pm$ 12.36 <sup>b</sup> | 0.82 $\pm$ 0.03 <sup>b</sup>  |
| LSD                 | 2.00                          | 13.00                           | 0.029                         |

\*Values significantly different to control at ( $p \leq 0.05$ ).

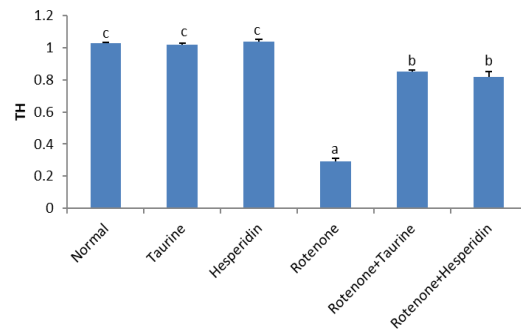
\*Data are expressed as mean  $\pm$  SE.

\*Values which share the same superscript symbol are not significantly different.

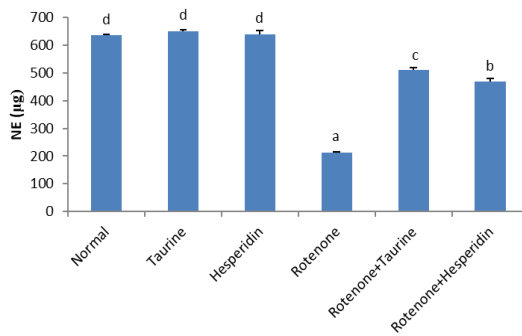
\*F-Probability:  $P < 0.05$



**Fig. 1:** The effect of taurine and hesperidin administration on midbrain epinephrine level in normal control and rotenone administered rats.

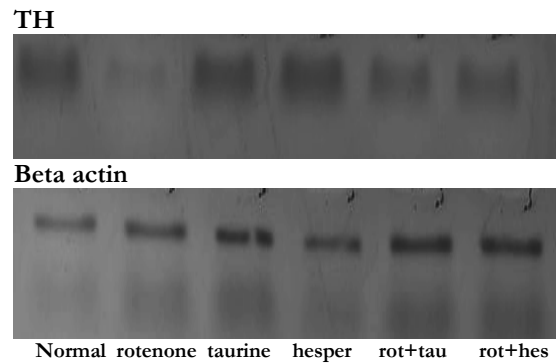


**Fig. 3:** The effect of taurine and hesperidin administration on striatum tyrosine hydroxylase level in normal control and rotenone administered rats.



**Fig. 2:** The effect of taurine and hesperidin administration on midbrain norepinephrine level in normal control and rotenone administered rats.

**Fig. 4:** Western blotting analysis showing the effect of taurine and hesperidin administration on striatum tyrosine hydroxylase levels in normal control and rotenone administered rats.



**Table 2:** Effect of taurine and hesperidin on midbrain oxidative stress in normal control and rotenone-administered rats.

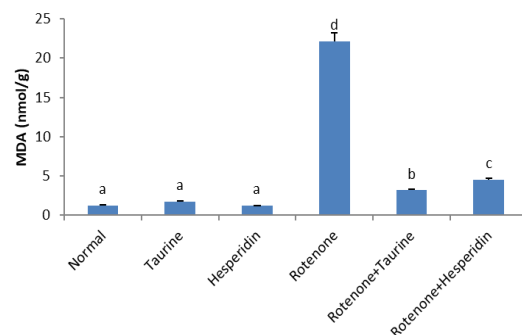
| Groups              | MDA (nmol/g.tissue)       | CAT (U/g.tissue)           |
|---------------------|---------------------------|----------------------------|
| Normal              | 1.23 ± 0.06 <sup>a</sup>  | 126.85 ± 0.56 <sup>d</sup> |
| Taurine             | 1.75 ± 0.05 <sup>a</sup>  | 123.80 ± 1.24 <sup>d</sup> |
| Hesperidin          | 1.19 ± 0.04 <sup>a</sup>  | 124.95 ± 0.93 <sup>d</sup> |
| Rotenone            | 22.16 ± 1.08 <sup>d</sup> | 61.22 ± 1.46 <sup>a</sup>  |
| Rotenone+taurine    | 3.16 ± 0.12 <sup>b</sup>  | 101.60 ± 3.45 <sup>b</sup> |
| Rotenone+Hesperidin | 4.49 ± 0.21 <sup>c</sup>  | 108.56 ± 1.95 <sup>c</sup> |
| LSD                 | 0.64                      | 2.6                        |

\*Values significantly different to control at (p≤0.05).

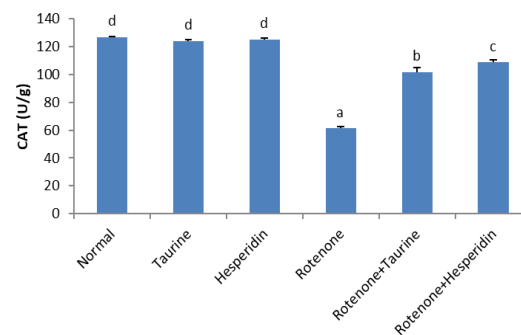
\*Data are expressed as mean ± SE.

\*Values which share the same superscript symbol are not significantly different.

\*F-Probability: P < 0.05



**Fig. 5:** The effect of taurine and hesperidin administration on midbrain malondialdehyde level in normal control and rotenone administered rats.



**Fig. 6:** The effect of taurine and hesperidin administration on midbrain catalase activity in normal control and rotenone administered rats.

## Discussion

Mitochondrial dysfunction and neuroinflammation are common features of chronic neurodegenerative diseases of the central nervous system (CNS). Both conditions can lead to increased oxidative stress by excessive release of harmful reactive oxygen and nitrogen species, which further promote damage of neurons and subsequent inflammation resulting in a feed-forward loop of neurodegeneration (Roman and Olaf, 2015).

Rotenone (ROT), a potent retinoid which is used as a pesticide and insecticide, has been shown to cause systemic inhibition of mitochondrial complex I activity, with consequent degeneration of dopaminergic neurons within the substantia nigra and striatum, as observed in PD (Carriere *et al.*, 2014). It is highly lipophilic in nature enabling it to cross the blood-brain barrier (BBB), and unlike many other toxic agents it can bypasses the dopamine transporter for cellular entry (Nidhika *et al.*, 2016). Once in the cell, it accumulates in subcellular organelles including the mitochondria where it binds specifically to complex I leading to disruption of mitochondrial respiration and increasing the production of reactive oxygen species (ROS) and oxidative stress (Nistico *et al.*, 2011).

Our results obtained in the present work can be discussed in two main aspects: first, the development of neurodegenerative disease model induced by rotenone; second, the effects of taurine and hesperidin against changes induced by rotenone. According to the first aspect, it was possible to observe that the injection of rotenone at the dose of 1.5mg/kg.b.wt. caused several changes in antioxidant system that can induce neurodegeneration. Our results showed that administration of rotenone caused a significant decrease in epinephrine, norepinephrine and tyrosine hydroxylase levels. These results run parallel to those of Nidhika *et al.*, (2016) whose results showed that administration of rotenone for 28 days significantly decreases levels of norepinephrine, serotonin and dopamine. Gunduluru and Wudayagiri (2014) speculated that norepinephrine levels were decreased in rotenone-induced rats may be due to the 50% loss of neurons in Parkinson's disease. Although the rotenone microtubule-depolymerizing activity is not cell type-specific either, it significantly contributes to the selective dopaminergic neurons death because it disrupts microtubule-based transport of dopamine vesicles (Yong *et al.*, 2005). These results in accumulation of vesicle in the soma, which leads to oxidative stress increasing due to oxidation of dopamine leaked from the vesicles (Eisenhofer *et al.*, 2004). Thus, the combination of both rotenone activities would generate far more ROS in dopaminergic neurons than in other types

of cells, rendering these neurons vulnerable particularly to this environmental PD toxin. Thus, catecholaminergic neurons that depend on long range microtubule based transport to move their oxidizable cargoes are vulnerable to microtubule-depolymerizing agents such as colchicine or rotenone (Yong *et al.*, 2005). In the same way, Lamberto *et al.*, (2007) revealed that the concomitant decline in the levels of dopamine and norepinephrine mediators might indicate the inhibition of neurotransmitter synthesis through the tyrosine hydroxylase inactivation and/or mitochondrial dysfunction and cell damage. As for tyrosine hydroxylase level, Zhaoqiang *et al.*, (2015) indicated that the tyrosine hydroxylase-immunoreactive neurons number and the tyrosine hydroxylase expression levels were decreased in the substantia nigra of rats treated with rotenone. It has been found that treatment with rotenone leads to nigrostriatal dopaminergic neurodegeneration, resulting in a loss of tyrosine hydroxylase-positive neurons in the substantia nigra (Nuramatjan *et al.*, 2016). In the same way, Amparo *et al.*, (2013) revealed that 1-methyl-7-phenylpyridine (MPP<sup>+</sup>) or rotenone treatment decreased the number of tyrosine hydroxylase-positive neurons in chicken midbrain dopaminergic neuron culture, thus allowing the possibility to test neuroprotective capabilities of potential trophic factors *in vitro*.

In our study, administration of taurine and hesperidin to rotenone treated rats resulted in elevation of the lowered epinephrine, norepinephrine and tyrosine hydroxylase levels as compared to rotenone group. These results go parallel with Chepkova *et al.*, (2005) whose results revealed that extracellular addition of taurine could activate the glycine receptor and the specific taurine transporter, increase the efflux of dopamine, following the release of other neurotransmitters in the central nervous system. Also, Xiaohui *et al.*, (2013) showed that the number of synaptic vesicles was increased in the brains exposed to arsenic and taurine together, therefore these results indicated that taurine had a protective effect on the decreased of norepinephrine that might be a reasons for taurine protection effect on the arsenic induced the decreased neurotransmitters concentration in the brains. They also showed that the expression of tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH) and dopamine beta hydroxylase (DBH) mRNA were significantly increased in the cerebellum of mice exposed to arsenic and taurine together, except that the changed in TPH mRNA in the cerebrum wasn't significant and hence these results indicated that taurine had a protective effect on the decreased levels of biogenic amine neurotransmitter in the brain of mice exposed to arsenic through elevating the DBH, TH, and TPH mRNA expression.

On the other hands, Priya *et al.*, (2014) stated that the protective effect of hesperidin may be due to neurotransmitters such as norepinephrine and epinephrine regulation which may play an important role in protection of neurobehavioral activities and antioxidant properties. Also, Priya and Vijayalakshmi (2016) observed that tyrosine immunoreactive neurons of striatum and mid brain were reduced after treatment with 6-hydroxydopamine and this decrease was reversed by hesperidin administration and much better by hesperidin in combination with L-dopa.

The oxidative stress usually results from either excessive production of ROS, impaired antioxidant system, dysfunction of mitochondria or a combination of these factors (Malgorzata and Andrzej, 2016). Sushruta *et al.*, (2012) revealed that decreased activities of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, catalase and glutathione in neurodegenerative states signify the role of antioxidant potential reduction during neurodegeneration. Rotenone inhibits complex I of the protein mitochondrial electron transport chain leading to reduced ATP production and leakage of electron that can form reactive oxygen species such as superoxide, subsequently causing glutathione levels reduction and oxidative stress (Johnson and Bobrovskaya, 2015).

In the present study, our results revealed that rotenone administration resulted in increased level of lipid peroxidation and caused significant decrease in catalase level. These results go parallel with Omar *et al.*, (2015) who observed that rotenone resulted in increased nitric oxide and lipid peroxidation concentrations while decreasing antioxidant mechanisms such as catalase, reduced glutathione level and Paraoxonase 1(PON1) activities in different brain regions. In the same way, Neha and Pallavi (2012) observed that the rotenone per selenium group showed a significant increase in the levels of thiobarbituric acid (which is an indication of lipid peroxidation extent), decrease in the superoxide dismutase and glutathione reduced levels in the brain as compared to the vehicle treated control animals, therefore all these indicate an oxidative stress increase in the brain of rotenone treated animals. Also, Yasser *et al.*, (2016) stated that rotenone induced a significant increase in striatal lipid peroxidation in the striatum. The depletion of glutathione reduced, ATP and the increase of malondialdehyde and protein carbonyl levels might support the oxidative stress occurrence resulting in peroxidation of lipid and protein and mitochondrial dysfunction, which lead to energy crisis and cell damage (Lamberto *et al.*, 2007).

Administration of taurine and hesperidin to rotenone intoxicated rats resulted in a significant decrease in malondialdehyde level and resulted in a

significant increase in catalase level. These results are in accordance with (Zuhal and Nedret, 2011) who stated that the useful effects of taurine in biological systems as an antioxidant have been attributed to its ability to stabilize biomembranes, to scavenge ROS, and to decrease the peroxidation of unsaturated membrane lipids. It has been shown that taurine exhibits its antioxidant capacity by the antioxidant system enhancement, formation of chloramines with hypochlorous acid and replacement of glutathione in biological systems during oxidative stress (Devi and Anuradha, 2010). Jagadeesan and Sankarsami (2007) concluded that taurine reduces the oxidative stress through lipid peroxidation inhibition and also through increased catalase, glutathione peroxidase and superoxide dismutase which replenish glutathione reduced stores and allows for correct cell defense against ROS. Also, Ezekiel *et al.*, (2015) stated that taurine may inhibit lipid peroxidation by superoxide dismutase and glutathione peroxidase induction and also observed that the antioxidant taurine prevented oxidative stress and cellular antioxidants loss and suggested that taurine protected forebrain from restrain stress-induced oxidative damage and also, shown that taurine offsets lipid peroxidation either through ROS scavenging directly or by binding to copper ion or ferrous ion through its sulphonic acid group. In the same way, Rosemberg *et al.*, (2010) revealed that treatments with taurine prevented the alterations promoted in catalase and superoxide dismutase activities by ethanol (EtOH), suggesting a modulatory role in enzymatic antioxidant defenses. On the other hands, Hiam *et al.*, (2012) revealed that there is an increase in the glutathione reduced content and decrease in the extent of lipid peroxidation with the hesperidin treatment and demonstrated that hesperidin administration to group treated with Chlorpyrifos (CPF) showed an improvement in the levels of endogenous antioxidant enzymes (superoxide dismutase, catalase and glutathione S transferase), glutathione reduced and acetylcholinesterase. In the same regard, Syed *et al.*, (2011) demonstrated that significantly antioxidant enzymes, glutathione peroxidase, catalase, glutathione reductase and superoxide dismutase and content of glutathione depleted activity in Middle cerebral artery occlusion (MCAO) group were protected significantly in MCAO group pretreated with hesperidin. The antioxidant/neuroprotective properties of flavanoids including hesperidin, involves metal ions chelation such as copper and iron resulted in inhibition of transition metal-catalyzed free radical formation (Kuppusamy *et al.*, 2013). Pretreatment with hesperidin significantly resulted in malondialdehyde and nitrite concentration improvements in striatum and cortex regions of the brain suggesting its antioxidant like effects, therefore hesperidin has been reported to offer neuroprotection by lipid peroxidation side chain

termination rather than extracellular non-lipid radicals scavenging that initiate lipid peroxidation (Vaibhav *et al*, 2011). In the same way, hesperidin therapy could significantly attenuate formation of ROS by reducing the levels of thiobarbituric acid reactive substances (TBARS) and restored glutathione reduced and antioxidant enzyme activity to physiological levels in the brain (Kamislı *et al*, 2013) and cultured PC12 cells (Kuppusamy *et al*, 2013).

## Conclusion

Taurine and hesperidin administration exhibited a beneficial therapeutic effect on rats with neurodegeneration due to their ability to regulate neurotransmitters and due to their antioxidative properties.

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