Original Article

The Role of Eruca Sativa Extract on the Toxic Effect of Proton Pump Inhibitor on Cerebellar Cortex in Adult Males Albino Rat

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ABSTRACT

Introduction: Proton pump inhibitors produce marked histopathological changes in the cerebellar cortex that it could disturb the normal function of cerebellum. The aim of this work is to study, for the first time, the role of eruca sativa in the protection and treatment of these neuropathological changes that could be detected in the cerebellar cortex by using proton pump inhibitor.

Material and Methods: Sixty adult males albino rat were used and divided into five main groups; Group I: contained twenty animals and was further subdivided into two subgroups, Group II: (Eruca treated group) included ten animals, Group III: (Proton pump inhibitor group) included ten animals that received treatment of pantoprazole in an oral dose of 1.3 mg /kg dissolved in 1ml phosphate–buffered saline by gastric tube once daily for 4 weeks. Group IV: (Protected group) included ten animals received Eruca sativa seeds extract daily for 4 weeks and pantoprazole daily for 4 weeks started from 2nd day of the experiment. Group V (Treated group): included ten animals received pantoprazole once daily for 4 weeks followed by a daily oral dose of Eruca sativa seeds extract for 4 weeks.

Results: Regardingto the histological, immunohistochemical and morphometric studies; eruca sativa significantly protected the cerebellar cortex from the damaging effects of pantoprazole and significant improvement was also observed when it was used as a treatment.

Conclusion: Eruca sativa played an important role in protection and treatment of the cerebellar cortex against the neuropathological changes that could be detected by using the proton pump inhibitor; pantoprazole.

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Key Words: Cerebellar histopathology; eruca sativa; INOS and GFAP; proton pump inhibitors.

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INTRODUCTION

Pantoprazole is a new proton-pump inhibitor (PPI) which blocks the gastric H+/K+ ATPase proton pump so it inhibits the secretion of gastric acid. This effect allows peptic ulcers healing, gastro-esophageal reflux improvement and shares in the treatment of helicobacter pylori[1].

The cerebellum is the nervous organ that controls the motor function in the body. It shares in cognitive functions like language. It also plays an important role in regulating fear and pleasure[2]. Cerebellum has the highest levels of nitric oxide (NO) that plays an important role in the aging of the brain. The expression of the inducible nitric oxide synthase (iNOS) is one of the results of the oxidative damage[3]. Moreover expression of glial fibrillary acidic protein (GFAP) increases in response to inflammatory process after central nervous system injury to decrease the damage[4].

The choice of Eruca sativa is to withstand the histopathological changes of the PPI in the cerebellar cortex depending on the fact that, Eruca sativa is a green leafy vegetable with high levels of bioactive components. It has a high mineral content and many health supporting substances with powerful active components which may play an important role in improving the human health and acts as an anticancer agent[5]. It also significantly scours many reactive oxygen species[6].

MATERIALS AND METHODS

Materials

Proton pump inhibitor (Pantoprazole)

It was purchased from Sigma Chemical Company and it was given in a dose equivalent to 1.3 mg /kg dissolved in 1ml phosphate–buffered saline by gastric tube once daily for 4 weeks[7].

Eruca sativa seeds extract (SE)

Eruca sativa seeds were purchased from the Chemistry Department, Agricultural Research Center, Cairo, Egypt. They were soaked in 95% ethanol in an incubator shaker (150 rpm) at 30°C for two days. The extract was concentrated using a rotatory evaporator to yield the dried ethanolic extract, then the ethanolic extract was converted to powder using lyophilizer[8].

Inducible nitric oxide synthase (iNOS)

It was used to detect oxidative stress (3). It was rabbit polycolonal antibodies (IgG) and was obtained from Abcam Company (Cairo, Egypt).

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Glial fibrillary acidic protein (GFAP)

It was for detecting inflammatory response[4]. It was rabbit polycolonal antibodies (IgG) and was obtained from Abcam Company (Cairo, Egypt).

Biotinylated secondary antibody

It was goat anti-mouse IgG and was obtained from Sigma Aldrich Company (Cairo, Egypt).

Animals and experimental design

Sixty adult males albino rats were used in this study weighing from 150-200 gm. They were housed in separate cages under standardized conditions, fed on standard diet and water in the Anatomy and Embryology Department, Faculty of Medicine, Menoufia University, according to the guidelines recommended by ethical committee for animal research.

The animals were divided into 5 groups as follows:

Group I (control group): It included twenty animals and it subdivided equally into 2 subgroups as follows:

- Subgroup IA: Animals were kept without any treatment throughout the experimental period.
- Subgroup IB: Animals received phosphate – buffered saline for 4 weeks.

Group II (Eruca treated group): It included ten animals and they received Eruca sativa seeds extract in an oral dose of 500 mg/ kg dissolved in 1 ml distilled water by gastric tube once daily for 4 weeks.

Group III: (Proton pump inhibitor group): It included ten animals and they received Pantoprazole in an oral dose of 1.3 mg /kg dissolved in 1ml phosphate – buffered saline by gastric tube once daily for 4 weeks.

Group IV (Protected group): It included ten animals. They received an oral dose of 500 mg/kg /day of Eruca sativa seeds extract dissolved in 1 ml distilled water by gastric tube once daily for 4 weeks then they were given Pantoprazole 1.3 mg /kg dissolved in 1 ml phosphate – buffered saline by gastric tube once daily for additional 4 weeks.

Group V (Treated group): It included ten animals and they were given Pantoprazole 1.3 mg /kg dissolved in 1 ml phosphate –buffered saline by gastric tube once daily for 4 weeks followed by a daily oral dose of 500 mg/kg of Eruca sativa seeds extract for additional 4 weeks.

After 8 weeks from the onset of the experiment, all animals were anaesthetized lightly by diethyl ether inhalation then they were sacrificed and decapitated, the cerebellum was removed carefully, fixed in 10% neutral-buffered formalin for 24 hours and then embedded in paraffin wax. Dehydration was carried out in ascending grades of alcohol. The cleaning was done by xylol followed by impregnation in soft then hard paraffin to form paraffin blocks. These blocks were sectioned in a sagittal plane at 4-6 µm in thickness by microtome and processed for histological and immunohistochemical studies[9].

Histological study

1. Haematoxyline and Eosin stain.
2. Toludine blue.

Immunohistochemical studies

The immunoreactivity of inducible nitric oxide synthase (iNOS): is for detection of oxidative stress[3] and the immunorativity of glial fibrillary acidic protein (GFAP) is for detecting inflammatory response[4]. The sections were deparaffinized, rehydrated, and after antigen retrieval with 10m mol/l citrate acid solution (pH 6), the specimens were preincubated with goat serum for 5 min and were then incubated overnight at 4°C with anti iNOS (Abcam, 178945) and GFAP (Abcam, 37150) (Working dilution 1:500). Binding was detected using biotinylated secondary antibody (goat anti-mouse IgG; Sigma Aldrich) for 10 min. The specimens were then incubated with streptavidin-peroxidase complex for 5 min, followed by incubation with 3, 3 –diaminobenzidinetetrahydrochloride (DAB; Sigma Aldrich) for 3 min. Slides were counterstained with hematoxylin and mounted

Morphometric and statistical studies

Data obtained from five different sections from each rat of all subgroups were examined using image J analyzer software program to determine:

- The number of Purkinje cells in H & E stained sections.
- Color intensity in toluidine blue stained sections.
- The percentage of immune positive cells in INOS and GFAP immunohistochemical stained sections.

Image analysis was done in the Anatomy and Embryology Department, Faculty of Medicine, Menoufia University.

Data obtained from morphometric study was subjected to statistical analysis using SPSS software version 20 (SPSS, Inc., Chicago, IL, USA). Data was presented as mean ± standard deviation. Differences among the study groups were detected by using Mann-Whitney U test. The results were considered statistically significant with $p < 0.05$[10].

RESULTS

There was no significant difference between the subgroups IA, IB and group II in all results; therefore, both groups I & II were considered as a control group and the group IA was considered the standard control group for other study groups.

Histological study

Haematoxylin and Eosin (H&E) stain: (Figure 1).

The neural cells in the cerebellar cortex of the rat in

control group showed normal arrangement in three layers, scattered neurons in intact neuropil of superficial molecular layer. The Purkinje cells appeared flask in shape with large central nuclei. They were arranged in a linear appearance in the Purkinje cells layer. Numerous closely arranged granular neurons were detected in the third granular layer (Figure 1a).

The PPI group showed scattered neurons with appearance of multiple linear gaps in neuropil of molecular layer. In Purkinje cells layer, significant decrease in the number of Purkinje cells which appeared distorted deeply stained with loss of their nuclei. Also no Purkinje cells were detected in some sections (Figure 1c). Empty spaces between the Purkinje cells layer and granular layer were noticed. Spaces in between the crowded granular neurons in the granular layer were also observed. (Figure 1b).

The protected group showed scattered cells with appearance of few small gaps in neuropil of molecular layer. Significant increase in the number of Purkinje cells as compared to the PPI group. Few disturbed deeply stained Purkinje cells were detected among nearly normal ones in the Purkinje cells layer. Small few spaces were also observed in between granular neurons in granular layer. (Figure 1d).

The treated group showed scattered cells with appearance of multiple gaps in neuropil of molecular layer. In Purkinje cells layer, significant increase in the number of Purkinje cells as compared to the PPI group. Some Purkinje cells appeared distorted in shape. Some spaces were observed in between the granular neurons in the granular layer (Figure 1e).

Toluidine blue stain: (Figure 2).

The cerebellar cortex sections of control group showed dark blue staining of the Purkinje cells which detect the presence of dense Nissl's granules (Figure 2a). The Purkinje cells of PPI group showed significant decrease in the color intensity as compared to the control group denoting decreased production of Nissl's granules (Figure 2b). Purkinje cells of protected group showed significant increase in the color intensity of toluidine blue stain as compared to that of PPI group (Figure 2c). Purkinje cells of treated group showed non- significant increase in the color intensity of toluidine blue stain as compared to that of PPI group (Figure 2d).

Immunohistochemical studies: (Figure 3).

The cerebellar cortex sections of PPI group showed a significant upregulation in the percentage of immunoreactivity positive cells for iNOS (Figure 3b1) and GFAP (Figure 3b2) immunostaining as compared to the iNOS immunostaing in control group (Figure 3a1) and the GFAP immunostaing in control group (Figure 3a2) respectively.

The protected group showed a significant down-regulation of immunoreactivity positive cells for iNOS (Figure 3c1) and GFAP (Figure 3c2) immunostaining as compared to the PPI group

The treated group showed a significant down-regulation of immunoreactivity positive cells for iNOS (Figure 3d1) and GFAP (Figure 3d2) immunostaining as compared to the PPI group.

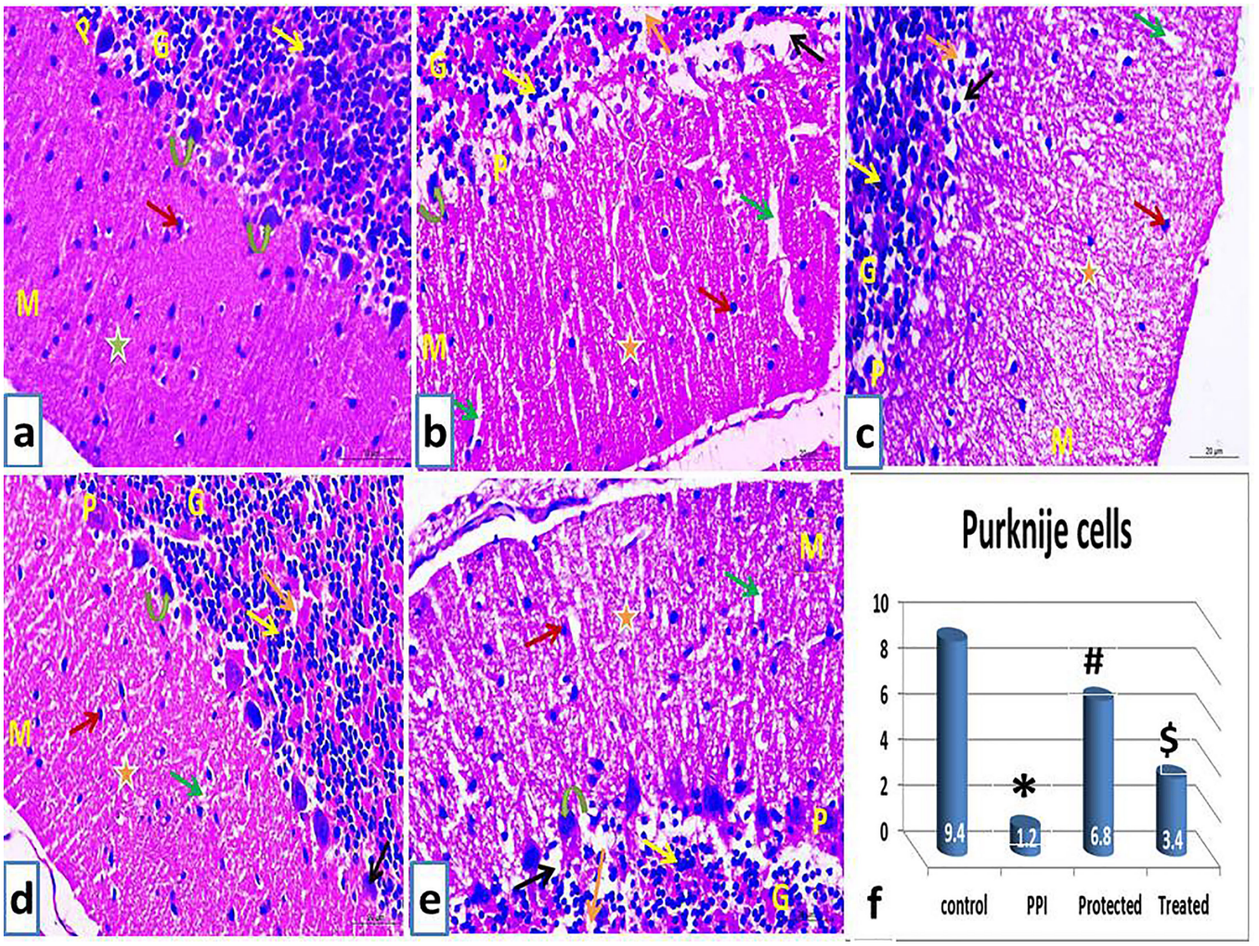

Fig. 1 (a-f): Photomicrographs of H&E-stained cerebellar cortex sections from animals of different groups.
a: The control group shows normal arrangement of 3 cerebellar layers; molecular (M) with normally scattered neurons (red arrow) in intact neuropil (star), intermediate Purkinje cell layer (*P*) contains one layer of flask shape Purkinje cells with prominent nuclei (curved arrows). Granular layers (G) with numerous closely arranged granular neurons (yellow arrow) are seen. (Hx&E, x400).
(b, c): b; The cerebellar cortex of PPI group shows scattered neurons (red arrow) and multiple linear spaces (green arrows) in the neuropil (star) of molecular layer (M). Distorted deeply stained Purkinje cells (curved arrow) in a Purkinje cell layer (*P*) separated from the granular layer by large empty spaces (black arrow).c; No Purkinje cells are seen in some sections. Multiple spaces (orange arrow) in between clumping granular neurons (yellow arrow) are detected in granular layer (G). (Hx&E, x400).
d: The cerebellar cortex of protected group shows few small spaces (green arrow) in between scattered neurons (red arrow) in neuropil (star) molecular layer (M). Decrease the number of disturbed Purkinje cells (black arrow) among nearly normal ones (curved arrow) is detected. Small few spaces (orange arrow) in between clumping granular neurons (yellow arrow) are noticed in granular layer (G). (Hx&E., x400).
e: The cerebellar cortex of treated group shows many spaces (green arrow) in between scattered neurons (red arrow) in neuropil (star) of molecular layer (M). Also disturbed shape and size of some Purkinje cells (curved arrow) are detected but less than PPI group in Purkinje cell layer (*P*). Clumped cells (yellow arrow) are noticed in granular layer (G) which separated from the Purkinje cell layer (*P*) by empty spaces (black arrow). Small few spaces (orange arrow) in between numerous closely arranged granular neurons (yellow arrow) are noticed in granular layer (G). (Hx&E., x400).
f: In the statistical analysis; the number of Purkinje cells is significantly decreased (*p) in PPI group as compared to the control group. On the other hand, it is significantly increased (#p) in the protected group as compared to the PPI group. Significant increase ($$p$) in treated group as compared to the PPI group (Foot note: *p, #p and $$p$ < 0.05%)

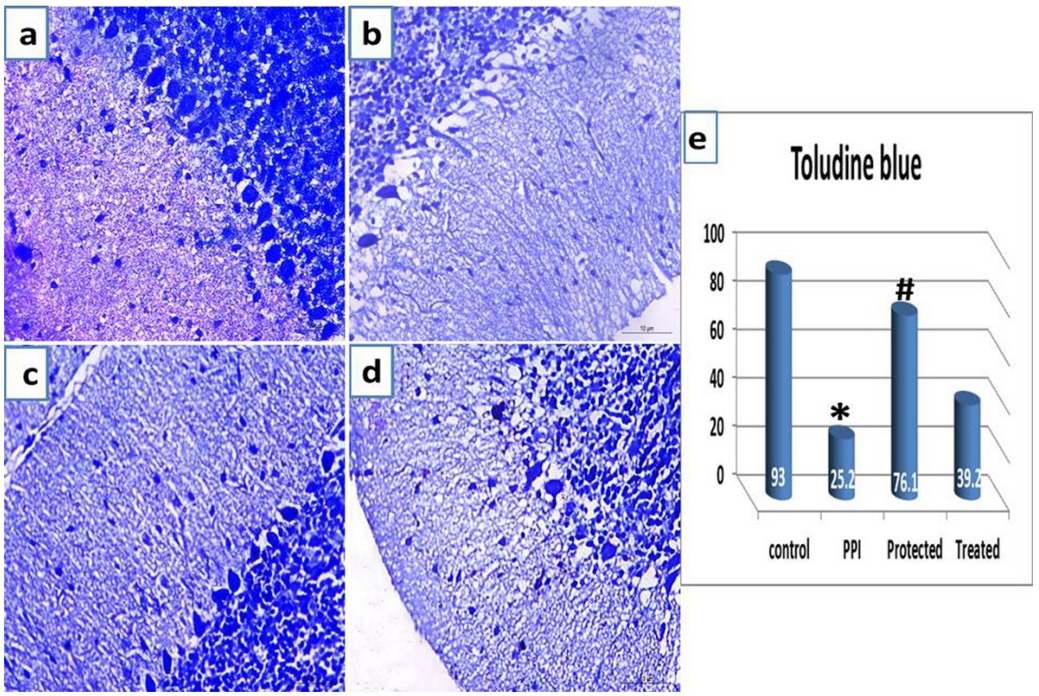

Fig. 2: Photomicrographs of toluidine blue-stained cerebellar cortex sections from animals of different groups' representative; control group (a) shows dark blue staining of cytoplasm that surrounded central nucleus of Purkinje cells as dense Nissl's granules. (b) The color intensity is significantly decreased (*p; fig 2: e) in PPI group as compared to the control group. (c) On the other hand, it is significantly increased (#p; fig 2:e) in the protected group as compared to the PPI group. (d) Non- significant increase in treated group is revealed as compared to PPI group. (Foot note: *p & #p < 0.05%). (Toluidine blue., x400).

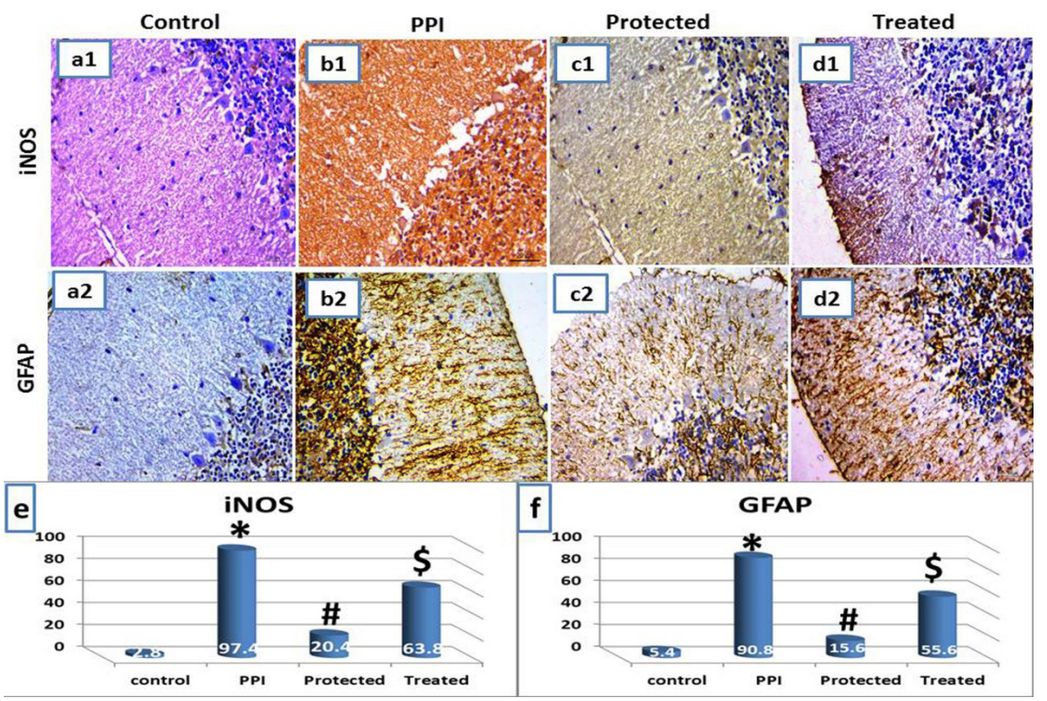

Fig. 3: Photomicrographs of iNOS and GFAP stained cerebellar cortex sections from animals of different groups representative: the control group shows minimal expression of iNOS (a1) and GFAP (a2). The PPI group shows significant up- regulation (*p; fig 3: e & f) in the percentage of immunoreactivity positive cells of iNOS (b1) and GFAP (b2) as compared to the control group. The protected group shows significant down – regulation (#p; fig 3: e & f) in the percentage of immunoreactivity positive cells in iNOS (c1) and GFAP (c2) as compared to the PPI group. The treated group shows significant down – regulation ($p; fig3:e & f) in the percentage of immunoreactivity positive cells in iNOS (d1) and GFAP (d2) as compared to the PPI group. (The counter stain is haematoxyline, *p, #p and $*p* < 0.05%) (iNOS & GFAP., x400).

DISCUSSION

Drug extract from natural products is a challenging task that gives a considerable attention for production of treatments to many diseases[11]. The present study was performed to detect the neurotoxicity of proton pump inhibitor on the cerebellar cortex and to investigate the possible protecting and/ or treating role of Eruca sativa by histological and immunohistochemistry studies. For the author's knowledge, this work is the first study in the world to evaluate the role of Eruca sativa on the toxic effect of proton pump inhibitor in experimental animals.

In the present study, histopathological changes accompanying the proton pump inhibitor (PPI) group showed multiple linear spaces in between scattered neurons in neuropil of molecular layer. Purkinje cell layer showed significant decrease in the number of the Purkinje cells which also were disturbed in their shape and size. Some cerebellar cortex sections revealed loss of Purkinje neurons in some sectors of this layer. Empty spaces were detected among Purkinje cells layer and granular layer. Moreover, appearance of empty spaces in between granular neurons in granular layer was also observed.

These histological findings were supported by a significant ($P < 0.05$) decrease of the toluidine blue color intensity of Purkinje cells in PPI group as compared to control group which is most likely an indication of a decrease in Nissl's granules that surround the central nucleus in Purkinje cells. This finding was explained by[12] who mentioned that chromatolysis is a process which detected in the neuronal cytoplasm in the form of disintegration of the basophilic Nissl's bodies after metabolic or traumatic injuries. These above mentioned histological findings might be due to increase production of free radicals in the nervous system by using PPI. These findings were also explained by[13] who reported that neural membranes in the central nervous system are affected rapidly by free radicals, especially by high level of unsaturated fatty acids and lipid peroxidation so increase the production of free radicals leading to disturbance in neurons function and structure.

In supporting to the above mentioned explanation of histological results; immunohistochemical studies revealed that, there was a significant increase ($P < 0.05$) of inducible nitric oxide synthase (iNOS) expression in cerebellar cortex sections of PPI group as compared to control group and these results may explain that why oxidative stress in cerebellar cortex was considered one of pathogenesis factors. It is also further explained by[14] who mentioned that induction of the high-output of iNOS usually occurs in an oxidative environment and thus high levels of NO have the opportunity to react with superoxide leading to peroxynitrite formation (free radicals) and cell toxicity.

GFAP is a specific marker of mature astrocytes of the central nervous system and its expression is importance for the normal architecture of the white matter and integrity of blood brain barrier as revealed by[15]

Moreover, there was a significant increase ($P < 0.05$) of GFAP immunoreaction in PPI group as compared to control group which gave explanation that PPI induces the astrocytes cells to proliferate. This finding is also explained by[16] who reported that any chemical or mechanical or degenerative factors give the brain a chance to stimulate astrocyte proliferation with increase GFAP synthesis in response to inflammatory process. Also[17] reported that it may be due to compensatory mechanism after neurodegeneration or neurotoxicity.

Histologically in protected and treated groups, the present study showed great improvement in all three layers of cerebellar cortex. Few linear spaces were detected among scattered neurons in neuropil of molecular layer. Significant increase ($P < 0.05$) in the number of Purkinje cells were detected in Purkinje cells layer. Moreover, few disturbed Purkinje cells appeared among the nearly normal ones which were arranged in one layer in protected group and more disturbed Purkinje cells in treated group. Few spaces appeared among the granular neurons in granular layer. These results may explain the powerful anti-oxidant effects of Eruca sativa extract on neural cells of the cerebellar cortex. This explanation was in agreement with[18] who reported that Eruca sativa seeds have a potent antioxidant role as it decrease the elevated lipid peroxidation. It decreases the free radicals production.

In our study, there was a significant ($P < 0.05$) increase of the toluidine blue color intensity of Purkinje cells in protected group as compared to PPI group which meant an increase in Nissl's granules content that surround the central nucleus in Purkinje cells.

Supporting to the above-mentioned findings, these histological results were confirmed by a significant ($P < 0.05$) decrease of percentage of iNOS immune-positive cells in protected and treated groups as compared to PPI group.

Moreover, there were significant decrease ($P < 0.05$) in GFAP immune-reaction in protected and treated groups as compared to PPI group. It may be due to decrease the secretion of inflammatory cytokines and also decrease production of free radicals which cause neuronal damage by glial cells as mentioned by[19]. The later finding may give the explanation that Eurca stiva has the capability to withstand the toxic effect of PPI in the astrocytes, and that Eurca stiva has a great anti-inflammatory role. These findings may reveal that reducing inflammation and oxidative stress could be a novel therapeutic strategy to decrease the nervous toxicity of PPI on cerebellar cortex.

CONCLUSION

Using of Eruca sativa with or after the use of proton pump inhibitor gave the chance to protect the neural cells structure and consequently maintain their function against the oxidative and inflammatory effects of PPI. These improvements were more pronounced in protected group than treated group.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

دور مستخلص الجرجير على التأثير السام لمثبط مضخة البروتون على قشرة المخيخ فى ذكر الجرذ الأبيض البالغ

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الغرض من البحث: يلعب مثبط مضخة البروتون دور مهم وفعال فى علاج الكثير من أمراض المعدة وارتجاع المرئ، و لسوء الحظ لوحظ أن له آثاراً ضارة على قشرة المخيخ. و لذلك تم عمل هذا البحث لدراسة مدى فاعلية مستخلص الجرجير للوقاية وأيضا للعلاج من التاثير الضار الذى يمكن أن يحدثه مثبط مضخة البروتون بالخلايا العصبية لقشرة المخيخ.

خطة البحث: تم استخدام ستون من ذكور الجرذ البالغ خلال البحث وتم تقسيمهم كما يلى: المجموعة الأولى: تتكون من عشرون جرذاً، تم تقسيمهم بالتساوى إلى مجموعتين. المجموعة الثانية: تتكون من عشر جرذان تم إعطائهم مستخلص الجرجيربالفم. المجموعه الثالثة: تتكون من عشر جرذان تم إعطائهم عقار بانتوبرازول عن طريق الفم بجرعة ١,٣ مجم/كجم تذوب فى ١ ملى محلول ملح ومعاير الفوسفات مرة واحدة يوميا لمدة ٤ أسابيع. المجموعة الرابعه: تتكون من عشر جرذان تم إعطائهم مستخلص الجرجير يومياً لمدة ٤ أسابيع، و عقار بانتوبرازول الذى بدأ إعطاؤه من اليوم الثانى من بداية التجربة يومياً لمدة ٤ أسابيع. المجموعة الخامسة: تتكون من عشر جرذان تم إعطائهم عقار بانتوبرازول عن طريق الفم يومياً لمدة ٤ اسابيع، ثم تم إعطائهم مستخلص الجرجيرعن طريق الفم يومياً لمدة ٤ أسابيع أخرى.

نتائج البحث: طبقاً لكل من نتائج الدراسات الهستولوجية والصبغات المناعية وعمل قياسات عن طريق جهاز تحليل الصورة بالكمبيوتر، تم التوصل إلى أن مستخلص الجرير له دور فعال فى وقاية أنسجة قشرة المخيخ من الأضرار التى تلحق به من استخدام مثبط مضخة البرتون البنتوبرازول، كما لوحظ وجود تحسن فعال فى حالة إستخدامه كعلاج.

التوصيات: تم استخلاص ما يلى من البحث:

يوصي البحث باستخدام مثبط مضخة البرتون تحت إستشارة الطبيب.. ولمدة زمنية غير طويلة. كما يوصي باستخدام مستخلص الجرير كمادة وقائية فى المرضى الذين يستخدمون مثبط مضخة البرتون لمدة طويلة، كما أنه يمكن إستخدامه كعلاج و للتقليل من آثار إستخدام مثبط مضخة البرتون على قشرة المخيخ.

كما يوصي أيضاً البحث بإجراء دراسات أخرى على الدور الوقائي و العلاجي المحتمل للجرجير لأعضاء الجسم الأخرى المعرضة للآثارالجانبية عند استخدام أدوية مضخة البروتون المزمن.