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Inhibitive property of chamomile against gamma-rays induced neurodegenerative disorders in mice

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► ***Original article***

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ABSTRACT

Background: Chamomile is a supplementary food all over the world. The chamomile inhibitive effect on neurodegenerative disorders in γ-irradiated mice was investigated. ***Materials and Methods:*** Twenty-four mice were divided into 4 groups; control, chamomile-treated, γ-irradiated (8 Gy), and chamomile-treated and irradiated. Brain total thiols, lipid peroxidation (LP), nitric oxide (NO), reduced- and oxidized-glutathiones (GSH & GSSG), protein carbonyl (PC), antioxidant enzymatic activities and acetylcholinesterase (AChEA) were measured. The brain histopathology sections were observed. ***Results:*** A significant increase of levels of total thiols, LP, NO, GSSG, PC and AChEA activity and a decrease of the antioxidant enzymatic activities in the 8 Gy gamma-irradiated group compared to the controls. In chamomile-treated all estimated indices were considerably ameliorated in respect to control standards. Also, the chamomile intake has diminished the histopathological cerebrum alterations such as severe congestion, perivascular oedema, several apoptotic neurons and spongy degenerative changes. ***Conclusion:*** Chamomile may protect the brain from oxidative injury induced by γ-rays through its ability to inhibit LP, replenish the GSH level and antioxidant enzymes activity.

INTRODUCTION

Oxidative tensions arise when the antioxidant protection system is exhausted by the production of reactive oxygen species (ROS) and free radicals. These ROS can prompt lipid and protein oxidation, triggering cell death [1]. There are growing indications that longstanding oxidative tension plays a dangerous role in the presentation and progress of several disorders, including radiation syndrome, cancer and neurocognitive function decline [2].

Ischemic stroke brain injury is categorised as the second most common cause of death worldwide [3]. Also, Feigin *et al.* [4] concluded that stroke, the most common complication of cerebrovascular disease, is the main cause of death and disability all over the world. Brain is susceptible to oxidative stress that is associated with γ-rays-related brain dysfunction. Neurodegenerative disorders effects of γ-irradiation have been recognised in humans and animals. Subsequently, it has been pointed out that a dramatic decrease of GSH level occurs in the rat brain after whole body γ-irradiation [5, 6]. Recently, it has been stated that the available therapeutic methods to treat or improve ischemic brain injury are lacking. Thus, exploration for neuro-defensive agents with the least dangerous properties must, therefore continue [7, 8].

Matricaria chamomilla L. (*M. chamomilla*), known as "chamomile" and grown in Egypt has long been used as an herbal tea or supplementary food all over the world [9]. It is commonly used in traditional medicine for animals and humans as anti-allergic, anti-pyretic, anti-depressant and to treat infections, gastrointestinal, respiratory, liver and neuron illnesses [10]. Chamomile is a biologically effective virucidal, anti-parasitic, antimicrobial, antifungal, insecticidal, anti-diabetic, antioxidant, anti-inflammatory, anti-cancer, non-toxic, non-mutagenic, and nutraceutical flavonoid herb [11, 10, 12], it contains over 120 active constituents including, terpenoids like α-bisobolol, chamazulene, sesquiterpenes and flavonoids like apigenin, luteolin, quercetin, coumarins and other compounds like polyphenols and polyacetylenes [10, 13]. It is used in different herbal medicinal combinations in the European Pharmacopoeia [13]. Apigenin is a flavonoid found in chamomile that has neuroprotective impacts against oxidative pressure-induced peripheral neurodegenerative illnesses and cerebral ischemic damage [14].

Till now, no review has publicized the protective effect of chamomile against neuron degeneration induced by γ-rays-exposure in mice. This study assesses the inhibitive property of chamomile against

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γ-rays-induced neurodegenerative disorders in mice.

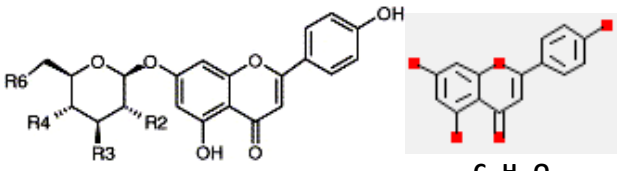
MATERIAL AND METHODS

Animals

Twenty-four adult male mice (25±2g, 9±1 weeks) were housed at controlled environmental temperature (23±1°C), 12-h light/ 12-h darkness cycles and were allowed food and clean water *ad-libitium*. The trial protocol used on the animals was approved by the Research Ethics Committee (REC-NCRRT), protocol number: 26A/21.

Preparation of extracts

Dry chamomile flower of M. chamomilia was purchased from ISIS Co. for Food Industries, Cairo, Egypt. The chamomile flowers were weighed and crushed into a smooth powder using a table white marble mortar and pestle then, a suspension (5% w/ v) was arranged in a cylindrical glass flask by adding boiling water. The glass flask was then put on a lab shaker device (200 rpm) for 4 hours at maintained temperature (37°C). After shaking, the suspension was filtered via a series of Whatman filter papers (Sigma-Aldrich, USA) and finally passed through very fine microfiber papers (WHA TMAN, England), according to Malik *et al.* [15] and Srivastava *et al.* [16], then stored at 4°C. The mice were fed a diet containing 1.2% w/w of water extract of dry chamomile flower for 11 days, according to Kobayashi *et al.* [17].



5,7-dihydroxy-2-(4-hydroxyphenyl) chromen-4-one

$C_{15}H_{10}O_5$
SID: 153919

Figure 1. Chamomile structure. (https://pubchem.ncbi.nlm.nih.gov).

Brain sampling

The brain was dissected, separated and washed in chilled normal saline, kept on ice and consequently dried on filter paper and weighed. The brain homogenate was prepared in 10 % (w/v) phosphate buffer (0.05M, pH7.4). Then, the homogenate was centrifuged (10.000×g) at 4°C for 10 minutes and the post-mitochondrial supernatant was stored on ice till assessed.

Radiation facility

Whole body γ-irradiation was performed with a Canadian ^{137}Cs Gamma Cell-40 at NCRRT, Cairo, Egypt; at a dose rate of 0.38 Gy/ minute. Mice were exposed to 8.0 Gy applied as a shot dose to induce distinct radiobiological changes in mice [18].

Experimental design

Mice were divided into the following four groups each consisting 6 mice. Control group: Mice received normal diet food. Chamomile-treated group: Mice received a technical diet containing chamomile (1.2% w/w of chamomile extract) for 11 days. Irradiated group: Mice were submitted to a single dose of whole -body γ-radiation (8 Gy). Chamomile-treated and irradiated group: Mice received a technical diet containing chamomile for 11 days and after 2hours of the last dose were submitted to whole body γ-radiation (8 Gy). Mice were killed by cervical dislocation 5 days following the end of the experiment after an overnight fast.

Biochemical analysis and histopathology

The brain tissues were homogenised to evaluate total thiol using a commercial kit (MET-5053, Cell Biolabs, Inc. San Diego, USA). The absorbance was read at 450 nm. Estimation of LP, expressed as thio-barbituric acid reactive substances (TBARs, ZB-MDA-48A), and the relative antioxidant enzyme activity of superoxide dismutase (SOD, ZB-SOD-48A), catalase (CAT, ZB-CAT-48A), and glutathione peroxidase (GPx, ZB-GPX-A48) was carried out using a kit provided by Zellbio GmbH, Germany. The absorbance was read at 535 nm, 420 nm, 405 nm, and 412 nm, respectively. Assessment of content of nitric oxide (NO, ab65328), reduced and oxidized glutathiones (GSH & GSSG, ab239709), protein carbonyl (PC, ab126287), and acetylcholinesterase (AChEA, ab138871) activity was carried out using kits obtained from Abcam, UK. The absorbance was read at 540 nm, 412 nm, 562 nm, and 410 nm, respectively. Protein level was evaluated using Bradford [19] technique.

The cerebral hemispheres from all mice groups were fixed in 10% formalin, embedded in paraffin wax and cut into sections of 5µm thickness. For histo-pathological observation. The slices were stained using haemotoxylin and eosin (H&E) dye [20] and examined under a light microscope (Olympus, Tokyo, Japan).

Statistical analysis

Data was tabulated as mean±S.E. The significance of difference among groups was determined using ANOVA (one-way analysis of variance) then, the multiple comparisons Dunnett's test was applied. A value of $P<0.05$ was considered statistically significant [21].

RESULTS

Biochemical interpretation

The levels of all enzymatic (SOD, CAT, GPx and AChEA) and non-enzymatic (total thiols, LP, NO, GSH, GSSG and PC) parameters were insignificant in

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groups of animals treated with chamomile extract, tables 1-3.

Table 1. Contents of total thiols, LP and NO in mice brain of different groups.

Mouse groups	Total thiols µmol/ mg protein	LP (TBARs) nmol/ mg protein	NO nmol/ g protein
Control	14.2 ±1.12	9.9 ± 2.18	2.4 ± 0.11
Chamomile-treated	12.5 ±1.01	9.1 ± 1.06	2.2 ± 0.27
Irradiated (8 Gy)	7.5 ± 0.87*,§	33.4 ± 5.17*,§	6.9 ± 0.42*,§
Chamomile-treated & irradiated	10.3 ± 0.81$^{*,§,\#}$	21.5 ± 3.22$^{*,§,\#}$	4.4 ± 0.24$^{*,§,\#}$

*p<0.05 (vs. control group), §p<0.05 (vs. chamomile-treated group), and #p<0.05 (vs. irradiated group).

The results revealed a remarkable neuroprotective action of *M. chamomilla* extract. The contents of total thiols, TBARs, NO, GSSG and PC and AChEA activity showed significant increases and all other enzymatic and non-enzymatic parameters (GSH, SOD, CAT, and GPx) exhibited significant decreases in the irradiated group, tables 2, 3.

Table 2. Contents of GSH, GSSG and CP in mice brain of different groups.

Mouse groups	GSH nmol/ mg protein	GSSG nmol/ mg protein	PC nmol/ mg protein
Control	5.3±1.12	0.22±0.063	4.1±0.58
Chamomile-treated	5.5±1.21	0.21±0.045	4.2±0.46
Irradiated (8 Gy)	3.6±0.93*,§	0.52±092*,§	7.1±0.84*,§
Chamomile-treated & irradiated	4.7±0.63$^{*,§,\#}$	0.31±0.43$^{\#}$	4.7±0.43$^{\#}$

*p<0.05 (vs. control group), § p<0.05 (vs. chamomile-treated group), and # p<0.05 (vs. irradiated group).

Table 3. Activities of SOD, CAT, GPx and AChEA in mice brain of different groups.

Mouse groups	SOD U/ g protein	CAT U/ g protein	GPx U/ mg protein	AChEA U/ mg protein
Control	129±16	6±0.4	16±1.7	8.4±0.7
Chamomile-treated	122±21	6±0.2	16±1.7	8.3±0.4
Irradiated (8 Gy)	37±17*,§	2±0.5*,§	10±2.2*,§	11.1±1.4*,§
Chamomile-treated & irradiated	113±16$^{\#}$	4±0.4$^{*,§,\#}$	13± 1.8$^{*,§,\#}$	8.9± 0.9$^{\#}$

*p<0.05 (vs. control group), § p<0.05 (vs. chamomile-treated group), and # p<0.05 (vs. irradiated group).

The levels of the non-enzymatic and enzymatic parameters were considered next. They were significantly ameliorated in the animal group supplemented with chamomile extract before irradiation (Chamomile-treated and irradiated) compared to the irradiated group. The contents of GSSG and CP and activities of SOD and AChEA were insignificant compared to the corresponding control and chamomile-treated group levels, tables 2, 3.

Histopathological findings

The control animals, figures 2A and B and chamomile-treated animals, figures 3A and B groups did not show any pathological changes. Gray matter of irradiated mice showed dilated blood vessel, many pyknotic nervous cells with rise of glial cells, figure 4A, demonstrates while white matter of irradiated mice showing spongy degeneration and focal gliosis around nerve axons (figure 4B). In chamomile-treated before irradiation mice group, cerebrum gray matter of mice treated with chamomile and radiation showed the majority of neurons and matrix appear normal morphological picture. Furthermore, the white matter revealed spongiform degeneration and proliferation of neuroglia, figures 5A and B.

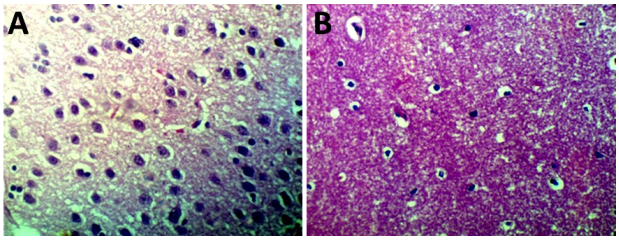


Figure 2. A) Cerebrum gray matter of control mice showing normal structure. **B)** Cerebrum white matter of control mice showing normal structure (H & E ×400).

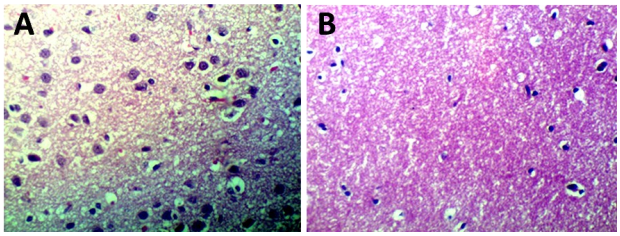


Figure 3. A) Cerebrum gray matter of mice treated with chamomile showing normal structure. **B)** Cerebrum white matter of mice treated with chamomile showing normal structure (H & E ×400).

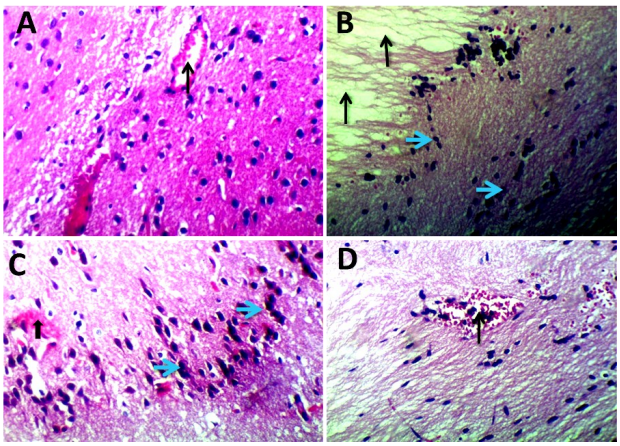


Figure 4. A) Cerebrum gray matter of irradiated mice showing congested blood vessel (↑) with numerous pyknotic neurons with proliferation of glia cells. **B)** Cerebrum white matter of irradiated mice showing spongiform degeneration (↑) and focal gliosis around nerve axon (→). **C)** Gray matter of γ-rays rat showing hemorrhage (↑), pyknotic neurons (→) and microcavitation. **D)** Cerebrum white matter of irradiated mice showing hemorrhage (↑), microcavitation and focal gliosis around nerve axons (H & E ×400).

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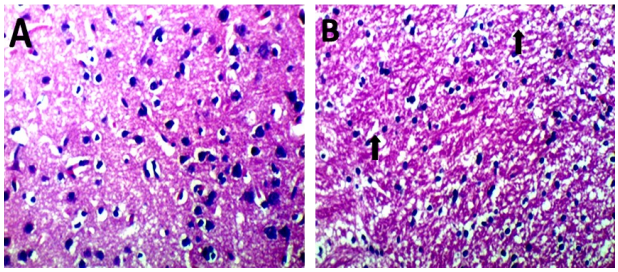


Figure 5. A) Gray matter in chamomile-treated & irradiated mice, the neurons and matrix appear normally structure. **B)** White matter in the same group showing spongiform degeneration (↑) and proliferation of neuroglia (H & E ×400).

DISCUSSION

In mouse primary neuron cells, it has been observed that brain tissue is highly predisposed to oxidative tension, because of its increase content of peroxidisable unsaturated fatty acids, high oxygen intake and poorly recovered antioxidative defence tools [22].

Oxidative insults, whether overexcitation, ischemia may start a number of signalling cascade causing an apoptotic cell death and neurons injury [23]. This study is conducted to assess *M. chamomilla* neuroprotective action on mouse model in which γ-rays caused inclusive cerebral ischemic reperfusion injury leading to brain damage.

Chamomile is economical and easily available, measured safe, with no identified adverse reactions in children. It caused no adverse effects in the human trials discussed earlier [24]. Balanced consumption of chamomile tea is concomitant with an enhanced antioxidant status in vivo that may protect against neurodegenerative illnesses [25]. These effects could be associated to several mechanisms; free radicals' scavenger activity that produce LP and stimulate antioxidant restoration via improved protein synthesis [26].

Oxidative alteration of proteins, assessed based on CP, can be an early indicator of oxidative brain injury induced by γ-rays [27]. In the current study, a significant increase in CP was documented in the mouse brain tissue, compared to control group. Protein degradation compromises the metabolic efficiency of cells. The protease enzymes and antioxidant proteins were inactivated due to the failure of the antioxidant schemes to counteract the steadily influx of ROS.

Thus, the increases of free radicals-induced CP and cells become progressively more susceptible to ROS-mediated destruction [28]. Furthermore, it has known that, CP induces neurodegeneration in the central nervous system [29].

In this study, γ-irradiation induced oxidative insults in the mouse brain, revealed significant intensification of TBARs and NO contents, while total thiols and GSH levels were decreased. Furthermore, this change in oxidative stress indices was linked to a rise of brain GSSG and CP levels.

GSH shows a critically vital role in cellular function activity; in detail, the preservation of GSH homeostasis is critical for the animal to carry out its numerous functions. Definitely, GSH levels could be monitored as a non-specific indicator of cellular toxicity, because a decline in GSH and consequently a rise of its oxidised form; GSSG are indicative of an augmented-stimulation for cellular damage [30]. Besides, an exhaustion of either total thiols or GSH can be explained by subsequent formation of GSSG. Generating free radicals in the brain due to irradiation are reduced by GSH, which, in turn, is irreversibly depleted. GSH exhaustion occurs because it is a ROS-scavenger and at the same time, a substrate of the antioxidant enzymes; GPx and glutathione reductase [31].

Dysfunction of the glutathione-system has been implicated in the neurodegenerative diseases and is an important cause of oxidative impairment next to ischemic injury [32]. The rise of oxidant/ antioxidant activity of the tissue caused by ischemia or reperfusion is of great value for the main endogenous defence against the free radical-induced injury, as was notice in the present experiment in the irradiated animals' group accompanied with an increase in LP and a reduction in protective enzyme levels. In certain, evidence exists that the SOD activity in the brain is reduced in rats and mice exposed to ionising-radiation [33, 34].

Radiation induced excessive generation of NO [35, 36]. NO has been considered as a biological transmitter constituent, and it is recognised as a noxious active free radical in the central nervous system. Increased oxidant end-products by the reactions of NO with other reactive free radicals maybe contribute to the neuropath physiology brain damage because of the special susceptibility of the brain to oxidative insults [37, 38]. NO can be coupled with O2 − to initiate peroxynitrite (ONOO−), a destructive radical for cellular structures. Pro-apoptotic effects are often observed when NO reacts with O2 − to produce the highly toxic ONOO− that is able to initiate LP and deplete cellular GSH under oxidative stress conditions [39, 40].

Antioxidative enzymes are part of the primary cellular protection against ROS produced by ionising-radiation [41]. The antioxidant markers play a role in the antioxidant protection scheme. In the present study, increased antioxidant enzyme activities served as a compensatory mechanism in response to irradiation [42]. Irradiation markedly declined SOD, CAT and GPx activities, indicating the progressive development of oxidative stress and a prompt defensive response to oxidative injury [43].

AChEA contributes in many important neuronal developments including modulation of the release of many neuro transmitters, mediation of postsynaptic

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excitatory responses, and protection of neurons against toxicity in mice [44]. The oral intake of chamomile reversed the cholinergic impairment of brain tissue and modulated AChEA. Furthermore, current indication suggests that AchEA can be a module of the synaptic transmission [45]. In addition, pretreatment with chamomile was shown to offer neuroprotection by enhancing free radical scavengers of ROS and the stimulating scavengers of superoxide anions or hydrogen peroxide in agreement with a similar study [46]. Furthermore, chamomile induced an increase of GSH level and SOD, CAT, and GPx activities in the brains of rats treated with chamomile, in agreement with Jabri *et al.* [47]. The probable neuroprotective activity of chamomile was showed by its ability to diminish elevated LP and severity of oxidative damage in brain tissue that was markedly decreased by the increased levels of antioxidant enzymes SOD, CAT and GPx, and non-enzymatic markers like GSH and total thiols.

The flavonoid; apigenin is the best studied component of chamomile [13]. The present findings, suggested that chamomile contains flavonoids like apigenin and other phenolic compounds that may be liable for neuroprotective activity intermediated via the lipid membrane stabilization because LP produces a progressive loss of membrane fluidity.

Chamomile has been known for centuries as a remedial herb for its anti-inflammatory properties. It has been approved to ameliorate various conditions such as wound healing [48]. Other studies have demonstrated its antioxidant property [49].

Numerous phenolic constituents of herbal sources, specifically flavonoids have antibacterial, antioxidant, anti-inflammatory, antitumor, neuroprotective, and ROS-scavenging properties. The number of phytochemically active principles isolated and distinguished continues to increase (50). Certain polyphenols and terpenes have significant and valuable pharmacological and nutraceuticals effects for health performance and illness protection by decreasing the course of continuous inflammation that characterises acute and chronic neurodegenerative diseases [51]. Chamomile comprises various flavonoids and terpenes which are thought to contribute to the widespread variety of therapeutic effects attributed to chamomile. Alpha-bisabolol is an unsaturated monocyclic sesquiterpene found as the major constituent of chamomile flower and essential oils, contributes to rescue effects of chamomile against inflammation disorders [10].

Data suggests that treatment with chamomile is related to the recovery of pharyngeal inflammatory conditions, infections of throat and oral mucosa, and diseases of gingivitis and periodontitis [52]. It mitigates the neurobehavioral disorders, the biochemical disturbances and the neuro inflammation related to obesity in rats [47].

The flavonoids of chamomile such as apigenin, luteolin, quercetin, rutin and others appear to be the most powerful flavonoids for protecting the body against ROS. These flavonoid constituents could add to the endogenous scavenging complexes and increase the action of the endogenous antioxidant enzymes. The flavonoids interrupt the LP-chain reaction and thereby inhibit AChEA-production and prevent GSH-depletion that plays a critical role in cellular defence (SOD, CAT, and GPx) against oxidative stress induced neurotoxicity (53).

The generation of ROS and other free radical overwhelms cellular defences; these unstable radicals react with cell' essential molecules such as lipids, proteins, and DNA leading to biochemical disorders and histological changes.

The histopathological reviews of the present work revealed that exposure mice to γ-rays, induced deteriorating changes of brain tissue in different parts of the CNS (cerebrum, brainstem, and cerebellum), represented by severe congestion, perivascular oedema, numerous apoptotic neurons, and spongiform degeneration changes, which were demonstrated in the grey matter. Also, the white matter revealed spongiform degeneration, focal gliosis around nerve axons with haemorrhage, and proliferation glial cells. Cerebrovascular obstacles, diminutions in cerebral blood flow, disturbance of the blood brain barrier and cerebral oedema were all observed. All these neurochemical and neurophysiological alterations finally contribute to the complications associated with radiation-exposure, including morphological abnormalities and increased exposure to pathophysiological events. These results were in agreement with several related studies [54-56]. Meanwhile, there was a marked improvement in brain injury in chamomile-treated and irradiated group as compared to the irradiated group. Chamomile extracts exhibited marked protection against γ-rays-induced ischemia and reperfusion in the mouse brain.

In summary, our findings provide understanding to the mechanism(s) through which chamomile, as an aqueous extract of dried flower included in the mice's diet, and possibly other related flavonoids may prove to be beneficial in the prevention and managing of many inflammatory and radiation syndromes. Oxidative injuries have been associated with several neurodegenerative disorders (Parkinson's disease, Alzheimer, stroke, cerebrovascular ischemia) and brain-associated illnesses which affect more people.

CONCLUSIONS

These results suggest a possible protecting activity of chamomile against the mouse cerebrovascular ischemia/ reperfusion-induced brain toxicity. Further studies are required to follow the interesting lead emerging from the present results to

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exploit the full therapeutic potential of chamomile as a neuroprotective compound.

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***Conflict of interest statement*:** The authors declare that they have no conflicts of interest. The authors alone are accountable for the content and script of the article.

***Authors Contributions*:** All authors conceived, designed the study and analyzed the data. R.E. and W.E-k. performed the biochemical studies. A.E-k. and A.E-M.A. performed the pathological studies. All authors prepared the manuscript.

***Consent to participate*:** Not applicable.

***Availability of data and materials*:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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