Saudi Journal of Biological Sciences 30 (2023) 103792

HOSTED BY

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

The neuroprotective effect of quercetin nanoparticles in the therapy of neuronal damage stimulated by acrolein

Samia M. Sanad [a,1], Reham Farouk [a,1], Safaa E. Nassar [a], Mohammad Y. Alshahrani [b], Muath Suliman [b], Ahmed Ezzat Ahmed [c], Ibrahim Eid Elesawi [d,*]

[a] Zoology Department, Faculty of Science, Zagazig University, Sharkia 44519, Egypt
[b] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid University, P.O. Box 61413, Abha 9088, Saudi Arabia
[c] Biology Department, College of Science, King Khalid University, P.O. Box 61413 Abha 9088, Saudi Arabia
[d] Agricultural Biochemistry Department, Faculty of Agriculture, Zagazig University, Zagazig 44511, Egypt

ARTICLE INFO

Article history:
Received 3 July 2023
Revised 14 August 2023
Accepted 27 August 2023
Available online 29 August 2023

Keywords:
Quercetin nanoparticles
Cerebellum
Bax
Bcl-2
GFAP
TNF-α
Acrolein

ABSTRACT

A gradual loss of neuronal function or structure causes neurodegenerative disorders such as Parkinson's and Alzheimer's. Neurological damage might cause cell death. Acrolein is a high-risk air and water contaminant that causes neurodegenerative disorders. Quercetin has several strategies for treating neurodegenerative disorders but has limited bioavailability inside the body. One of the hypotheses offered to improve quercetin's bioavailability is to convert it into quercetin nanoparticles. This study aims to comprehend the immunohistochemical devastation that might arise in the cerebellum because of acrolein treatment. Furthermore, the protective and ameliorative roles of quercetin nanoparticles against oxidative stress and neurotoxicity induced in mice by acrolein were assessed. Ninety male albino rats weighing 120 to 200 g were used in the present investigation. The animals were split up into the following six groups: the control group, the acrolein-treated group: animals were given acrolein (3 mg/kg) for 30 days, quercetin nanoparticles treated group: animals were given quercetin nanoparticles (30 mg/kg) for 30 days. The administration of acrolein was found to be connected to immunohistochemical abnormalities in the cerebellum. Marked differences were observed in Bax, Bcl-2, TNF-α, and GFAP expressions in the cerebellum. Treatment of rats with quercetin nanoparticles either before or after treatment with acrolein has been found to preserve the cerebellum tissues from the toxic impacts and oxidative stress induced by acrolein. This may open the door to more nanomedicine studies and a new avenue for employing nanoparticles as a therapeutic intervention in neurodegenerative illnesses.

1. Introduction

Neurodegenerative disease refers to various conditions that predominantly damage neurons in the human brain (Spead et al., 2022). They are a major cause of death and disability around the world, and they are influenced by a variety of factors such as age, genetics, and trauma. The accumulation and spread of abnormal proteins are frequently assumed to be the cause of these illnesses (Rahman et al., 2023). Health risks caused by neurodegenerative diseases are high; because of recent increases in the senior population, many age-related ailments are becoming increasingly prevalent (Franceschi et al., 2018). Instances of neurodegenerative illnesses incorporate Alzheimer's illness, Huntington's sickness, Parkinson's infection, frontotemporal dementia, amyotrophic sidelong sclerosis, and spinocerebellar ataxia (Makkar et al., 2020). Neurodegenerative diseases are long-term and catastrophic diseases that induce nerve cell deterioration and/or death. This hinders physical and mental processes, movement, speech, and breathing (Perlikowska, 2021).

Acrolein is one of the simplest common unsaturated aldehydes. In addition, it is a colorless liquid at room temperature, characterized by a pungent odor, and is easily flammable. It has a charred, sweet, spicy, stifling stench that occurs naturally in the atmo-

* Corresponding author.
E-mail addresses: smsanad@zu.edu.eg (S.M. Sanad), rfbayoumy@zu.edu.eg (R. Farouk), sinassar@zu.edu.eg (S.E. Nassar), moyahya@kku.edu.sa (M.Y. Alshahrani), mmaied@kku.edu.sa (M. Suliman), aabdelrahman@kku.edu.sa (A. Ezzat Ahmed), ibrahimeid@zu.edu.eg (I. Eid Elesawi).
[1] These authors contributed equally to this work.

Peer review under responsibility of King Saud University. Production and hosting by Elsevier.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2023.103792
1319-562X/

sphere as a result of wood burning (De Woskin, 2003). There are many natural sources of acrolein, with varying concentrations of 10–600 μg/kg present in cheeses, cake, fishes, potatoes, wine, and rum (Conklin et al., 2010). Acrolein is produced in kitchens when food is cooked or fried in solid or liquid oils at high temperatures (Wang et al., 2022). It is flowing into the environment as a result of the fire of petroleum products, including diesel fuel and biofuel, acrylic and materials for plastics, and wood combustion (Wheat et al., 2011). Endogenous avenues for acrolein include oxidative stress-induced threonine breakdown by neutrophil myeloperoxidase and the amine oxidases' spermine and spermidine oxidation. Furthermore, polyunsaturated fatty acids are oxidized by free oxygen radicals in the lipid bilayers of cell membranes, producing acrolein (Henning et al., 2017).

The strongest electrophile is thought to be acrolein. As a by-product and a stimulant of lipid peroxidation, acrolein causes oxidative stress. Acrolein is both a product and an initiator of lipid peroxidation, making it an oxidative stress perpetrator (Uchida et al., 1998). It produces oxidative damage, resulting in membrane rupture, DNA and mitochondrial damage, and aggravation of apoptosis. It substantially raised oxidant levels by reducing glutathione, antioxidant enzymes (Superoxide dismutase and glutathione-peroxidase), and total and nuclear levels of the antioxidant regulator nuclear factor erythroid 2-related factor 2, which coincided with decreased mitochondrial activity (Jia et al., 2007). Acrolein, a prevalent environmental pollutant, has been shown to have damaging consequences on the central and peripheral nervous systems (Butler et al., 2017), respiratory tract (Tulen et al., 2022), and indifferent cardiovascular organs (Conklin et al., 2017).

Quercetin is a primary bioflavonoid found in onions, apples, tea, brassica vegetables, nuts, seeds, bark, flowers, and leaves and can also be derived from various medicinal plants (Verma and Trehan, 2013). In addition to its heart-protective and neuroprotective qualities, it has anti-inflammatory, antioxidant, and anti-cancer effects (Edwards et al., 2007). It is also exceedingly used to treat many disorders, including cerebrovascular and neurodegenerative diseases (Amanzadeh et al., 2019). Its antioxidant and anti-inflammatory abilities benefit neurons (Dajas, 2012). It has been related to avoiding neurodegenerative diseases via the Sirtuin 6 (SIRT6) pathway (Jakaria et al., 2019).

The major characteristic of quercetin is the presence of many OH groups in its structure, which can bind to reactive oxygen species and preserve cell viability, and it has a stronger antioxidant capacity than many flavonoids (Lesjak et al., 2018). It may prevent the aggregation of the amyloid-beta peptide Aβ (1–42), the most damaging species in the amyloid cascade, indicating its significant promise as a neuroprotector and anti-aging drug (Grewal et al., 2021). Furthermore, it inhibits nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, enhances endothelial nitric oxide synthase (eNOS) activity, and avoids endothelial dysfunction (Kim and Jang, 2009).

Quercetin is poorly soluble in water, limiting its potential for treatment (Nam et al., 2016). It is minimally bioavailable in the body due to its difficulty in absorption, rapid metabolism, and rapid elimination from the body (Cai et al., 2013). Moreover, since this water-insoluble polyphenolic compound cannot cross the blood–brain barrier, a tight connection throughout blood capillaries and interstitial fluids, it significantly impedes central nervous system treatments (Salamone et al., 2021) and may have negative effects when used for a long time or in large doses (Li et al., 2022).

To overcome this constraint, multiple ways to increase quercetin bioavailability have been presented in conjunction with advances in the field of nanotechnology and several advancements in drug delivery and nanomedicine systems (Gao et al., 2011). Drug nanoparticle technologies, recognized as one of the most effective approaches to manufacturing poorly soluble medications, have received much attention in recent years (Müller et al., 2011). Nanoparticles are defined as zero-dimensional nanomaterials, as opposed to one-and two-dimensional nanomaterials, which have one or two dimensions bigger than the nanoscale, respectively. They differ from bulk equivalents in terms of size, chemical reactivity, movement, energy absorption, and so on (Sajid and Płotka-Wasylka, 2020). The important technological advantages of using nanoparticles as drug carriers include high stability in biological systems, high carrier capacity, the ability to incorporate both hydrophilic and hydrophobic substances, and the ability to use different routes of administration. These nanoparticle characteristics allow for increased medication bioavailability and decreased loss frequency (Jiménez-Morales et al., 2022). They allow drugs to be delivered to target organs through the delivery system. Vesicular formulations' effectiveness is determined by their size and other physicochemical characteristics. As a result, it is critical to characterize the nanoparticles concerning their dimension and percentage encapsulation. The size and size distribution of nanoparticles affect their stability, drug release, and cellular uptake efficiency (Feng, 2014). They provide benefits over regular chemotherapy medicines. They may improve tumor-targeted delivery even further by regulating the nanoparticle surface with a particular tumor or cancer cell by targeting ligands such as biotin, folic acid, and antibodies (Xie et al., 2005).

Nanoparticles can enter the brain through two distinct mechanisms: *trans*-synaptic transport following inhalation through the olfactory epithelium and absorption across the blood–brain barrier (Tiwari and Amiji, 2006). They have the potential to penetrate the blood–brain barrier. They may solubilize the lipids in endothelial cell membranes, allowing for more efficient transport (De Jong and Borm, 2008). After crossing the blood–brain barrier, they tend to concentrate in certain brain areas, where they may reach neuronal cells such as neurons, astrocytes, and microglia (Teleanu et al., 2018).

Quercetin nanoparticles can be employed as a potent antioxidant in the cytoplasm to counteract reactive oxygen species by increasing their solubility and bioavailability (Minaei et al., 2016). Due to their distinct physicochemical properties, they can cross many barriers, including the blood–brain barrier. They are frequently utilized in medical research. Furthermore, their efficacy in cancer treatment has been proven. They induce cell death of cancer cells (Rahman et al., 2022). Their solubility in water was more than 55–60 μg/ml of the drug was dissolved between 4 and 72 h (Manca et al., 2020).

Because of nanoparticles' remarkable stability, high level of bioavailability and capacity to penetrate the blood–brain barrier quickly, nanoparticles have sparked great interest in treating neurodegenerative illnesses, particularly for hydrophobic compounds like quercetin. As a result of its limited oral bioavailability, low brain permeability, and hydrophobic nature, researching the posi-

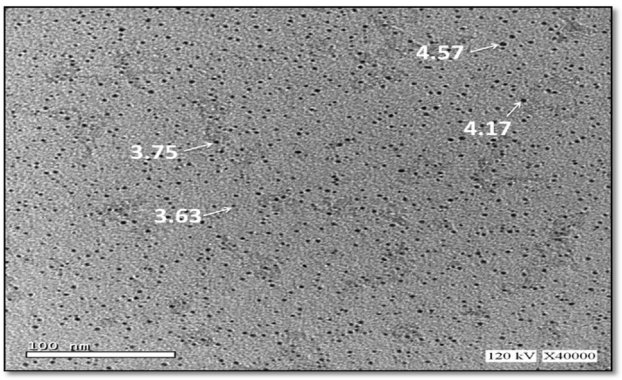

Fig. 1. TEM image of quercetin nanoparticles.

tive effects of quercetin remains a challenging problem. As a result, the current work sought to evaluate and assess the possible immunohistochemical modifications that might result from any potential toxic consequences produced by acrolein and the ameliorative and protective activity of quercetin nanoparticles.

2. Materials and methods

2.1. Experimental rats

About 90 mature *Rattus norvegicus* rats weighing between 150 and 200 g and aged around 10 to 12 weeks were employed in the current investigation. They were acquired from the National Research Center in Cairo, Egypt. The current experimental design has been authorized and evaluated by the ethical research committee of Zagazig University, Egypt (approval number Zu-IACUC/1/F/306).

2.2. Chemicals

Acrolein (99% pure) was obtained from Pharmachem Fine Chemicals for Research and Industry, Mumbai, India. Quercetin (more than 98% pure) was purchased from Fine-Chem Limited (SDFCL), Industrial Estate, 248, Worli Road, Mumbai, Maharashtra,

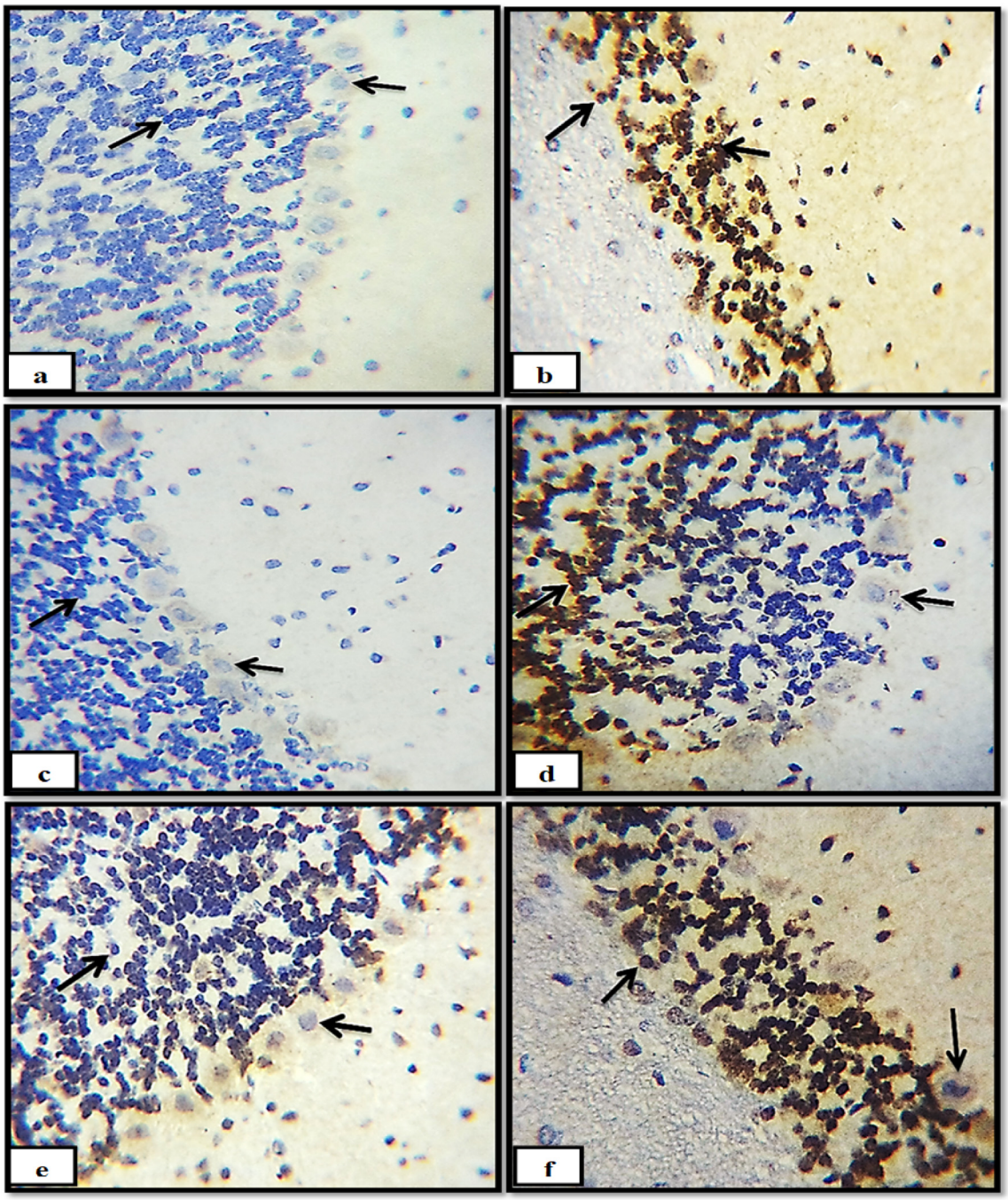

Fig. 2. Photomicrograph of Bax immunohistochemical staining in the cerebellum from the (a) Control group illustrating minimal Bax expression (arrows). (b) Acrolein-treated group indicating strong Bax antibody immunostaining (arrows). (c) Quercetin nanoparticles-treated group indicating a weak Bax antibody expression (arrows). (d) Ameliorative group revealing a decrease in Bax expression (arrows). e) Protective group revealing a significant reduction in Bax immunostaining (arrows). f) Recovery group revealing a slight reduction in Bax immunostaining within the cerebellum layers (arrows). (X400).

India. Bax monoclonal antibody (Invitrogen, MA5-13–0300, 1: 100), rabbit monoclonal anti Bcl-2 (Abcam, Cat-ab182858, 1: 500), rabbit polyclonal TNF-α (Invitrogen, USA, Catalog P300A) and GFAP monoclonal antibody (Invitrogen, MA5-11757, 1:200) were purchased from the Company of Sigma Aldrich, Egypt. The best commercial quality chemicals were used in this investigation.

2.3. Quercetin nanoparticle preparation and characterisation

The precipitation process reported by Kakran et al. (Kakran et al., 2012) was modified to produce quercetin nanoparticles. In the water bath at 40 °C, quercetin (5 mg) was dissolved in 1 ml of ethanol. The resultant solution was added to deionized water at a concentration of 1:40, and the anti-solvent was then magnetically stirred for 10 min at 3000 rpm. The prepared solution was infused into the water at a constant rate of 10 ml/min. All the ethanol was evaporated in a water bath with a temperature of 60 °C. vacuum drying and quercetin nanoparticle purification. The shape of the quercetin nanoparticles was examined using TEM (JEOL JEM 1400 TEM (Tokyo)).

2.4. Experimental design

After acclimating for two weeks, the animals were split into six groups, each with fifteen rats, as follows: Group 1 (G1, Control group): For 30 days, the animals were given 1 ml of distilled water orally. Group 2 (G2, Acrolein-treated group): Rats were given acrolein (3 mg/kg b.w.) via a gastric tube for 30 days (Erhan et al., 2021). Group 3 (G3, Quercetin nanoparticles treated group): For 30 consecutive days, Animals received quercetin nanoparticles (30 mg/kg b.w.) via a gastric tube (Rifaai et al., 2020). Group 4 (G4, Ameliorative group): animals received acrolein (3 mg/kg b. w.) and quercetin nanoparticles (30 mg/kg b.w.) at the same time for 30 straight days. Group 5 (G5, Protective group): Using a gastric tube, animals were given quercetin nanoparticles (30 mg/kg b.w.) for 30 straight days, then a dose of acrolein (3 mg/kg b.w.) for another 30 straight days. Group 6 (G6, Recovery group): Animals were given acrolein (3 mg/kg b.w.) for 30 days via a gastric tube, and then they were allowed for 30 days to recover without any extra therapy.

2.5. Necropsy schedule

Following the last treatment, the animals underwent cervical decapitation 24 h later to finish the experiment. To get intact cerebellar lobules, the cerebellum of all animals was removed after the skulls were opened. Rats in the control and treatment groups had the same thickness cuts to their cerebellums, then fixed in the same fixative.

2.6. Immunohistochemical studies

Immunohistochemical staining for Bax, Bcl-2, TNF-α, and GFAP for the demonstration of the astrocytes was performed using an avidin–biotin-peroxidase complex technique according to (Hsu et al., 1981); (Bancroft and Gamble, 2008). For the immunohistochemistry investigation, the following methods were briefly investigated: After being fixed in 10% neutral buffered formalin, the cerebellum underwent dehydration, clearing, and paraffin wax embedding. The thickness of the paraffin slices was 5 µm. Sections underwent deparaffinization in xylene, rehydration in a graded ethanol series, and a 5-minute washing in distilled water. To decrease endogenous activity, sections were incubated in 0.3% H2O2 for 15 min. The sections were next submerged in 0.05 M citrate buffer (pH 6.8) for antigen retrieval and prepared in a 700-watt microwave for 10 min. The sections were blocked in phosphate-buffered saline (PBS) containing 5% normal mouse serum for an hour to stop antibodies from binding non-specifically. After that, the sections were treated with Bax monoclonal antibody, rabbit monoclonal anti-Bcl-2, rabbit polyclonal TNF-α and GFAP monoclonal antibody. The sections were washed three times in PBS for 5 min and incubated with a goat anti-rabbit secondary antibody for polyclonal antibodies and a mouse monoclonal secondary antibody for monoclonal antibodies for 30 min at room temperature. The sections were washed in PBS for 10 min and incubated with avidin–biotin-peroxidase complex. After washing with PBS, the peroxidase activity was visualized with 0.05% 3′, 3′-diaminobenzidine (DAB). Sections were stained with Mayer's hematoxylin. Sections were cleaned in water, dehydrated in graded ethanol, put in xylene, and mounted with mounting media.

2.7. Morphometric analysis for Bax, Bcl-2, TNF-α, and GFAP immunoreactivity

The staining labeling indices of Bax and TNF-α were determined and given as a positive expression percentage in 1000 cells per 6 high power fields for the cerebellum in control and treated groups using 400x magnification via light microscopy. GFAP and Bcl-2 immunostainings were evaluated by estimating a positive area percentage employing Image J analysis program (NIH, USA) (Xu et al., 2007).

2.8. Statistical analysis

The data was utilized to express the mean ± SD of the several treatment groups. ANOVA and the Student's *t*-test were used to analyze the variations between the mean values using the computer program Minitab 12 (State College, USA). Statistically significant was defined as a P-value of $P < 0.05$.

3. Results

3.1. Characterisation of quercetin nanoparticles

We were able to successfully create quercetin nanoparticles, and we used TEM to investigate their structural details. Quercetin nanoparticles prepared by the precipitation method had a more uniform particle size and less crystallinity. TEM revealed that the quercetin nanoparticles were morphologically spherical with a

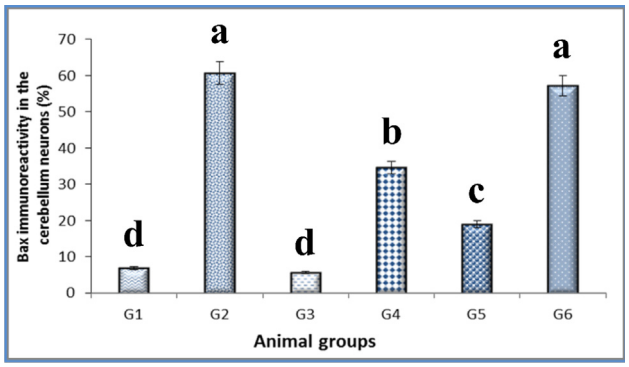

Fig. 3. Morphometric assessment of the Bax in the cerebellum of the examined groups (G1: Control group, G2: acrolein treated group, G3: quercetin nanoparticles treated group, G4: ameliorative group, G5: protective group, G6: recovery group). The data are presented as (mean ± SD) in the different treated groups ($P < 0.05$). a: Significant difference at $p < 0.05$ compared to the control group (G1). b: Significant difference at $p < 0.05$ compared to acrolein treated group (G2). C: Significant difference at $p < 0.05$ compared to quercetin nanoparticles treated group (G3).

homogeneous size distribution, as shown in Fig. 1. The quercetin nanoparticles had a diameter of 3.63 to 4.57 nm.

3.2. Bax (pro-apoptotic protein)

Positively expressed Bax protein appears as brown-colored particles in the cell membrane and cytoplasm. Mild expression of Bax was detected in the cerebellum layers of the control group (Fig. 2a). In the acrolein-treated group, Bax expression was markedly increased within the cerebellum layers (Fig. 2b) compared to the control group. Bax immunoactivity appeared normal in the cerebellum layers in the quercetin nanoparticles treated group. As shown in Fig. 2c, Bax antibody expression was very low within the cerebellum layers. In the ameliorative and protective groups, quercetin nanoparticles have been found to play a c nlear protective role. This was marked by the significant decrease in Bax expression within the cerebellum layers, as expressed in Fig. 2d-e. The recovery signs were highlighted in the recovery group where Bax expression was slightly reduced within the cerebellum layers, as shown in Fig. 2f.

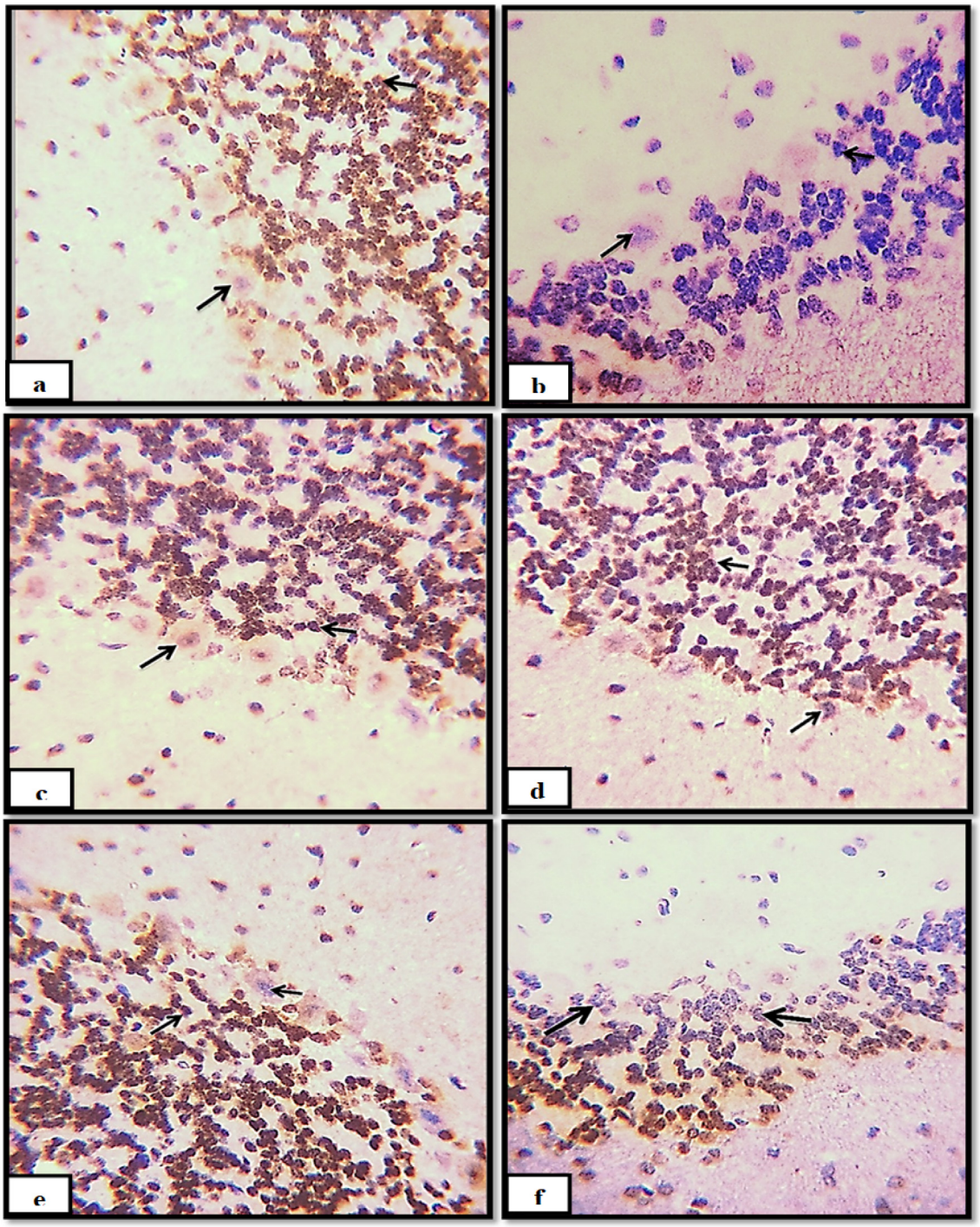

Fig. 4. Photomicrograph of Bcl-2 immunohistochemical staining in the cerebellum from (a) Control group illustrating marked Bcl-2 immunostaining (arrows). (b) Acrolein-treated group illustrating a marked decrease of Bcl-2 immunostain (arrows). (c) Quercetin nanoparticles treated group illustrating strong immunostaining of Bcl-2 (arrows). (d) Ameliorative group illustrating an increase in Bcl-2 immunostaining (arrows). (e) Protective group illustrating a strong increase in Bcl-2 (arrows). (f) Recovery group illustrating a mild increase in Bcl-2 within the cerebellum layers (arrows). (X400).

3.3. Bcl-2 (anti-apoptotic protein)

Bcl-2 expression has been observed in the present study as brown, heavily stained granules that were mostly found in the cell membrane and cytoplasm, and it was found to be high in the layers of the cerebellum in the control group, as indicated in Fig. 4a. As presented in Fig. 4b, Bcl-2 expression in the acrolein-treated group was drastically reduced. The immunoactivity of Bcl-2 in the cerebellum of the quercetin nanoparticles treated group appeared normal. Bcl-2 antibody expression was very strong within the cerebellum layers, as shown in Fig. 4c. The role of quercetin nanoparticles in the ameliorative and protective groups was obvious. The cerebellum showed a visible increase in Bcl-2 reactivity in its layers compared to the acrolein-treated group, as shown in Fig. 4d-e. In the recovery group, the recovery signs were distinguished. Bcl-2 expression was slightly raised within the cerebellum layers, as shown in Fig. 4f.

3.4. Glial fibrillary acidic protein (GFAP)

The immunohistochemistry staining of the cerebellum with an anti-GFAP antibody was done to see how the astrocytes responded to neuronal degeneration. There were little sporadic positive fibrous astrocytes with thin processes in all the layers of the cerebellum in the control group, which indicated insufficient GFAP expression in all the layers of the cerebellum, as shown in Fig. 6a. The acrolein-treated group showed substantial GFAP immunoreactivity inside the cerebellum layers, as illustrated in Fig. 6b. The quercetin nanoparticles treated group demonstrated faint immunostaining of GFAP in the cerebellar layers, as shown in Fig. 6c. In this case, a relatively small number of thinly branched, dispersed positive fibrous astrocytes within the cerebellar layers were observed. In the ameliorative and protective groups, the expression of GFAP was noticeably diminished in the cerebellum layers, as found in Fig. 6d-e. The expression of GFAP in the cerebellum layers declined slightly in the recovery group (Fig. 6f) contrasted to the acrolein-treated group.

3.5. Tumor necrosis factor alpha (TNF-α)

Immunohistochemical expression TNF-α in the control group (Fig. 8a) is barely discernible within the cerebellar layers. TNF-α immunoreactivity in the acrolein-treated group showed pronounced expression within the cerebellum layers (Fig. 8b). TNF-α immunoactivity in the cerebellum of the quercetin nanoparticles treated group appeared normal. In this case, expression of TNF-α was very mild within the cerebellum layers, as found in Fig. 8c. In the ameliorative and protective groups, experimental rats given quercetin nanoparticles reported a substantial decrease in TNF-α in the cerebellum layers, indicating that quercetin nanoparticles may have a neuroprotective effect during or after cell death, as shown in Fig. 8d-e. TNF-α antibody expression was mildly reduced within the cerebellum layers of specimens obtained from the recovery group compared to the acrolein-treated group, as indicated in Fig. 8f.

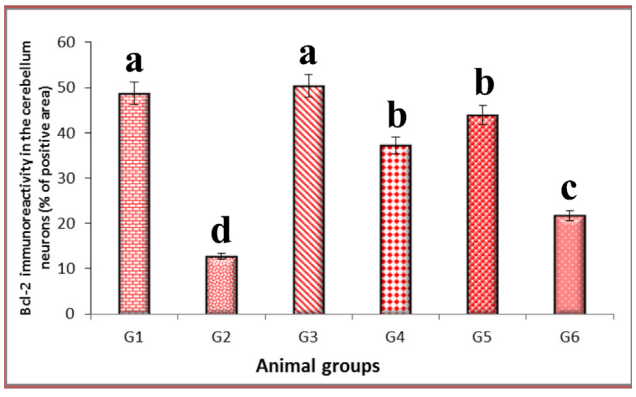

Fig. 5. Morphometric assessment of the Bcl-2 in cerebellum of the examined groups (G1: Control group, G2: acrolein treated group, G3: quercetin nanoparticles treated group, G4: ameliorative group, G5: protective group, G6: recovery group). The data are presented as (mean ± SD) in the different treated groups ($P < 0.05$). a: Significant difference at $p < 0.05$ compared to the control group (G1). b: Significant difference at $p < 0.05$ compared to acrolein treated group (G2). C: Significant difference at $p < 0.05$ compared to quercetin nanoparticles treated group (G3).

3.6. Morphometric analysis for Bax, Bcl-2, TNF-α, and GFAP immunoreactivity

The number of Bax-positive cells, GFAP positivity, and TNF-α immunoreactivity in the cerebellar neurons were considerably higher in acrolein-treated group. The treatment with quercetin nanoparticles in the ameliorative and protective groups has resulted in a substantial decrease in Bax, GFAP, and TNF-α immunoreactivity in the cerebellar neurons. Bax, GFAP, and TNF-α immunoreactivity in the cerebellar neurons was marginally lower in the recovery group, as indicated in Figs. 3, 7 & 9.

Bcl-2-positive cells number in the cerebellum was dramatically reduced in acrolein-treated group. Administration of quercetin nanoparticles in the ameliorative and protective groups virtually completely inhibited the effect of acrolein on Bcl-2 immunoreactivity, as evidenced by the increase in Bcl-2-positive cells in the cerebellum compared to the acrolein-treated group. Bcl-2 positivity in the cerebellum was somewhat greater in recovery group (Fig. 5) than in acrolein-treated group.

4. Discussion

The risk of neurodegenerative diseases on human health is substantial. Part of the reason for the increase in the elderly population in recent decades is that certain age-related ailments are becoming more prevalent (Grodzicki and Dziendzikowska, 2020). Parkinson's, Alzheimer's diseases, multiple system atrophy, amyotrophic lateral sclerosis, and multiple sclerosis are only a few of the neurodegenerative diseases (Juźwik et al., 2019). Neurodegeneration can be detected at several stages of neuronal circuitry in the brain, varying from molecular to systemic. These disorders are deemed incurable since there is no known means to halt the gradual degradation of neurons; nevertheless, research has established that oxidative stress and inflammation are the two primary contributing elements to neurodegeneration (Reddy and Abeygunaratne, 2022). Neurodegeneration is a defining feature of many chronic, incurable diseases, the prevalence of which is continuously increasing. To combat these heinous diseases, new and more effective treatment approaches are desperately needed (Xu et al., 2021).

In this study, TEM was utilised to investigate the structure of nanoparticles. The outcomes showed that the quercetin nanoparticles were uniformly sized and morphologically spherical. Using TEM, quercetin nanoparticles with a size range of 3.63 to 4.57 nm were discovered. According to the principles of nanoscience, nanoparticles should have a size range of 1–100 nm. The size between 20 and 100 nm is excellent for crossing the blood–brain barrier. As a result, medication delivery is more effective with the smaller size of the nanoparticles (Meng et al., 2022).

The present study aimed to evaluate the possible immunohistochemical alterations that might occur due to any possible toxic

effects induced by acrolein and assess the ameliorative and protective roles of quercetin nanoparticles in the cerebellum of rats. Moreover, it provides evidence about the changes underlying the pathogenesis of neurodegenerative disorders caused by acrolein.

Quercetin was already identified as a potential chemical with neuroprotective properties against neurodegenerative disorders associated with age especially Alzheimer's disease (Puerta et al., 2017). It has been demonstrated to prevent oxidative stress, lipid peroxidation, and neurons death associated with neurodegenerative diseases (Angelova et al., 2021). Because of its limited water solubility, it is currently challenging to employ as a chemopreventive medication when taken orally (Sirvi et al., 2022). The promise of quercetin hasn't been fully exploited due to several possible variables, including low brain permeability, low oral bioavailability

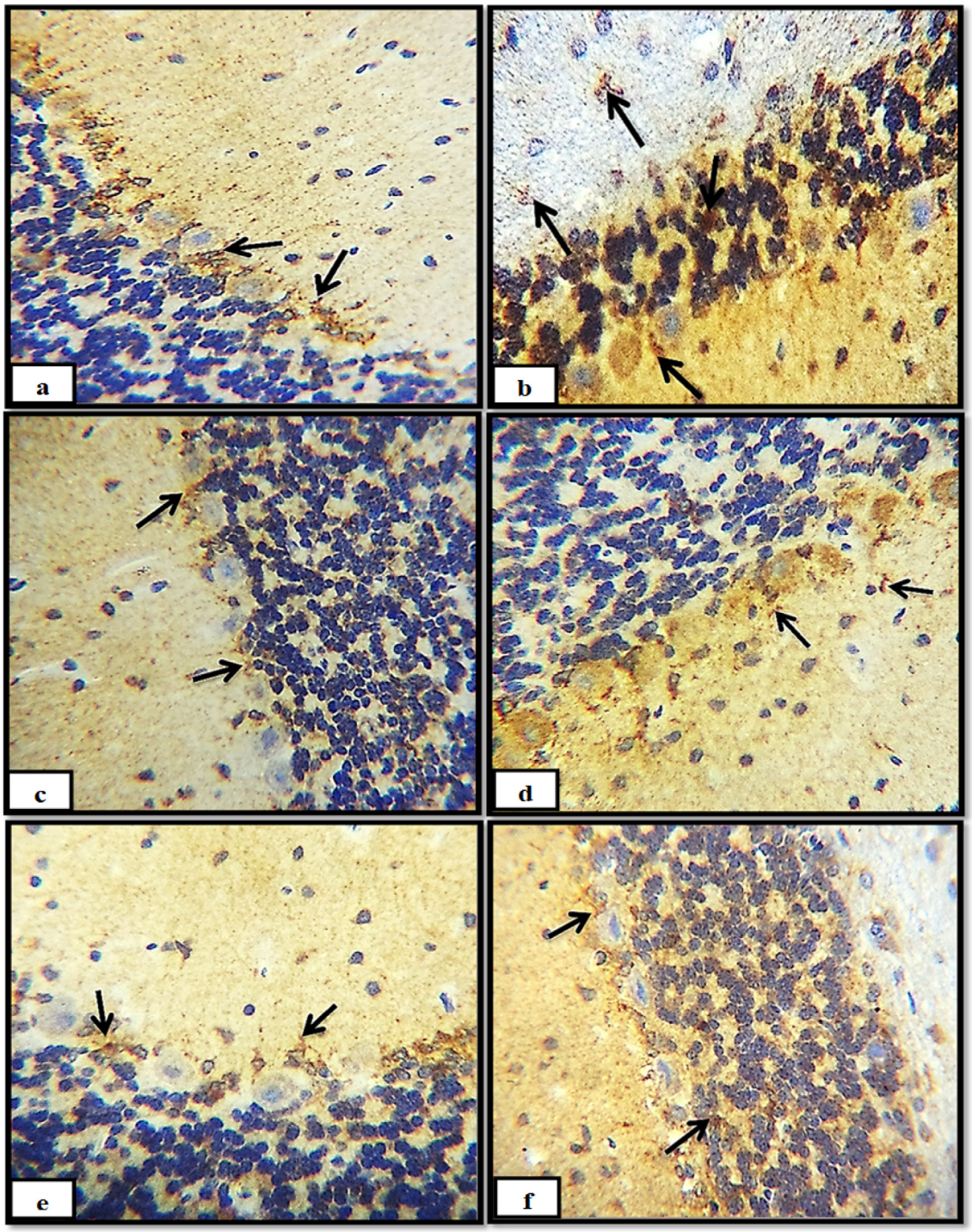

Fig. 6. Photomicrograph of GFAP immunohistochemical staining in the cerebellum from (a) Control group indicating scanty GFAP (arrows). (b) Acrolein-treated group indicating a marked increase of GFAP immunostaining (arrows). (c) Quercetin nanoparticles treated group indicating mild immunostaining of GFAP (arrows). (d) Ameliorative group indicating a decrease in GFAP immunostaining (arrows). (e) Protective group indicating a substantial decrease in GFAP (arrows). (f) Recovery group indicating a weak decrease in GFAP immunostaining (arrows represent astrocytes with numerous processes). (X400).

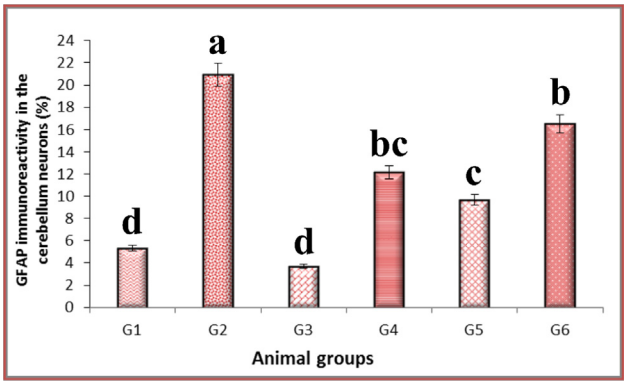

Fig. 7. Morphometric assessment of GFAP in cerebellum of the examined groups (G1: Control group, G2: acrolein treated group, G3: quercetin nanoparticles treated group, G4: ameliorative group, G5: protective group, G6: recovery group). The data are presented as (mean ± SD) in the different treated groups ($P < 0.05$). a: Significant difference at $p < 0.05$ compared to the control group (G1). b: Significant difference at $p < 0.05$ compared to acrolein treated group (G2). C: Significant difference at $p < 0.05$ compared to quercetin nanoparticles treated group (G3).

(2%), hydrophobic nature, physiological pH instability, significant first-pass metabolism, and photodegradation (Bagad and Khan, 2015).

This difficulty can be solved using nanotechnology, which increases the chemical's bioavailability and makes it possible to target it to certain tissues and organs (Li et al., 2016). Nanotechnology has made possible drug-loaded structures that can pass the blood–brain barrier, targeted medication delivery, and increased drug bioavailability (Gao et al., 2018). When quercetin nanoparticles were utilized, the relative oral bioavailability rose by 523%, indicating the possibility of dosage reduction (Sánchez-Jaramillo et al., 2022).

Immunohistochemical examination of Bax and Bcl-2 in the cerebellum treated with acrolein showed a higher increase in Bax immunoactivity and a marked decrease in Bcl-2 immunoactivity. These findings suggest that a lower than normal ratio of Bcl-2 to Bax caused by an increase in Bax and a reduction in Bcl-2 may damage neuronal cells and promote inflammation (Xiaodan et al., 2016). Both Bax and Bcl-2, perform roles in initiating and inhibiting apoptosis (Green, 2022). The nerve damage, there was a decrease in Bcl-2 expression in motor neurons, which was associated with motor neuron death. Acrolein encourages the Bax to travel from the cytoplasm to the mitochondria and Bcl-2 to move from the mitochondria to the cytoplasm (Suroto et al., 2021). Pro-apoptotic proteins translocation including Bax to mitochondria is an important step in removing Bcl-2′s inhibitory impact on apoptosis (Tanel and Averill-Bates, 2007).

The immunohistochemical examination of Bax and Bcl-2 in the cerebellum treated with quercetin nanoparticles in the ameliorative and protective groups revealed a visible reduction in Bax immunoactivity and a significant increase in Bcl-2 immunoactivity in the current study. These findings indicate that Bcl-2 to Bax increased when Bax dropped, and Bcl-2 arosed in the ameliorative and protective treated groups. These findings match the work done by Xiaodan et al. (2016), who demonstrated that the ratio of Bcl-2 to Bax steadily increased as quercetin concentration increased (Khalfaoui et al., 2010). (Bao et al., 2017) observed that quercetin treatment caused rat pheochromocytoma cells to upregulate Bcl-2 and downregulate Bax in response to oxidative stress-induced cytotoxicity. They made assumptions about quercetin's potential to reduce cell membrane lipoperoxidation and block H_2O_2.

The immunohistochemistry distribution of GFAP was investigated in this study to investigate astrocytes distribution and their reaction to neuronal degeneration or injury. The immunohistochemical analysis of GFAP immunoactivity in the cerebellum treated with acrolein indicated a considerable increase in GFAP. GFAP levels rise in Alzheimer's illness, and its expression has been linked to the course of the illness in humans (Ekong et al., 2017). GFAP is a recognized indicator of mature nervous system astrocytes (Mohamed and Mohamed, 2018). In response to neurodegenerative illnesses or neurotoxic exposure, astrocytes and GFAP expression are increased (Slovinska et al., 2022). Because astrocyte reactivity has been linked to morphological alterations such as hypertrophy, process remolding, and GFAP overexpression (Ben Haim et al., 2015), this might explain, the substantial rise in GFAP in neural tissues of the acrolein-treated groups. Increased GFAP has been found as a neurotoxic indication (Baydas et al., 2006).

The immunohistochemical analysis of GFAP expression in the cerebellum treated with quercetin nanoparticles in the ameliorative and protective groups demonstrated a significant decrease in GFAP immunoactivity. (Khan et al., 2018) found that quercetin therapy dramatically decreased the number of GFAP-positive cells. (Elblehi et al., 2022) found that the antioxidant quercetin dropped GFAP production in neural tissue.

In the present investigation, the immunohistochemistry of TNF-α in the cerebellum treated with acrolein showed a considerable increase in TNF-α immunoactivity. These results are in accordance with (Erhan et al., 2021), who demonstrated that TNF-α levels in vestibulocochlear nerve tissues increased dramatically in the acrolein-treated group, which had high amounts of oxidants and low levels of antioxidants. According to (Dheeb, 2014), TNF-α is a key proximal signal and is important in the control of host defense and immunological response. TNF-α, an inflammatory cytokine generated by macrophages and monocytes during severe inflammation, regulates many cells signaling mechanisms that lead to apoptosis and necrosis (Idriss and Naismith, 2000). Previous research has linked TNF-α overexpression to a range of neurodegenerative diseases (Zahra et al., 2022).

The immunohistochemical evaluation of the cerebellum TNF-α immunoactivity treated with quercetin nanoparticles before or after acrolein administration in the ameliorative and protective groups revealed a significant decrease. These results agree with the work done by (Granado-Serrano et al., 2012), who demonstrated that quercetin inhibits the TNF-α, which in turn leads to at least partial activation of nuclear factor kappa B (NF-κB). According to (Cheng et al., 2019), the two processes of phosphorylation of NF-κB and translocation induced by TNF-α are decreased by quercetin. Quercetin inhibits neuroinflammatory processes and promotes neuronal regeneration by lowering the release of proinflammatory cytokines (Caruana et al., 2016). Furthermore, quercetin regulates the processes of NF-kB transcription, which could prevent neuroinflammatory processes that lead to neurodegeneration (Chen et al., 2005).

5. Conclusions

Acrolein has been demonstrated to cause immunohistochemistry changes in the rat cerebellum, which are manifested by significant variances in Bax, Bcl-2, TNF-α, and GFAP immunoreactivity expression. These findings demonstrated the damaging consequences of acrolein. Therefore, the amount of acrolein in the environment must be restricted. Oxidative stress and inflammatory processes caused by acrolein are significantly decreased by quercetin nanoparticles. Therefore, it is recommended that they be used in nanomedicine to protect and improve neuronal tissues. This might open the gate for additional research on the therapeutic uses of quercetin nanoparticles. Quercetin nanoparticles provide a new line of therapeutic intervention in Alz-

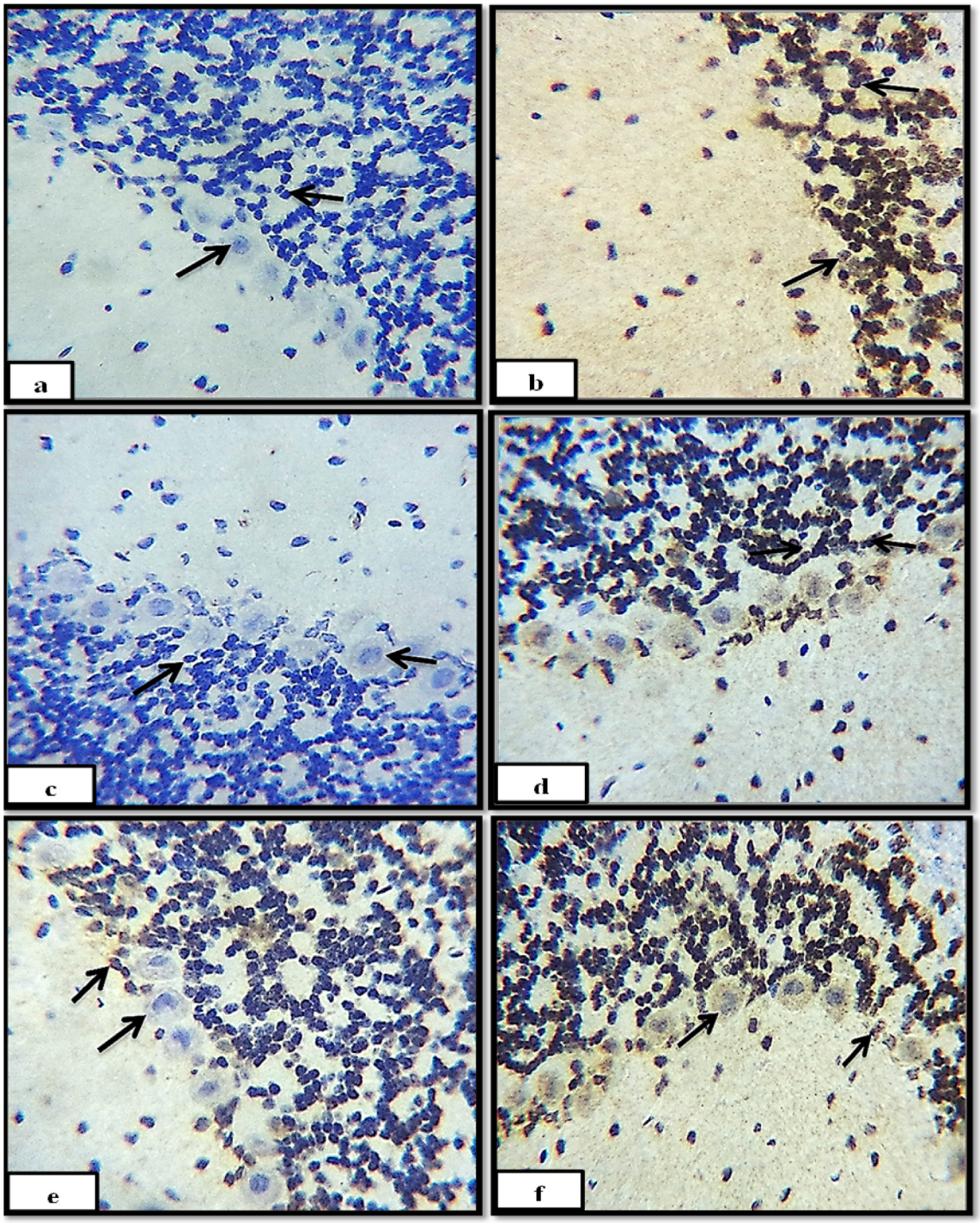

Fig. 8. Photomicrograph of TNF-α immunohistochemical staining in the cerebellum from (a) Control group pointing to scanty TNF-α (arrows). (b) Acrolein-treated group pointing to a marked TNF-α antibody (arrows). (c) Quercetin nanoparticles treated group pointing to a weak TNF-α immunostaining (arrows). (d) Ameliorative group pointing to a decrease in TNF-α (arrows). (e) Protective group pointing to a marked decrease in the TNF-α immunostaining (arrows). (f) Recovery group pointing to a mild decrease in TNF-α antibody (arrows) (arrows). (X400).

heimer's illness, Huntington's sickness, Parkinson's infection, frontotemporal dementia, amyotrophic sidelong sclerosis, spinocerebellar ataxia, and other neurodegenerative diseases.

Author contributions

All authors contributed to the study conceptualization and design. RF, SMS, SEN conducted experiments with IEE, MYS, and AEA support. RF, SMS, IEE, and SEN conducted data curation, and they have written the draft manuscript. SMS and RF, IEE reviewed the manuscript. The manuscript's published was approved by all authors after they had read it.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

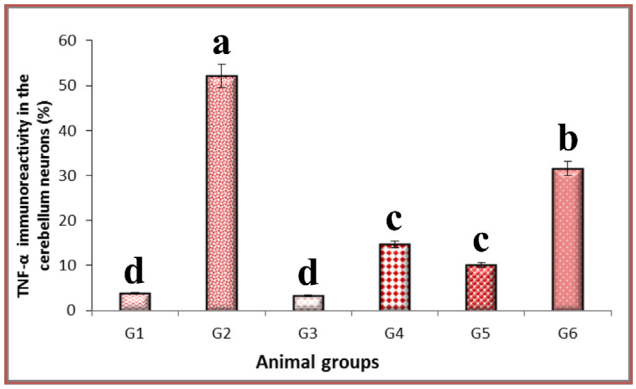

Fig. 9. Morphometric assessment of TNF-α immunoreactivity in the groups' cerebellum (G1: Control group, G2: acrolein treated group, G3: quercetin nanoparticles treated group, G4: ameliorative group, G5: protective group, G6: recovery group). The data are presented as (mean ± SD) in the different treated groups ($P < 0.05$). a: Significant difference at $p < 0.05$ compared to the control group (G1). b: Significant difference at $p < 0.05$ compared to acrolein treated group (G2). C: Significant difference at $p < 0.05$ compared to quercetin nanoparticles treated group (G3).

References

Amanzadeh, E., Esmaeili, A., Rahgozar, S., Nourbakhshnia, M., 2019. Application of quercetin in neurological disorders: From nutrition to nanomedicine. Rev. Neurosci. 30 (5), 555–572. https://doi.org/10.1515/revneuro-2018-0080.

Angelova, P.R., Esteras, N., Abramov, A.Y., 2021. Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: Finding ways for prevention. Med. Res. Rev. 41 (2), 770–784. https://doi.org/10.1002/med.21712.

Bagad, M., Khan, Z.A., 2015. Poly(n-butylcyanoacrylate) nanoparticles for oral delivery of quercetin: preparation, characterization, and pharmacokinetics and biodistribution studies in Wistar rats. Int. J. Nanomed. 10, 3921–3935. https://doi.org/10.2147/ijn.S80706.

Bancroft, J.D., Gamble, M., 2008. Theory and practice of histological techniques. Elsevier health sciences. https://doi.org/10.1097/PAS.0b013e3181805089.

Bao, D., Wang, J., Pang, X., Liu, H., 2017. Protective effect of quercetin against oxidative stress-induced cytotoxicity in rat pheochromocytoma (PC-12) cells. Mol. 22 (7), 1122. https://doi.org/10.3390/molecules22071122.

Baydas, G., Ozer, M., Yasar, A., Koz, S., Tuzcu, M., 2006. Melatonin prevents oxidative stress and inhibits reactive gliosis induced by hyperhomocysteinemia in rats. Biochem.. 71, S91–S95. https://doi.org/10.1134/s0006297906130153.

Ben Haim, L., Carrillo-de Sauvage, M.-A., Ceyzériat, K., Escartin, C., 2015. Elusive roles for reactive astrocytes in neurodegenerative diseases. Front. Cell. Neurosci. 9, 278. https://doi.org/10.3389/fncel.2015.00278.

Butler, B., Acosta, G., Shi, R., 2017. Exogenous Acrolein intensifies sensory hypersensitivity after spinal cord injury in rat. J. Neurol. Sci. 379, 29–35. https://doi.org/10.1016/j.jns.2017.05.039.

Cai, X., Fang, Z., Dou, J., Yu, A., Zhai, G., 2013. Bioavailability of quercetin: problems and promises. Curr. Med. Chem. 20 (20), 2572–2582. https://doi.org/10.2174/09298673113209990120.

Caruana, M., Cauchi, R., Vassallo, N., 2016. Putative role of red wine polyphenols against brain pathology in Alzheimer's and Parkinson's disease. Front. Nutr. 3, 31. https://doi.org/10.3389/fnut.2016.00031.

Chen, J.-C., Ho, F.-M., Chao, P.-D.L., Chen, C.-P., Jeng, K.-C.G., Hsu, H.-B., Lee, S.-T., Wu, W.T., Lin, W.-W., 2005. Inhibition of iNOS gene expression by quercetin is mediated by the inhibition of IκB kinase, nuclear factor-kappa B and STAT1, and depends on heme oxygenase-1 induction in mouse BV-2 microglia. Eur. J. Pharmacol. 521 (1–3), 9–20. https://doi.org/10.1016/j.ejphar.2005.08.005.

Cheng, S.-C., Wu, Y.-H., Huang, W.-C., Pang, J.-H.S., Huang, T.-H., Cheng, C.-Y., 2019. Anti-inflammatory property of quercetin through downregulation of ICAM-1 and MMP-9 in TNF-α-activated retinal pigment epithelial cells. Cytokine 116, 48–60. https://doi.org/10.1016/j.cyto.2019.01.001.

Conklin, D.J., Barski, O.A., Lesgards, J.-F., Juvan, P., Rezen, T., Rozman, D., Prough, R.A., Vladykovskaya, E., Liu, S., Srivastava, S., 2010. Acrolein consumption induces systemic dyslipidemia and lipoprotein modification. Toxicol. Appl. Pharmacol. 243 (1), 1–12. https://doi.org/10.1016/j.taap.2009.12.010.

Conklin, D.J., Haberzettl, P., Jagatheesan, G., Kong, M., Hoyle, G.W., 2017. Role of TRPA1 in acute cardiopulmonary toxicity of inhaled acrolein. Toxicol. Appl. Pharmacol. 324, 61–72. https://doi.org/10.1016/j.taap.2016.08.028.

Dajas, F., 2012. Life or death: neuroprotective and anticancer effects of quercetin. J. Ethnopharmacol. 143 (2), 383–396. https://doi.org/10.1016/j. jep. 2012. 07.005.

De Jong, W.H., Borm, P.J., 2008. Drug delivery and nanoparticles: applications and hazards. Int. J. Nanomed. 3 (2), 133–143.

De Woskin, R.G., M., Pepelko, W., Strickland, J., 2003. Toxicological review of acrolein (cas no. 107- 446-02-08) in support of summary information on the integrated risk information system (Iris). Washington, 447 DC: US Environmental Protection Agency.

Dheeb, B.I., 2014. Immunohistochemical study of Tumor Necrosis Factor-alpha (TNF-α) expression in lung, liver, and spleen during aspergillosis infection. BMC Genom. 15 (2), 1. https://doi.org/10.1186/1471-2164-15-S2-P71.

Edwards, R.L., Lyon, T., Litwin, S.E., Rabovsky, A., Symons, J.D., Jalili, T., 2007. Quercetin reduces blood pressure in hypertensive subjects. J. Nutr. 137 (11), 2405–2411. https://doi.org/10.1093/jn/137.11.2405.

Ekong, M.B., Ekpo, M.M., Akpanyung, E.O., Nwaokonko, D.U., 2017. Neuroprotective effect of Moringa oleifera leaf extract on aluminium-induced temporal cortical degeneration. Metab. Brain Dis. 32, 1437–1447. https://doi.org/10.1007/s11011-017-0011-7.

Elblehi, S.S., Abd El-Maksoud, E.M., Aldhahrani, A., Alotaibi, S.S., Ghamry, H.I., Elgendy, S.A., Soliman, M.M., Shukry, M., 2022. Quercetin abrogates oxidative neurotoxicity induced by silver nanoparticles in Wistar rats. Life 12 (4), 578. https://doi.org/10.3390/life12040578.

Erhan, E., Salcan, I., Bayram, R., Suleyman, B., Dilber, M., Yazici, G.N., Coban, T.A., Altuner, D., Suleyman, H., 2021. Protective effect of lutein against acrolein-induced ototoxicity in rats. Biomed. Pharmacother. 137,. https://doi.org/10.1016/j.biopha.2021.111281 111281.

Feng, S.S., 2014. Effects of Particle Size and Surface Coating on Cellular Uptake of Polymeric Nanoparticles for Oral Delivery of Anticancer Drugs. In Chemotherapeutic Engineering, 756–775. https://doi.org/10.1016/j.biomaterials.2004.07.050.

Franceschi, C., Garagnani, P., Morsiani, C., Conte, M., Santoro, A., Grignolio, A., Monti, D., Capri, M., Salvioli, S., 2018. The continuum of aging and age-related diseases: common mechanisms but different rates. Front. Med. 5, 61. https://doi.org/10.3389/fmed.2018.00061.

Gao, Y., Chen, X., Liu, H., 2018. A facile approach for synthesis of nano-CeO2 particles loaded co-polymer matrix and their colossal role for blood-brain barrier permeability in Cerebral Ischemia. J. Photochem. Photobiol. B Biol. 187, 184–189. https://doi.org/10.1016/j.jphotobiol.2018.05.003.

Gao, L., Liu, G., Wang, X., Liu, F., Xu, Y., Ma, J., 2011. Preparation of a chemically stable quercetin formulation using nanosuspension technology. Int. J. Pharm. 404 (1–2), 231–237. https://doi.org/10.1016/j.ijpharm.2010.11.009.

Granado-Serrano, A.B., Martín, M.Á., Bravo, L., Goya, L., Ramos, S., cancer, 2012. Quercetin attenuates TNF-induced inflammation in hepatic cells by inhibiting the NF-κB pathway. Nutr. 64 (4), 588–598. https://doi.org/10.1080/01635581.2012.661513.

Green, D.R., 2022. The mitochondrial pathway of apoptosis Part II: The BCL-2 protein family. Cold Spring Harb. Perspect. Biol. 14, (6). https://doi.org/10.1101/cshperspect.a041046 a041046.

Grewal, A.K., Singh, T.G., Sharma, D., Sharma, V., Singh, M., Rahman, M.H., Abdel-Daim, M.M., 2021. Mechanistic insights and perspectives involved in neuroprotective action of quercetin. Biomed. Pharmacother. 140, 111729–111746.

Grodzicki, W., Dziendzikowska, K., 2020. The role of selected bioactive compounds in the prevention of Alzheimer's disease. Antioxid. 9 (3), 229. https://doi.org/10.3390/antiox9030229.

Henning, R.J., Johnson, G.T., Coyle, J.P., Harbison, R.D., 2017. Acrolein can cause cardiovascular disease: a review. Cardiovasc. Toxicol. 17 (3), 227–236. https://doi.org/10.1007/s12012-016-9396-5.

Hsu, S.-M., Raine, L., Fanger, H., 1981. Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures. J. Histochem. Cytochem. 29 (4), 577–580. https://doi.org/10.1177/29.4.6166661.

Idriss, H.T., Naismith, J.H., 2000. TNFα and the TNF receptor superfamily: Structure-function relationship (s). Microsc. Res. Tech. 50 (3), 184–195. https://doi.org/10.1002/1097-0029(20000801).

Jakaria, M., Azam, S., Jo, S.-H., Kim, I.-S., Dash, R., Choi, D.-K., 2019. Potential therapeutic targets of quercetin and its derivatives: its role in the therapy of cognitive impairment. J. Clin. Med. 8 (11), 1789. https://doi.org/10.3390/jcm8111789.

Jia, L., Liu, Z., Sun, L., Miller, S.S., Ames, B.N., Cotman, C.W., Liu, J., 2007. Acrolein, a toxicant in cigarette smoke, causes oxidative damage and mitochondrial dysfunction in RPE cells: protection by (R)-α-lipoic acid. Invest. Ophthalmol. Vis. Sci. 48 (1), 339–348.

Jiménez-Morales, J.M., Hernández-Cuenca, Y.E., Reyes-Abrahantes, A., Ruiz-García, H., Barajas-Olmos, F., García-Ortiz, H., del Carmen Abrahantes-Pérez, M., 2022. MicroRNA delivery systems in glioma therapy and perspectives: A systematic review. J. Control. Release 349, 712–730. https://doi.org/10.1016/j.jconrel.2022.07.027.

Juźwik, C.A., Drake, S.S., Zhang, Y., Paradis-Isler, N., Sylvester, A., Amar-Zifkin, A., Douglas, C., Morquette, B., Moore, C.S., Fournier, A.E., 2019. microRNA dysregulation in neurodegenerative diseases: A systematic review. Prog. Neurobiol. 182,. https://doi.org/10.1016/j.pneurobio.2019.101664 101664.

Kakran, M., Sahoo, N.G., Li, L., Judeh, Z., 2012. Fabrication of quercetin nanoparticles by anti-solvent precipitation method for enhanced dissolution. Powder Technol. 223, 59–64. https://doi.org/10.1016/j.powtec.2011.08.021.

Khalfaoui, T., Basora, N., Ouertani-Meddeb, A., 2010. Apoptotic factors (Bcl-2 and Bax) and diabetic retinopathy in type 2 diabetes. J. Mol. Histol. 41, 143–152. https://doi.org/10.1007/s10735-010-9271-9.

Khan, A., Ali, T., Rehman, S.U., Khan, M.S., Alam, S.I., Ikram, M., Muhammad, T., Saeed, K., Badshah, H., Kim, M.O., 2018. Neuroprotective effect of quercetin against the detrimental effects of LPS in the adult mouse brain. Front. Pharmacol. 9, 1383. https://doi.org/10.3389/fphar.2018.01383.

Kim, G.N., Jang, H.D., 2009. Protective Mechanism of Quercetin and Rutin Using Glutathione Metabolism on H2O2-induced Oxidative Stress in HepG2 Cells. Ann. N. Y. Acad. Sci. 1171 (1), 530–537.
Lesjak, M., Beara, I., Simin, N., Pintać, D., Majkić, T., Bekvalac, K., Mimica-Dukić, N., 2018. Antioxidant and anti-inflammatory activities of quercetin and its derivatives. J. Funct. Foods 40, 68–75.
Li, Z., Deng, H., Guo, X., Yan, S., Lu, C., Zhao, Z., Feng, X., Li, Q., Wang, J., Zeng, J., 2022. Effective dose/duration of natural flavonoid quercetin for treatment of diabetic nephropathy: A systematic review and meta-analysis of rodent data. Phytomedicine. https://doi.org/10.1016/j.phymed.2022.154348 154348.
Li, S., Peng, Z., Dallman, J., Baker, J., Othman, A.M., Blackwelder, P.L., Leblanc, R.M., 2016. Crossing the blood–brain–barrier with transferrin conjugated carbon dots: A zebrafish model study. Colloids Surf. B 145, 251–256. https://doi.org/10.1016/j.colsurfb.2016.05.007.
Makkar, R., Behl, T., Bungau, S., Zengin, G., Mehta, V., Kumar, A., Uddin, M.S., Ashraf, G.M., Abdel-Daim, M.M., Arora, S., 2020. Nutraceuticals in neurological disorders. Int. J. Mol. Sci. 21 (12), 4424. https://doi.org/10.3390/ijms21124424.
Manca, M.L., Lai, F., Pireddu, R., Valenti, D., Schlich, M., Pini, E., Sinico, C., 2020. Impact of nanosizing on dermal delivery and antioxidant activity of quercetin nanocrystals. J. Drug Deliv. Sci. Technol. 55, 101482–101486.
Meng, Q., Meng, H., Pan, Y., Liu, J., Li, J., Qi, Y., Huang, Y., 2022. Influence of nanoparticle size on blood–brain barrier penetration and the accumulation of anti-seizure medicines in the brain. J. Mater. Chem. B 10 (2), 271–281.
Minaei, A., Sabzichi, M., Ramezani, F., Hamishehkar, H., Samadi, N., 2016. Co-delivery with nano-quercetin enhances doxorubicin-mediated cytotoxicity against MCF-7 cells. Mol. Biol. Rep. 43, 99–105. https://doi.org/10.1007/s11033-016-3942-x.
Mohamed, H.K., Mohamed, H.-Z.-E.-A., 2018. A histological and immunohistochemical study on the possible protective role of silymarin on cerebellar cortex neurotoxicity of lactating albino rats and their pups induced by gibberellic acid during late pregnancy and early postnatal period. Egypt. J. Histol. 41 (3), 345–371. https://doi.org/10.21608/ejh.2018.3019.1001.
Müller, R.H., Gohla, S., Keck, C.M., 2011. State of the art of nanocrystals–special features, production, nanotoxicology aspects and intracellular delivery. Eur. J. Pharm. Biopharm. 78 (1), 1–9. https://doi.org/10.1016/j.ejpb.2011.01.007.
Nam, J.-S., Sharma, A.R., Nguyen, L.T., Chakraborty, C., Sharma, G., Lee, S.-S., 2016. Application of bioactive quercetin in oncotherapy: from nutrition to nanomedicine. Molecules 21 (1), 108. https://doi.org/10.3390/molecules21010108.
Perlikowska, R., 2021. Whether short peptides are good candidates for future neuroprotective therapeutics? Peptides 140,. https://doi.org/10.1016/j.peptides.2021.170528 170528.
Puerta, E., Suárez-Santiago, J.E., Santos-Magalhães, N.S., Ramirez, M.J., Irache, J.M., 2017. Effect of the oral administration of nanoencapsulated quercetin on a mouse model of Alzheimer's disease. Int. J. Pharm. 517 (1–2), 50–57. https://doi.org/10.1016/j.ijpharm.2016.11.061.
Rahman, M.M., Islam, M.R., Akash, S., Harun-Or-Rashid, M., Ray, T.K., Rahaman, M.S., Islam, M., Anika, F., Hosain, M.K., Aovi, F.I., 2022. Recent advancements of nanoparticles application in cancer and neurodegenerative disorders: At a glance. Biomed. Pharmacother. 153,. https://doi.org/10.1016/j.biopha.2022.113305 113305.
Rahman, M.M., Islam, M.R., Tumpa, M.A.A., Shohag, S., Ferdous, J., Kajol, S.A., et al., 2023. Insights into the promising prospect of medicinal chemistry studies against neurodegenerative disorders. Chem. Biol. Interact. 110375
Reddy, D.S., Abeygunaratne, H.N., 2022. Experimental and Clinical Biomarkers for Progressive Evaluation of Neuropathology and Therapeutic Interventions for Acute and Chronic Neurological Disorders. Int. J. Mol. Sci. 23 (19), 11734. https://doi.org/10.3390/ijms231911734.
Rifaai, R.A., Mokhemer, S.A., Saber, E.A., Abd El-Aleem, S.A., El-Tahawy, N.F.G., 2020. Neuroprotective effect of quercetin nanoparticles: A possible prophylactic and therapeutic role in alzheimer's disease. J. Chem. Neuroanat. 107,. https://doi.org/10.1016/j.jchemneu.2020.101795 101795.
Sajid, M., Płotka-Wasylka, J., 2020. Nanoparticles: Synthesis, characteristics, and applications in analytical and other sciences. Microchem. J. 154, 104623–104629. https://doi.org/10.1016/j.microc.2020.104623.
Salamone, S., Nieddu, M., Khalili, A., Sansaro, A., Bombardelli, E., Rosa, A., Pollastro, F., 2021. Effects of quercetin and artemetin prenylation on bioavailability and bioactivity. Chem. Phys. Lipids 240,. https://doi.org/10.1016/j.chemphyslip.2021.105137 105137.
Sánchez-Jaramillo, E.A., Gasca-Lozano, L.E., Vera-Cruz, J.M., Hernández-Ortega, L.D., Gurrola-Díaz, C.M., Bastidas-Ramírez, B.E., Vargas-Guerrero, B., Mena-Enríquez, M., Martínez-Limón, F.D.J., Salazar-Montes, A.M., 2022. Nanoparticles Formulation Improves the Antifibrogenic Effect of Quercetin on an Adenine-Induced Model of Chronic Kidney Disease. Int. J. Mol. Sci. 23 (10), 5392. https://doi.org/10.3390/ijms23105392.
Sirvi, A., Kuche, K., Chaudhari, D., Ghadi, R., Date, T., Katiyar, S.S., Jain, S., 2022. Supersaturable self-emulsifying drug delivery system: A strategy for improving the loading and oral bioavailability of quercetin. J. Drug. Deliv. Sci. Technol. 71,. https://doi.org/10.1016/j.jddst.2022.103289 103289.
Slovinska, L., Harvanova, D., Janockova, J., Matejova, J., Cibur, P., Moravek, M., Spakova, T., Rosocha, J., 2022. Mesenchymal Stem Cells in the Treatment of Human Spinal Cord Injury: The Effect on Individual Values of pNF-H, GFAP, S100 Proteins and Selected Growth Factors, Cytokines and Chemokines. Curr. Issues Mol. Biol. 44 (2), 578–596. https://doi.org/10.3390/cimb44020040.
Spead, O., Zaepfel, B.L., Rothstein, J.D., 2022. Nuclear pore dysfunction in neurodegeneration. Neurother. 19 (4), 1050–1060. https://doi.org/10.1007/s13311-022-01293-w.
Suroto, H., Asriel, A., De Vega, B., Samijo, S.K., 2021. Early and late apoptosis protein expression (Bcl-2, BAX and p53) in traumatic brachial plexus injury. J. Musculoskelet. Neuronal Interact. 21 (4), 528.
Tanel, A., Averill-Bates, D.A., 2007. Inhibition of acrolein-induced apoptosis by the antioxidant N-acetylcysteine. J. Pharmacol. Exp. Ther. 321 (1), 73–83. https://doi.org/10.1124/jpet.106.114678.
Teleanu, D.M., Chircov, C., Grumezescu, A.M., Volceanov, A., Teleanu, R.I., 2018. Impact of nanoparticles on brain health: An up-to-date overview. J. Clin. Med. 7 (12), 490–498.
Tiwari, S.B., Amiji, M.M., 2006. A review of nanocarrier-based CNS delivery systems. Curr. Drug Deliv. 3 (2), 219–232.
Tulen, C., Snow, S., Leermakers, P., Kodavanti, U., van Schooten, F., Opperhuizen, A., Remels, A., 2022. Acrolein inhalation acutely affects the regulation of mitochondrial metabolism in rat lung. Toxicology 469,. https://doi.org/10.1016/j.tox.2022.153129 153129.
Uchida, K., Kanematsu, M., Sakai, K., Matsuda, T., Hattori, N., Mizuno, Y., Suzuki, D., Miyata, T., Noguchi, N., Niki, E., 1998. Protein-bound acrolein: potential markers for oxidative stress. PNAS 95 (9), 4882–4887. https://doi.org/10.1073/pnas.95.9.4882.
Verma, N., Trehan, N., 2013. HPLC analysis of methanolic extract of herbs for quercetin content. J. pharmacogn. phytochem. 2 (1), 159–162.
Wang, B., Yu, L., Liu, W., Yang, M., Fan, L., Zhou, M., Ma, J., Wang, X., Nie, X., Cheng, M., Qiu, W., Ye, Z., Song, J., Chen, W., 2022. Cross-sectional and longitudinal associations of acrolein exposure with pulmonary function alteration: Assessing the potential roles of oxidative DNA damage, inflammation, and pulmonary epithelium injury in a general adult population. Environ. Int. 167,. https://doi.org/10.1016/j.envint.2022.107401 107401.
Wheat, L.A., Haberzettl, P., Hellmann, J., Baba, S.P., Bertke, M., Lee, J., McCracken, J., O'Toole, T.E., Bhatnagar, A., Conklin, D.J., 2011. Acrolein inhalation prevents vascular endothelial growth factor-induced mobilization of Flk-1+/Sca-1+ cells in mice. Arterioscler. Thromb. Vasc. Biol. 31 (7), 1598–1606. https://doi.org/10.1161/atvbaha.111.227124.
Xiaodan, W., Yongping, Y., Liu, Y., Mu, L., Xiuhui, Z., 2016. Effect of quercetin on the expression of Bcl-2/Bax apoptotic proteins in endometrial cells of lipopolysaccharide-induced-abortion mice. J. Tradit. Chin. Med. 36 (6), 737–742. https://doi.org/10.1016/S0254-6272(17)30008-0.
Xie, Y., Ye, L., Zhang, X., Cui, W., Lou, J., Nagai, T., Hou, X., 2005. Transport of nerve growth factor encapsulated into liposomes across the blood–brain barrier: in vitro and in vivo studies. J. Control. Release 105 (1–2), 106–119. https://doi.org/10.1016/j.jconrel.2005.03.005.
Xu, C., Shu, W.-Q., Qiu, Z.-Q., Chen, J.-A., Zhao, Q., Cao, J., 2007. Protective effects of green tea polyphenols against subacute hepatotoxicity induced by microcystin-LR in mice. Environ. Toxicol. Pharmacol. 24 (2), 140–148. https://doi.org/10.1016/j.etap.2007.04.004.
Xu, M.M., Zhou, M.T., Li, S.W., Zhen, X.C., Yang, S., 2021. Glycoproteins as diagnostic and prognostic biomarkers for neurodegenerative diseases: A glycoproteomic approach. J. Neurosci. Res. 99 (5), 1308–1324. https://doi.org/10.1002/jnr.24805.
Zahra, W., Birla, H., Singh, S.S., Rathore, A.S., Dilnashin, H., Singh, R., Keshri, P.K., Gautam, P., Singh, S.P., 2022. Neuroprotection by Mucuna pruriens in neurodegenerative diseases. Neurochem. Res. 47 (7), 1816–1829. https://doi.org/10.1007/s11064-022-03591-3.