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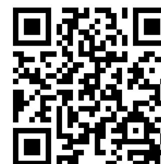

RESEARCH ARTICLE

Luteolin Mitigated Neuroinflammation and Glial Activation in Oxaliplatin-Induced Central and Peripheral Neuropathy in Rats

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ABSTRACT

The objective of the current study was to evaluate the potential of luteolin to mitigate the neurotoxic effects of OXL. Oxidative injury, inflammation, and mitochondrial dysfunction are the cardinal factors in OXL-triggered neuropathy. LUT modulates sensory and motor behavioral changes induced by OXL. Notably, LUT treatment significantly ($p \leq 0.05$) increased antioxidant activity by increasing paraoxonase-1 (PON-1) and heme oxygenase-1 (HO-1) levels, attenuating oxidative damage. Additionally, LUT inhibited neuroinflammation by repressing the levels of toll-like receptor-4 (TLR4) and intracellular adhesion molecule-1 (ICAM-1), while significantly increasing brain-derived neurotrophic factor (BDNF) and downregulating the relative gene expression level of mitogen-activated protein kinase 14 (MAPK-14). Moreover, LUT significantly reduced neuronal apoptosis (Caspase3; cysteine-aspartate-specific protease 3) and attenuated glial activation, while also restoring mitochondrial function. Furthermore, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in brain and sciatic nerve tissue, as well as glial fibrillary acidic protein (GFAP) immunohistochemical expression, were both markedly reduced by LUT. LUT protected neuronal structures from OXL-induced neuronal injury, as shown in histopathological examination. Lastly, both in vivo and in silico molecular docking findings confirmed the anti-inflammatory and neuroprotective effects of LUT, linked to MAPK-14 and GFAP. This study demonstrates that LUT provides a promising therapeutic effect in palliating OXL morbidity by targeting glial cells for neuropathy relief.

Keywords: GFAP, Glial cell, Luteolin, MAPK-14, Oxaliplatin, PON-1

Introduction

Third-generation platinum-based chemotherapeutic agents like oxaliplatin (OXL) are frequently utilized as first-line treatments for solid tumors like pancreatic and stomach cancer, as well as metastatic colorectal cancer.[1,2]

Extreme central and peripheral neuropathy are among the severe limiting adverse effects that are frequently linked to the clinical use of OXL.[3] The pathophysiology of neurotoxicity induced by OXL is caused by the accumulation of platinum products, which create highly cytotoxic nuclear and mitochondrial DNA adducts and generate a high rate of free radical species.[2,4] Thus, the clinical use of this chemotherapeutic agent is often discontinued due to its neurotoxicity. Moreover, the oxidative stress caused by OXL use leads to apoptosis, mitochondrial dysfunction, neuroinflammation, central glial cell activation, axonal degeneration, and focal demyelination.[5]

Furthermore, this anticancer drug significantly affects the quality of life of patients with cancer. Its severe side effects can be persistent and disabling.[6]

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Neuropathic pain associated with OXL treatment is a dose-limiting side effect for cancer patients. Currently, no drugs are recommended for the prevention or management of central and peripheral neuropathy caused by chemotherapy.[3] Therefore, studying the role of naturally occurring, safe phytochemicals may provide a promising therapeutic role in treating or preventing OXL-induced neuropathy. Medication that hinders reactive oxygen species (ROS) generation and mitochondrial malfunction can prevent OXL neuropathy.[7]

Luteolin (LUT) is a flavone compound found in several medicinal plants; its hydroxyl (OH^-) group is joined to the flavone backbone structure at the 5-, 7-, 3'-, and 4'-positions.[8] LUT is reported to possess several pharmacological health benefits; it is generally found in fruits, vegetables, and medicinal herbs.[9] Parsley, peppermint, celery, thyme, basil, and artichokes have been shown to have high LUT content;[10] broccoli, peppers, onion leaves, cabbage, carrots, apple skins, and peanut shells have also been discovered to contain LUT in variable amounts.[11]

Moreover, since LUT has anti-inflammatory, anti-tumor, neuroprotective, and anti-apoptotic properties, it is frequently used in traditional Chinese medicine.[12,13] Additionally, this flavone possesses antimicrobial, cardioprotective, anti-diabetic, anti-allergic, and chemopreventive properties.[9,14] Studies reported that LUT provides several pharmacological benefits at micromolar concentrations, and its use is safe.[14]

Previously, luteolin was examined for its neuroprotective effect against the acetamiprid pesticide.[15] Another study reported the role of luteolin in attenuating D-galactose-induced senescence.[16] Additionally, a study found that LUT protected against sodium valproic acid-induced autism spectrum disease.[17] The purpose of this study is to investigate the effect of luteolin treatment on peripheral and central neuropathy caused by the oxaliplatin in an in vivo model and to apply in silico studies to evaluate the interaction of luteolin with MAPK-14 and GFAP. We speculate that by inhibiting oxidative stress, glial activation, and neuronal death in rats, luteolin may have a therapeutic utility against neuropathy.

Materials and methods

Chemicals

Oxaliplatin (OXL) was obtained from Mylan Pharmaceuticals, France, and luteolin was purchased from Sigma Aldrich, USA.

Experimental animals

Thirty male adult albino Sprague Dawley rats, 220 ± 5 g, were purchased from the National Research Center, Doki, Egypt. Throughout 12 hours of acclimatization under a light/dark cycle, the rats were kept at a room temperature of 25 °C and a humidity level of 60–70%. The rats were supplied with water *ad libitum* and a standard chow diet as described by.[18] The study adheres to ethical standards set by the local animal ethics committee of the Women's Faculty, Ain Shams University. The Ethical Committee Approval Code was SCI-1432406002.

Experimental design

The rats were divided into three groups. Rats were fed a chow diet and received an intraperitoneal injection of normal saline; this group was designated as Group 1 (Normal control group). Group 2 (OXL group; positive control group)'Rats were fed a chow diet and received an intraperitoneal injection of OXL (4mg/kg b.wt.) Group 3 (OXL + LUT group): OXL-injected rats were fed a chow diet and administered luteolin (100 mg/kg b.wt./day; p.o.) daily.

To prepare the dosage, oxaliplatin was dissolved in 5% dextrose solution. Rats received intraperitoneal injections of 4 mg/kg b.wt. on the first, second, fifth, and sixth days (a cumulative dose of 16 mg/kg b.wt.).[3] Luteolin was administered daily via oral gavage (100 mg/kg b.wt./day) for four weeks.[19] The behavioral tests were applied two days before the rats' sacrifice.

Samples collection

At the end of the animal trial (4 weeks), the rats were sacrificed, and the entire brain was removed by making an incision on the dorsal side of the skull. The tissues of the sciatic nerve were then promptly dissected. Cold saline was used to cleanse the brain and sciatic nerve tissue. The samples were kept at –80 °C for biochemical and real-time PCR assays, while some were prepared for histopathological and immunohistochemical analyses.

Behavioral tests for sensory and motor neuropathy

a. The Hot Plate Test

For this test, rats were placed on a hot plate at 52°C, and the time interval between the rats' paws touching the plate and their initial reaction was recorded.[20]

b. The Tail Immersion Test

One-third of the rats' tails were submerged in a hot and cold water bath (regulated at 49°C and 4°C,

respectively) to assess the tail immersion test; the rats' initial reaction time was recorded.[21]

c. The Rota-rod Test

The duration of time the rats spent on the spinning bar at 10 r.p.m. was recorded three times for each rat using the non-slippery Rotarod device with a 6 cm diameter (UgoBasile).[21]

d. The Cold Hyperalgesia Test

A 4°C cold plate was used to conduct the cold hyperalgesia test. The rat's paw lifting, licking, and shaking activities were recorded for one minute after the rat was put on the plate. For each rat, this test was conducted three times at 5-minute intervals.[21]

Preparation of brain and sciatic nerve tissue homogenate

The brain and sciatic nerve tissues were homogenized using a buffer (potassium phosphate, 0.01 M, pH 7.4) via a low-temperature tissue homogenizer (Heidolph Diax 900, Germany) after washing with ice-cold saline. The homogenates were centrifuged for 10 minutes at 4 °C at 5000 rpm. The following parameters were then assessed in the resultant supernatant via the ELISA reader, Bio-Tek, USA.[3]

Determination of HO-1 and PON-1

Measuring the levels of heme oxygenase-1 (HO-1) and paraoxonase-1 (PON-1) was done using the quantitative sandwich enzyme-linked immunosorbent assay (ELISA) method using MyBioSource kits, USA (cat. no: MBS760394 and MBS453155, respectively).

Determination of Caspase 3 and Bax

The levels of apoptotic markers, such as Bcl-2-associated x-protein (Bax) and cysteine aspartate-specific protease 3 (Caspase3), were estimated. Following the manufacturer's kit manual, these apoptotic marker levels were assayed by the quantitative sandwich ELISA method with kits provided by Cloud-Clone Corp., USA (cat. no: SEA626Ra and SEB343Ra, respectively).

Determination of BDNF

Brain-derived neurotrophic factor (BDNF) level was analyzed by the quantitative sandwich ELISA method, following the manufacturer's kit manual by Cloud-Clone Corp. kits, USA (cat. no: SEA011Ra).

Determination of NADPH oxidase

The enzyme activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase was measured using the competitive inhibition ELISA technique with kits provided by MyBiosource, USA (cat. no: MBS2506694).

Molecular docking study

Using an in silico molecular docking assay, the type and strength of the interaction between luteolin and the targets (MAPK14 and GFAP) were identified. Hussein et al.[22] presented the protocol design for the in silico molecular docking research of the generated medicines with minimal modifications. The interactions between the synthesized chemicals and the proteins MAPK14 (PDB ID: 6SFO) and GFAP (PDB ID: 6A9P) were examined using AutoDock Vina v.1.2. The docked compounds' structures were built with the proper 2D orientation using Chem. 3D extreme 12.0 software [Chemical Structure Drawing Standard; Cambridge Soft Corporation, USA (2010)]. The energy of each molecule was minimized using ChemBio3D before being entered into AutoDock Vina to apply the docking simulation assay. The crystal structures of the enzymes GFAP (PDB ID: 6A9P) and MAPK14 (PDB ID: 6SFO) were provided by the Protein Data Bank.

Then, the protein was prepared according to the standard technique, and the target protein file was created by leaving the relevant residues with the protein using Auto creation of the target protein file, AutoDock 4.2 (MGLTools 1.5.6). The graphical user interface of the application was used to configure the docking simulation grid box. The grid was intended to surround the region of interest of the macromolecule. The docking method included with AutoDock Vina v.1.2.0 was used to determine the best-docked configuration between the ligand and the protein. Around nine conformers were measured for each ligand during the molecular docking process. To investigate the interactions between the ligands and the target receptor, configurations with the best (least) free binding energy were selected using PyMOL and Discovery Studio Visualizer.[23]

Real-time PCR gene expression quantitation

Quantitative measurement of the mRNA transcript levels of toll-like receptor 4 (TLR-4), mitogen-activated protein kinase-14 (MAPK-14) activity, and intercellular adhesion molecule-1 (ICAM-1) was performed by real-time PCR technique in brain and sciatic nerve tissues using the Real-time PCR system

Table 1. Primers.

Gene	Primers' sequence
GAPDH	
Forward Sequence	5' AGTGCCAGCCTCGTCTCATA '3
Reverse Sequence	5' GATGGTGATGGGTTTCCCGT '3
TLR4	
Forward Sequence	5' TGGATTTGGACGCATTGGTC '3
Reverse Sequence	5' TTTGCACTGGTACGTGTTGAT '3
MAPK-14	
Forward Sequence	5' GTGGCAGTGAAGAAGCTGTC 3
Reverse Sequence	5' GTCACCAGGTACACATCGTT '3
ICAM- 1	
Forward Sequence	5' AGGACTCTAGACGGCATCCA '3
Reverse Sequence	5' CAGTGAGACTTGGTGCAGTGA '3

(Applied Biosystem; Step One, Foster City, USA). GAPDH was used as a housekeeping gene, and the primers used are provided in Table 1. Total RNA from brain and sciatic nerve tissues was extracted using RNA extraction reagents and a Trizol kit (Cat no. R2072, ZYMO RESEARCH CORP, USA).

Moreover, the complementary DNA (cDNA) was reverse transcribed utilizing the reverse transcription kit (Cat no. 12594100, Thermo Fisher Scientific, USA), and the SYBR Green qPCR Master Mix (Cat no.330500, QIAGEN, Germany) was then used to determine the relative expression levels of mRNA using the $2^{-\Delta\Delta Ct}$ method to determine the relative fold of expressed genes.[24]

Histopathological examination

After being dissected, the brain and sciatic nerve tissues were quickly preserved in 10% neutral formalin, paraffin-embedded, and then stained with hematoxylin-eosin dye. An Olympus BX43 light microscope was used to analyze the stained tissue sections at 200x magnification, and an Olympus DP27 camera connected to Cellsens dimensions software was used to take pictures.[3]

Immunohistochemistry assay

Paraffin tissue blocks: 5-μm-thick sections of the brain and sciatic nerve tissues were used for immunohistochemical analysis of glial fibrillary acidic protein (GFAP). The sections were deparaffinized and rehydrated by applying a gradient of ethanol concentrations. 3% H_2O_2 was dropped for 10 minutes at room temperature to inhibit the endogenous peroxidase. Then the sections were rinsed in water and heated in antigen retrieval solution (0.01 M citrate-hydrochloric acid, pH 6.0) to unmask antigens for 15 minutes using a microwave. After blocking non-specific proteins, the GFAP antibody was applied to the sections and incubated at 4 °C overnight. After that, tissue sections were incubated for one hour at room temperature with primary anti-GFAP at a dilution of 1/100 (Santa Cruz). Then, the secondary HRP-labeled detection kit (Bio SB, USA) was used according to the manufacturer's manual. The primary antibody incubation stage was skipped to obtain negative control slides. Area% was used to quantify positive expression. A Leica digital microscope DM4B (Leica, Wetzlar, Germany) was used to view the sections at 200x magnification, and a Leica DMC 4500 digital camera connected to LAS-X software was used to take pictures.[6]

Statistical analysis

The results were statistically analyzed using the SPSS Statistics 21.0 program, USA. Means ± S.D. were used to express values. A one-way ANOVA test was used to assess quantitative differences between data at a significance level of ($p \leq 0.05$).[25]

Results

Behavioral test results

Behavioral test observations are illustrated in Fig. 1. A & B, which include the cold hyperalgesia test, the rota-rod test, the hot plate test, and the tail immersion test.

The rotarod test revealed that the OXL-treated group had impaired motor performance of rats compared to the normal control group. In contrast to the OXL group, the OXL + LUT group's motor function was noticeably improved. Additionally, the hot plate test results indicated that the OXL-treated group showed a significant ($p \leq 0.05$) decrease in the paw withdrawal threshold recorded as latency time (seconds) compared to the normal control group. The paw withdrawal threshold was significantly higher in the OXL + LUT group than in the OXL-treated group. According to the results of the cold hyperalgesia test, Fig. 1. A, OXL therapy considerably lengthened the hyperalgesia reaction time in comparison to the control group. When compared to the group that received OXL, LUT administration dramatically shortened the hyperalgesia response time. The tail immersion test results in both cold and hot water baths showed that the latency time of the OXL group was much lower than that of the control group. In contrast to the OXL group, it was noticeably higher in the OXL + LUT group.

The findings of this study showed that oxaliplatin induced oxidative stress in the brain and sciatic nerve tissues. The HO-1 and PON-1 activities in the OXL group were significantly lower than those in the NC

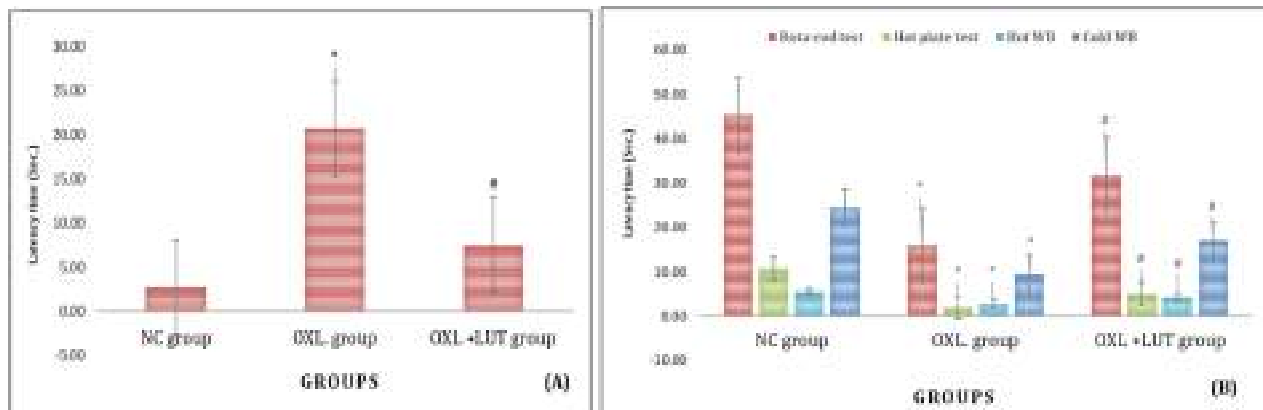

Fig. 1. Behavioral tests. (A) Cold hyperalgesia test and (B) the rotarod test, hot plate test, and tail immersion test (Hot water bath & Cold water bath). (NC; Normal control, OXL; Oxaliplatin, LUT; Luteolin, B; Brain, S; Sciatic nerve tissue). All data were expressed as mean ± SD. Symbol (*) shows a statistically significant difference compared to the NC group, and symbol (#) shows a statistically significant difference at p ≤0.05, using a one-way ANOVA test as compared to the OXL group.

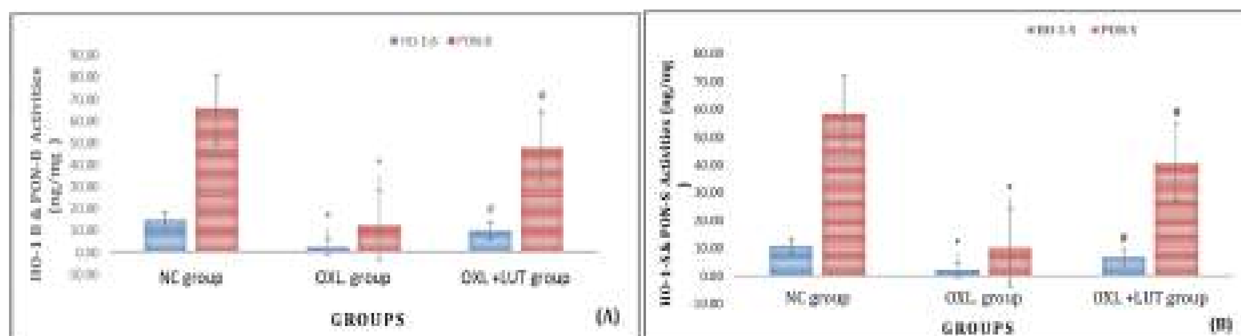

Fig. 2. (A) HO-1 and PON-1 activities in the rat's brain. (B) HO-1 and PON-1 activities in the rat's sciatic nerve tissue. (NC; Normal control, OXL; Oxaliplatin, LUT; Luteolin, B; Brain, S; Sciatic nerve tissue, HO-1; Hemeoxygenase-1, PON-1; Paraoxonase). The data were presented as mean ± S.D. In comparison to the NC group, the sign (*) indicates a statistically significant difference, while in comparison to the OXL group, the symbol (#) indicates a statistically significant difference at p ≤0.05, using a one-way ANOVA test.

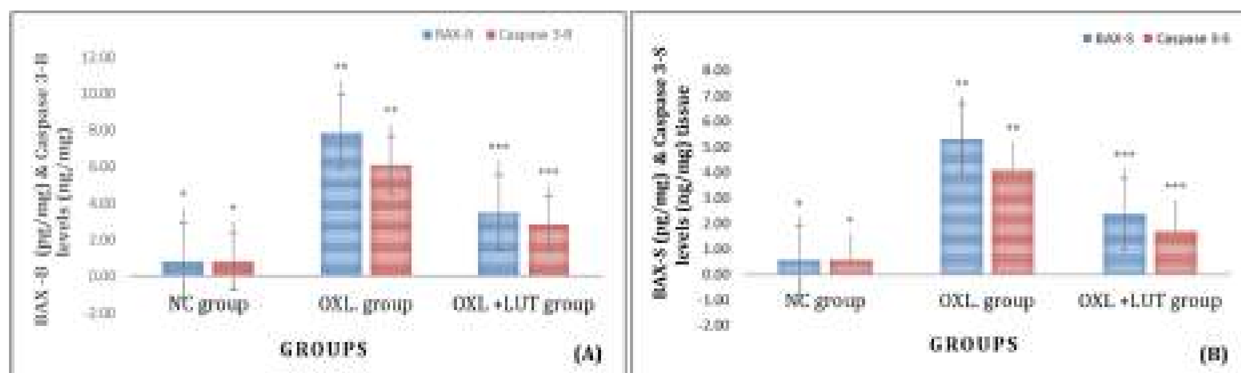

Fig. 3. (A) BAX and Caspase 3 activity in the rat's brain. (B) BAX and Caspase activity in the rat's sciatic nerve tissue. (NC; Normal control, OXL; Oxaliplatin, LUT; Luteolin, B; Brain, S; Sciatic nerve tissue, Caspase 3; Cysteine aspartate-specific protease 3 and Bax; Bcl 2-associated x protein). The data were presented as mean ± S.D. In comparison to the NC group, the sign (*) indicates a statistically significant difference, while in comparison to the OXL group, the symbol (#) indicates a statistically significant difference at p ≤0.05, using a one-way ANOVA test.

group, as shown in Fig. 2. A & B. When OXL was administered with LUT, HO-1 and PON-1 activity significantly ($p \leq 0.05$) increased, which decreased the oxidative damage that OXL caused.

Furthermore, Fig. 3. A&B showed that oxaliplatin intraperitoneal (i.p.) injection induced a significant increase in apoptotic marker activities (Bax and Caspase3) in the brain and sciatic nerve tissues in

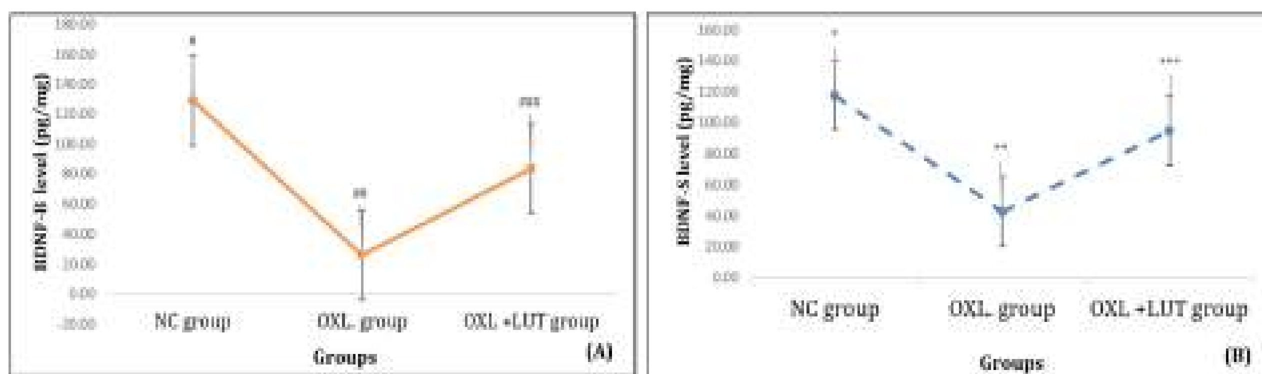

Fig. 4. (A) BDNF activity in the rat's brain. (B) BDNF activity in the rat's sciatic nerve tissue. (NC; Normal control, OXL; Oxaliplatin, LUT; Luteolin, B; Brain, S; Sciatic nerve tissue, BDNF; Brain-derived neurotrophic factor). The data were presented as mean ± S.D. In comparison to the NC group, the sign (*) indicates a statistically significant difference, while in comparison to the OXL group, the symbol (#) indicates a statistically significant difference at $p \leq 0.05$, using a one-way ANOVA test.

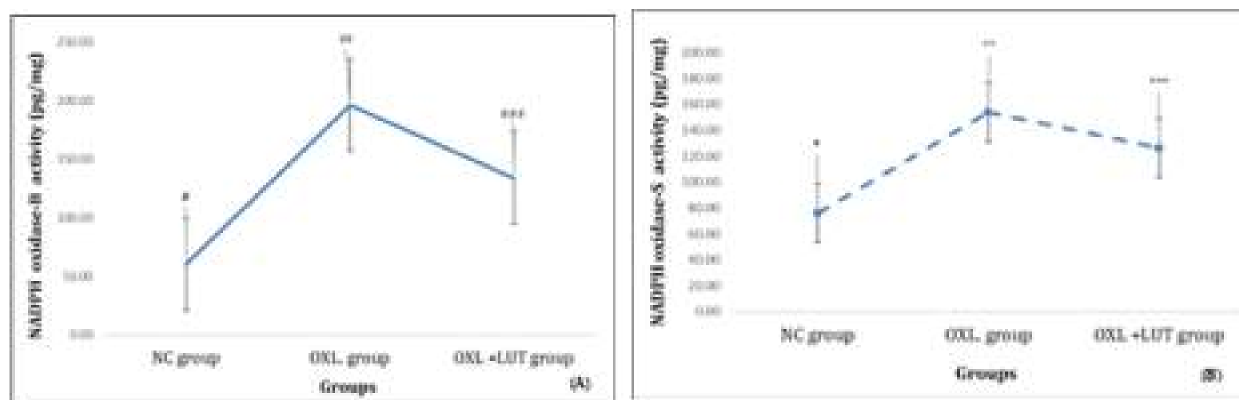

Fig. 5. (A) NADPH Oxidase activity in the rat's brain. (B) NADPH Oxidase activity in the rat's sciatic nerve tissue. (NC; Normal control, OXL; Oxaliplatin, LUT; Luteolin, B; Brain, S; Sciatic nerve tissues, NADPH oxidase; Nicotinamide adenine dinucleotide phosphate oxidase). The data were presented as mean ± S.D. In comparison to the NC group, the sign (*) indicates a statistically significant difference, while in comparison to the OXL group, the symbol (#) indicates a statistically significant difference at $p \leq 0.05$, using a one-way ANOVA test.

comparison to the NC group. Administration of luteolin resulted in a significant reduction in their levels.

Fig. 4. A & B show that the OXL-injected group had significantly lower levels of BDNF in the brain and sciatic nerve tissues than the NC group. Furthermore, compared to the OXL group, LUT treatment dramatically reduced the increased level of BDNF.

Additionally, NADPH oxidase activity in brain and sciatic nerve tissues was significantly higher in the OXL-injected group than in the NC group, and significantly reduced ($p \leq 0.05$) in the OXL + LUT group than in the OXL group, as shown in Fig. 5. A & B.

Furthermore, compared to the NC group, Fig. 6. A & B demonstrated that OXL injection significantly increased the mRNA expression of inflammatory biomarkers in the brain and sciatic nerve tissue. When LUT was given with OXL injection, the elevated mRNA transcripts of ICAM, MAPK-14, and TLR-4 were markedly downregulated.

Furthermore, a molecular docking assay was applied between luteolin, MAPK14, and GFAP. The docking simulations were performed using AutoDock Vina, a molecular docking tool. To investigate the interactions between the ligands and the target receptor, configurations with the highest (least) free binding energy were selected using PyMOL and Discovery Studio Visualizer.

Following the construction of luteolin using ChemBioDraw Ultra 12.0 and the representation of the ligands in various hues, the protein data bank was used to download the crystal structures of the MAPK14 (PDB ID: 6SFO) and GFAP (PDB ID: 6A9P) proteins.

Molecular docking of MAPK14 was used to investigate the binding location of luteolin, and the results showed that luteolin formed three hydrogen bonds with Lys53, Met109, and Asp168. Additionally, as shown in Fig. 7. A & B, LUT was involved in the creation of several hydrophobic

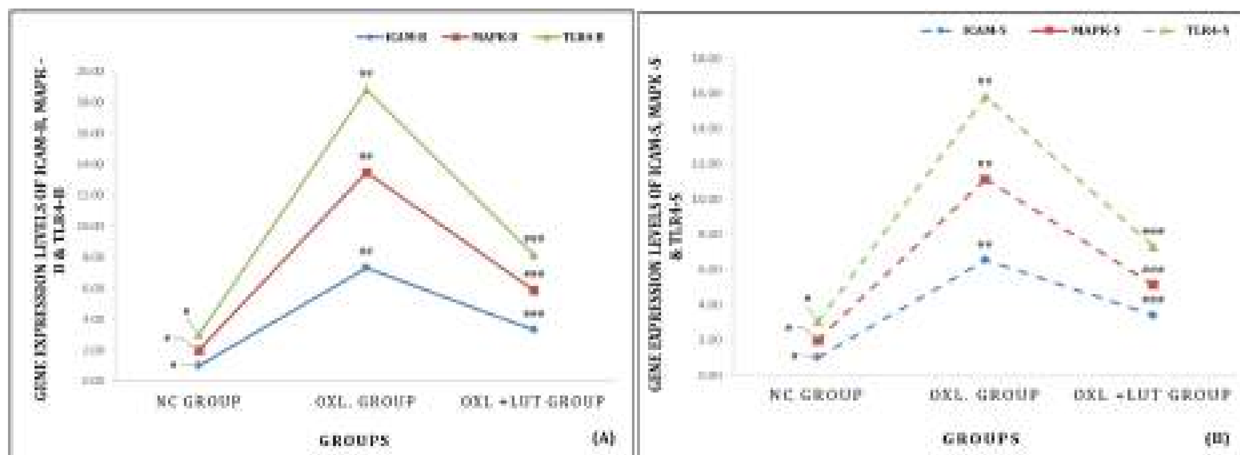

Fig. 6. (A) The relative gene expression levels of ICAM, MAPK, and TLR-4 in rats' brains. (B) The relative gene expression levels of ICAM, MAPK, and TLR-4 in the rat's sciatic nerve tissue. (NC; Normal control, OXL; Oxaliplatin, LUT; Luteolin, B; Brain, S; Sciatic nerve tissue, ICAM; Intercellular adhesion molecule-1, MAPK; Mitogen-activated protein kinase, TLR-4; Toll-like receptor 4). The data were presented as mean ± S.D. In comparison to the NC group, the sign (*) indicates a statistically significant difference, while in comparison to the OXL group, the symbol (#) indicates a statistically significant difference at $p \leq 0.05$, using a one-way ANOVA test.

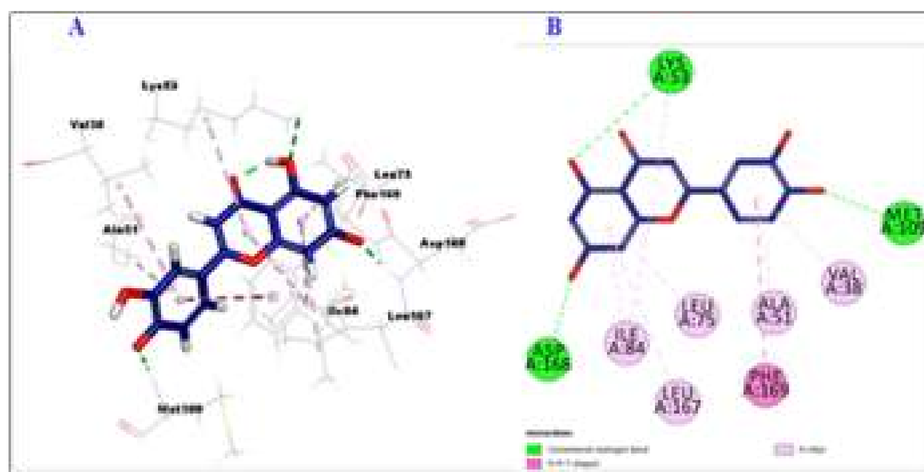

Fig. 7. 3D (A)/2D (B) Binding modes/interactions of luteolin into the active site of MAPK14 (PDB ID: 6SFO).

interactions, including the Pi-Pi T-shaped interaction with Phe169 and five Pi-alkyl connections with amino acid residues Val38, Ala51, Leu75, Ile84, and Leu167.

Meanwhile, the in silico molecular docking simulation results of GFAP showed that luteolin displayed dual interactions with one of the most essential residues in the protein's active site pockets. One Pi-Donor hydrogen bond and one salt bridge with the same amino acid residue, Arg124, were observed in the best confirmation of luteolin with GFAP (PDB ID: 6A9P); Fig. 8A & B.

Hereby, the molecular docking assay results found that the docking studies were in harmony with the in vivo assay results. Both in vivo and in silico findings confirm the anti-inflammatory and neuroprotective effects of LUT, revealing that LUT is effective in attenuating oxidative damage and neuroinflammation by suppressing NF-κB and MAPK pathways, the mainstream targets of the proinflammatory cascade, while activating the Nrf2 pathway. Also, the active binding of LUT to MAPK-14 and GFAP fosters the glioprotective and neuroprotective effects of LUT against OXL neuropathy.

Moreover, the histopathological examination and immunohistochemical photomicrographs of brain and sciatic nerve tissues reveal that LUT administration significantly ameliorated central and peripheral neuropathy induced by OXL. Microscopic analysis of brain sections from the NC group showed that the hippocampus and cerebral cortex, respectively, appeared with a normal architecture, Fig. 9. A & B. Significant histological alterations were seen in the hippocampus and cerebral cortex of the OXL group Fig. 9. C & D.

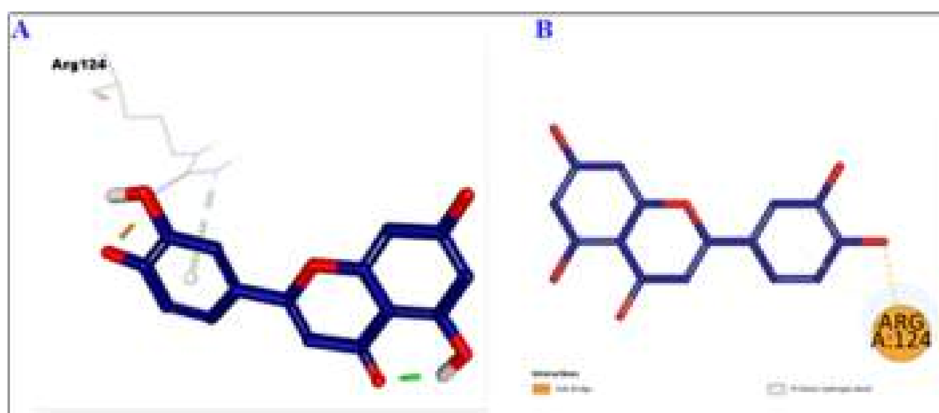

Fig. 8. 3D (A)/2D (B) Binding modes/interactions of luteolin into the active site of GFAP (PDB ID: 6A9P).

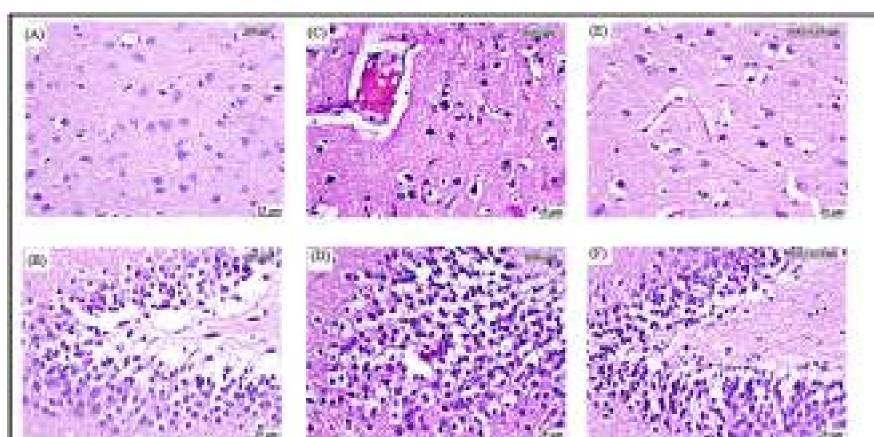

Fig. 9. Photomicrographs of the brain (cerebral cortex and hippocampus, respectively). (A&B) NC group; (G1) showing a normal cerebral cortex and hippocampus. (C & D) OXL injected group; (G2) showing numerous degenerated neurons in the cerebral cortex with congested blood vessels and degenerated neurons in the hippocampus. (E & F) OXL + LUT group; (G3), showing a few degenerated neurons in the tissues in the cerebral cortex and the hippocampus.

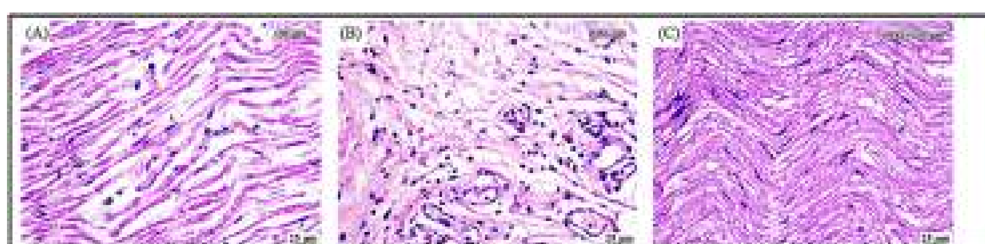

Fig. 10. Photomicrographs of sciatic nerve tissue (H&E). (A) The NC group (G1) showing a normal structure of nerve fibers. (B) OXL injected group; (G2) showing inflammatory cells between nerve fibers with dilated blood vessels and marked demyelination of nerve fibers. (C) OXL + LUT group; (G3), showing normal nerve fibers.

There were many deteriorated neurons and congested blood vessels in the cerebral cortex, together with gliosis. Dark degenerating neurons were also seen in the various hippocampal regions. Compared to the OXL group, the OXL + LUT group showed a marked improvement Fig. 9. E & F, with significantly fewer degenerated neurons in the hippocampus and cerebral cortex.

The microscopic examination of nerves from the NC group Fig. 10. A revealed a normal histological structure of nerve fibers. OXL group Fig. 10. B showed areas of demyelination within the nerve fibers associated with inflammatory cell infiltration between nerve fibers and in the perineuronal tissue. The OXL + LUT group, Fig. 10. C showed normal nerve fibers in almost all examined sections.

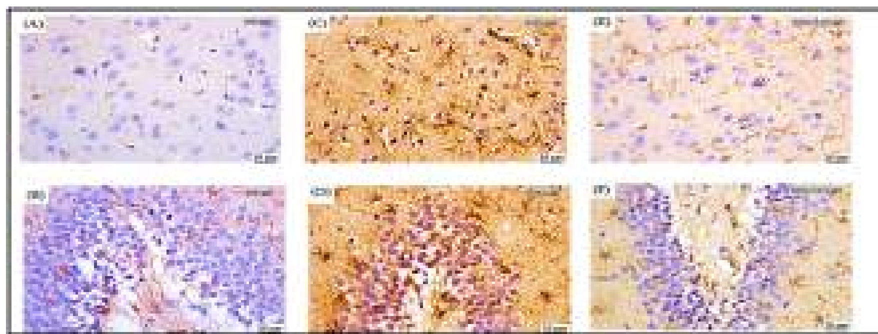

Fig. 11. Immunohistochemical results of GFAP in brain tissue (cerebral cortex (A, C, & E) and hippocampus (B, D, & F), respectively). (A&B) The NC group showed weak GFAP expression in the cerebral cortex and hippocampus. (C & D) The OXL-injected group showed higher GFAP expression in the cerebral cortex and hippocampus. (E & F) The OXL + LUT group showed moderate GFAP expression in the cerebral cortex and hippocampus.

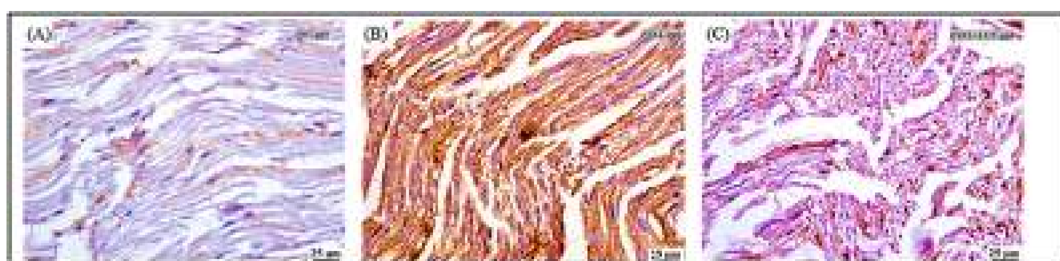

Fig. 12. Immunohistochemical results of GFAP in sciatic nerve tissue. (A) The NC group showed lower GFAP expression in nerve fibers. (B) The OXL-injected group showed higher GFAP expression in nerve fibers. (C) The OXL + LUT group showed moderate GFAP expression in nerve fibers.

Additionally, GFAP expression in the cerebral cortex and hippocampus was significantly higher in the OXL group than in the NC group and OXL + LUT group, according to immunohistochemistry analysis of brain tissue Fig. 11. A-F. When comparing the OXL group to the NC and OXL + LUT groups, the immunohistochemistry analysis of sciatic nerve fibers showed a markedly higher level of GFAP expression Fig. 12. A-C.

Discussion

Central and peripheral neuropathy, caused by the neurotoxic effects of antineoplastic medications, is often seen with platinum-based chemotherapy medicines. One platinum-based chemotherapeutic drug that is specifically used to treat metastatic colorectal cancer is oxaliplatin.[26,27] The severe neurotoxicity and neuropathic pain experienced by over 98% of cancer patients treated with oxaliplatin frequently result in dose reductions or even the cessation of OXL treatment, which impacts tumor control and cancer patient survival.[5,27]

Numerous studies have documented the potential use of flavonoids to treat neuropathic pain and neuritis, which can negatively impact cancer patients' quality of life.[7] Herein, this research aims to evaluate the effect of luteolin in mitigating the neuroinflammatory and neurotoxic effects of OXL and elucidate the possible mechanism by which luteolin ameliorates neuropathic pain.

Neuropathic pain is frequently caused by damage to the nervous system. The symptoms of OXL-induced neuropathy and neutritis include allodynia (pain triggered by typically painless stimuli) or hyperalgesia (increased sensitivity to pain). A person's quality of life may be significantly impacted by pain brought on by a chronic illness.[8] Neuronal damage results in neuropathy, a disruption of nerve function in the central or peripheral nervous systems.[7]

Natural chemicals have gained interest in recent years due to their possible therapeutic applications. Fruits, vegetables, and herbs are rich sources of flavonoids, a class of phytochemicals that are secondary metabolites of plants with a variety of pharmacological actions and safety profiles. They show promise as treatments for neuropathy and chronic inflammation.[8] Numerous therapeutic plants and herbs contain luteolin, a flavone that has been shown to have a wide range of pharmacological effects. The benefits that can be most helpful in managing pain include analgesic, neuroprotective, antioxidant, and anti-inflammatory effects.[9,12] Many herbs and

vegetables, including oregano, thyme, rosemary, lettuce, parsley, cabbage, and kale, contain LUT. Luteolin is a flavanone compound with several medicinal benefits due to its strong anti-inflammatory, antioxidant activity, and neuroprotective effects. Studies reported that flavonoids are a safe natural alternative therapy for alleviating neurotoxicity and neuroinflammation, besides their anticancer properties. [5,7]

The results of this study show that LUT administration mitigates neuropathy induced by OXL through the inhibition of oxidative damage, apoptosis, neuroinflammation, glial activation, and mitochondrial dysfunction.

Oxaliplatin-induced neuropathic pain, as shown in behavioral tests, showed that OXL caused motor dysfunction and increased hypersensitivity to pain. The results of the present study reported that OXL decreased paw latency withdrawal and increased allodynia and hyperalgesia, inducing neuropathic pain that affects the compliance of cancer patients with this antineoplastic drug, which coincides with previous reports. Similarly, a study examined the effect of LUT on the neuropathic pain model induced by chronic constrictive injury of sciatic nerve tissue. The authors concluded that LUT ameliorates behavioral alterations by repressing oxidative stress, neuroinflammation, and neuro-apoptosis. The effect of LUT in combating neuropathic pain is affirmed by decreased allodynia and hyperalgesia, the hallmarks of neuropathic pain. LUT inhibited glial activation and increased BDNF and glial-derived neurotrophic factor levels. [9,20]

Chemotherapeutic drugs often activate rapid ROS production, which disrupts the antioxidant pool. OXL induces platinum–DNA adducts in nuclear and mitochondrial compartments, which trigger ROS production and oxidative damage; thus, OXL is harmful either directly through DNA adduct production or indirectly through mitochondrial malfunction. [4,28] Furthermore, the brain and nervous system are sensitive to oxidative damage due to high oxygen requirements and also high content of polyunsaturated fatty acids. Moreover, ROS overproduction causes lipid peroxidation, DNA damage, and activates a proinflammatory cascade, which compromises nervous system functions and activates apoptotic pathways. [29] HO-1 regulates cellular antioxidant homeostasis, and PON is a regulator of antioxidant enzymes; its activation prevents neurodegeneration. [21]

One of the primary regulators of the pro-inflammatory mediators is the family of serine-threonine kinases known as mitogen-activated protein kinases (MAPK). Oxidative damage triggers MAPK, leading to an excessive buildup of ROS and a proinflammatory cascade. Therefore, excessive ROS generation and the production of pro-inflammatory cytokines are the main effectors in neuroinflammation and neurotoxicity associated with OXL use. [3] In this study, HO-1 and PON-1 activities were reduced, and the gene expression levels of TLR-4, ICAM-1, and MAPK-14 were upregulated in the OXL-treated group, indicating oxidative damage and neuroinflammation.

Moreover, mitochondrial collapse increases the permeability of the blood-brain barrier, which permits OXL to pass through the brain parenchyma and impact the glial and neuronal compartments. This, in turn, accelerates apoptosis and triggers neuroinflammation. [30] Mitochondrial ROS production activates the NADPH oxidase, which further activates ROS production. NADPH oxidase activates mitochondrial apoptosis-inducing factor, which contributes to further oxidative reactions. OXL reduces mitochondrial function by activating NADPH oxidase activity and increasing ROS production. [29] The results of this study revealed that OXL attenuates the heme oxygenase 1/Nuclear factor erythroid 2-related factor 2 complex pathway (HO-1/Nrf2), while activating NADPH oxidase; thus, OXL activates neuro-apoptosis and mitochondrial dysfunction.

Furthermore, MAPK14 upregulation by OXL has been reported to activate caspase-dependent neuronal apoptosis, activation of caspase-3 and Bax activities accelerates the apoptosis process, and the occurrence of central and peripheral neuropathy. [21] Results of this study showed that OXL caused an increase in caspase 3 and Bax activities, MAPK14 expression in the brain and sciatic nerve tissue, thereby activating the apoptotic pathway. [3] According to the previous studies' findings, OXL boosted the activities of caspase-3 and Bax as well as the expression of MAPK14 in brain and sciatic nerve tissue, all of which cause the apoptotic pathway to be activated. [3] This finding is in line with previous research showing that OXL results in mitochondrial malfunction and increases the production of proapoptotic proteins, such as cytochrome c, Bax, and caspase 3, in sciatic nerve tissue. [21] Consistent with our results, previous studies on the neuroprotective effect of luteolin concluded that luteolin regulates a variety of the MAPK signaling pathway targets. Accordingly, LUT treatment prevents the generation of pro-inflammatory cytokines and neuroinflammation. LUT exerts its anti-inflammatory activity by suppressing NF-κB and MAPK pathways, the mainstream targets of the proinflammatory cascade. Thereby, suppressing TLR-4, ICAM-1, and TNF-α and attenuating the proapoptotic genes via the suppression of MAPK signaling. [11]

Furthermore, the maintenance of neuronal survival and the control of synaptic plasticity, neuronal

differentiation, and peripheral and central nervous system regeneration depend on neurotrophins. One of these neurotrophins is a brain-derived neurotrophic factor (BDNF), which also regulates several pro-inflammatory transcriptional factors, such as NF-κB.[29]

Moreover, the glial fibrillary acidic protein (GFAP) regulates astrocyte function, maintains blood–brain barrier integrity, and supports nervous system function. Increased GFAP expression is associated with brain injury and neurological disorders. OXL was shown to increase GFAP expression, leading to central and peripheral neuropathy.[3] Toxic metabolites activate glial cells, generating inflammatory responses. Studies concluded that activated glial cells release several pro-inflammatory cytokines; thus, glial activation induces neuropathic pain.[30] Additionally, activated glial cells and elevated production of proinflammatory mediators, particularly TLR-4 and TNF-α, are characteristics of neuroinflammation caused by OXL.[6] Activated glial cells evoke a proinflammatory cascade by activating the MAPK signaling pathway, thus contributing to neuropathic pain, neuroinflammation, and nerve injury.[31]

Several studies investigated the therapeutic efficacy of natural compounds against neuropathy and neuroinflammation. These phenolic compounds provide antioxidant and anti-inflammatory activities, thus considered a safe natural candidate that supports both glial and neuronal survival against vast injuries. The therapeutic benefits arise from their ability to reverse oxidative imbalance, inhibit apoptosis, glial activation, and neuroinflammation.[30]

Oxidative stress activates several transcription factors. These transcriptional factors induce the expression of inflammatory genes, triggering a neuroinflammatory response.[3] Consequently, OXL-induced neuropathic pain may be treated by targeting the dilemma of oxidative stress and the suppression of the inflammatory signaling response, which was mediated by activated astrocytes.[6] Furthermore, platinum chemotherapeutics induce central and peripheral neuropathy by inducing oxidative stress-related mitochondrial damage. Neurons have high energy demands for signaling and communication; thus, they are severely affected by mitochondrial dysfunction. Recent studies are investigating the efficacy of promising natural antioxidants in reducing neuropathic pain induced by OXL by combating ROS production, thereby preserving the neuron's mitochondrial structure and function.[15] Thus, LUT can be an effective adjuvant therapy for mitigating OXL-induced central and peripheral neuropathy as indicated by the results of this study.

Moreover, flavonoids can alleviate neuropathic pain due to their anti-inflammatory activity by inhibiting vast proinflammatory mediators such as NF-κB, IL-1β, IL-6, and TNF-α.[7] One of the most prevalent flavones, luteolin (3', 4'- 5, 7 tetrahydroxyl flavone), is widely utilized in traditional medicine due to its pharmacological characteristics.[10] Luteolin showed its therapeutic effectiveness in neurodegenerative diseases through a variety of mechanisms, such as the regulation of oxidative injury, apoptosis, and the inflammatory cascade.[8] Additionally, LUT has demonstrated anti-inflammatory properties by inhibiting the activation of astrocytes and microglia, as well as their downstream targets, including toll-like receptors 2 and 4 (TLR2 and TLR4).[11,12] Thus, LUT exerts its neuroprotective effects by activating an antioxidant mechanism and inhibiting inflammatory pathways. This confirms the results of our study.

It is noteworthy that luteolin possesses an effective role in treating several neurodegenerative disorders by decreasing pro-inflammatory and pro-apoptotic gene expression. By activating the NRF-2 complex pathway, LUT lowers ROS levels and increases the expression of antioxidant enzymes like SOD and HO-1 activities. LUT was found to have anti-apoptotic effects by decreasing the activities of caspase 3 and BCL-2 in Parkinson's disease model.[32] Based on these findings, the current study clarified that LUT downregulates the MAPK-14 pathway, which lowers the activities of caspase 3 and Bax in brain and sciatic nerve tissues. Also, the LUT restored the disrupted antioxidant balance caused by OXL by increasing the activities of PON-1 and HO-1 in the brain and sciatic nerve tissues, inhibiting the pro-inflammatory cascade, thus LUT displays a neuroprotective effect against OXL-induced central and peripheral neuropathy by combating oxidative damage and dysregulated neuro-apoptotic cascade.

The same observation was obtained by a study that concluded that luteolin prevents neurotoxicity induced by the neuro-damaging pesticide acetamiprid. LUT protects against neurotoxicity via neutralizing free radicals, preserving nerve tissues from ROS-induced lipid peroxidation, activating antioxidant pools such as SOD, CAT, GP-X, and HO-1/NRF-2 signaling pathway, and also inhibiting neuroinflammation through decreasing levels of IL-1, TNF-α, and NF-κB.[15]

The brain tissue has a low antioxidant pool, a high mitochondrial capacity, and a high oxygen need, making it extremely susceptible to oxidative damage. In concordance with our results, LUT administration tackles senescence induced by D-galactose. This study elucidated the therapeutic utility of LUT in mitigating neuroinflammation, oxidative stress, glial activation,

and neuronal cell loss in hippocampal tissue through decreasing IL-1ßand TNF-α levels, upregulating antioxidant markers, and restoring the disrupted levels of BDNF and GFAP. Also, LUT downregulates caspase 3 gene expression level, providing anti-apoptotic and neuroprotective effects.[16] These observations are consistent with our results.

Moreover, increased ROS production is a cardinal factor in mitophagy and neuronal loss. Thus, a study examined the effect of LUT on glutamate-induced mitophagy and nerve cell loss. Results showed that LUT rescues mitochondria by attenuating oxidative stress, thereby hindering neuronal loss and mitophagy.[33] Another study showed that LUT exhibits a neuroprotective effect via combating excessive ROS production, upregulating the HO-1/NRF2 complex, reducing NADPH oxidase activity, and regulating the autophagy pathway (p62/ Keap-1/NRF2), thus modulating neuronal injury in intracerebral hemorrhage.[19] These studies elucidate the protective effect of LUT on mitochondrial function, which interprets our results. Also, beyond the therapeutic benefits of this natural flavonoid compound, LUT is a widespread flavonoid in several vegetables, healthy foods, and medicinal herbs, which makes it easily available.[10]

Lastly, the histopathological study showed that LUT modulates neuroinflammation and neurodegeneration in the cerebral cortex and hippocampus and protects the sciatic nerve tissue from injury induced by OXL, as confirmed by immunohistological results. A similar observation was reported by a study that examined the effect of LUT on D-galactose-induced senescence, which concluded that the synergistic antioxidant and anti-inflammatory effects of LUT promote normal nerve cell proliferation, differentiation, and maintain normal nerve architecture and function.[16] Thereby, biochemical results were affirmed by histopathological and immunohistochemical observations. Additionally, the molecular docking results were in concordance with the biochemical results; this present study was the first to use in-silico analysis to detect the interaction between luteolin, MAPK-14, and GFAP.

Conclusion

LUT administration inhibits glial activation, represses neuroinflammation and oxidative damage, tackling mitochondrial dysfunction and apoptosis induced by OXL. This study speculated that LUT mitigates the central and peripheral neuropathy associated with OXL treatment due to its antioxidant and anti-inflammatory activities. Thereby, LUT administration with OXL therapy confers a neuroprotective, glioprotective, and neurobehavioral effect, which decreases the OXL-associated morbidity. Future studies may be required to explore the therapeutic activity of LUT nanoparticles or identify miRNA targets for more extensive studies on the luteolin anticancer and neuroprotective effects.

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Author's declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours have been included with the necessary permission for re-publication, which is attached to the manuscript.
- The author has signed an animal welfare statement.
- No human studies are present in the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at Ain Shams University.

Authors' contributions statement

Conceptualization: A.A.R. and N.G.R. Data manipulation: A.A.R. and N.G.R. Formal analysis: A.A.R. and N.G.R. Funding acquisition: no funding. Investigation: A.A.R. and N.G.R. Methods and analysis: A.A.R. and N.G.R. did in vivo studies and biochemical analysis, while O.S. and M. F. A. M. did in-silico molecular docking studies. Project administration: no project. Resources: A.A.R. and N.G.R. Software: A.A.R. and N.G.R. Supervision: A.A.R. and N.G.R. Validation: A.A.R. and N.G.R. Visualization: A.A.R. and N.G.R.. Writing original draft: A.A.R. and N.G.R. wrote the research. While O.S and M. F. A. M. wrote in silico molecular docking study results. Writing–review & editing: A.A.R. and N.G.R.

Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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خفف اللوتيولين من الالتهاب العصبي وتنشيط الخلايا الدبقية في الاعتلال العصبي المركزي والطرفي الناجم عن أوكساليبلاتين في الجرذان

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الخلاصة

يهدف البحث إلى تقييم قدرة لوتيولين على تخفيف التأثيرات العصبية السمية لأوكساليبلاتين. تُعدّ الإصابة التأكسدية، والالتهاب، وخلل الميتوكوندريا العوامل الرئيسية في اعتلال الأعصاب الناتج عن OXL. عدّل LUT التغيرات السلوكية الحسية والحركية الناتجة عن OXL. كما عزز LUT بشكل ملحوظ ($p\leq0.05$) أنشطة مضادات الأكسدة عن طريق زيادة مستويات الباراوكسوناز 1 (PON) والهيم أوكسيجيناز 1 (HO-1)، مما خفف من الضرر التأكسدي. كما ثبّط LUT الالتهاب العصبي عن طريق تثبيط مستويات TLR 4 وICAM 1 ، مع زيادة ملحوظة في عامل التغذية العصبية المشتق من الدماغ (BDNF) وخفض مستوى التعبير الجيني النسبي ل MAPK-14. علاوة على ذلك، خفّض LUT من موت الخلايا العصبية المبرمج (Caspase3; Cysteine aspartate specific protease 3 and Bax; Bcl 2 associated x protein) مما خفف من نشاط الخلايا الدبقية، وأعاد وظيفة الميتوكوندريا. وايضاً انخفض كل من نشاط (NADPH) في نسيج المخ والتعبير المناعي النسيجي لGFAP بواسطة LUT. كما حمى LUT من الإصابة العصبية الناجمة عن OXL، كما هو موضح في الفحص النسيجي المرضي. وأخيرًا، أكدت نتائج الالتحام الجزيئي، ونتائج التجربة البيولوجية، التأثيرات المضادة للالتهابات والحماية العصبية لـ LUT، المرتبطة بـ MAPK-14 وGFAP. تُظهر هذه الدراسة أن LUT يوفر فعالية علاجية واعدة في تخفيف أعراض اعتلال الأعصاب الطرفية والمركزية المصحابة لعلاجOXL من خلال استهداف الخلايا الدبقية لتخفيف الاعتلال العصبي.

الكلمات المفتاحية: GFAP، الخلايا الدبقية، لوتولين، MAPK-14، أوكساليبلاتين، PON-1.