Egypt. J. Chem. **Vol. 65**, No. 6 pp. 433 - 440 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Molecular docking studies and biological evaluation of luteolin on cerebral ischemic reperfusion injury

Zaid Mahdi Jaber Al-Obaidi [a, b]*; Yasmeen Ali Hussein[c]; Dunya AL-Duhaidahawi[d]; Hayder A. Al-Aubaidy[e]

[a]*Department of Pharmaceutical Chemistry, College of Pharmacy, University of Alkafeel, Najaf, Postcode: 54001, Iraq*

[b]*Department of Chemistry and Biochemistry, College of Medicine, University of Kerbala, Karbala, Postcode: 56001, Iraq*

[c]*Department of Pharmacology, College of Pharmacy, University of Alkafeel, Najaf, Postcode: 54001, Iraq.*

[d]*Department of Pharmacognosy, College of Pharmacy; University of Kufa, Najaf, Postcode: 54001, Iraq.*

[e]*School of Life science, LaTrobe University, Bundoora, VIC, Postcode: 3086, Australia.*

Abstract

Introduction: Luteolin is highly distributed within plant species it is approved to be efficacious in the treatment of ischemic stroke caused by inflammation. Ischemic stroke (I/R) damage to the brain is a commonly diagnosed natural outcome of ischemic stroke.

The objectives of this paper are to use in silico molecular modelling to evaluate the primary biomarker proteins with which luteolin binds, as well as the benefits of luteolin in minimizing the harm caused by cerebellar (I/R) injury.

Methodology: The molecular modelling research was performed using AutodockFr. The Bcl-2, Caspase-3, IL-1β, MDA, TLR-2, and TNF-α values were observed, alongside the histological assessment which was used to determine the level of restoration from the cerebellar (I/R) injuries sustained in mouse models.

Results: Docking studies demonstrated that the luteolin structure can interact with both SOCS3/JAK and SYK Enzymes. Concomitantly, the physiological responses showed marked declines within Bcl-2, Caspase-3, IL-1β, MDA, TLR-2, and TNF-α brain chemicals, with huge rises observed with Bcl-2 concentrations. Moreover, the histopathological examination revealed that luteolin decreases ischemic injury.

Conclusions: Lutein could be able to decrease cerebral (I/R) damage by decreasing oxidative stress and trying to exert an anti-apoptotic overall impact.

Keywords: Luteolin docking; in silico studies; cerebral stroke; brain ischemia; toll-like receptor

*Corresponding author e-mail: zaid.alobaidi@alkafeel.edu.iq; zaid.alobaidi@uokerbala.edu.iq
DOI: 10.21608/EJCHEM.2021.106753.4898

1. Introduction

Cerebral stroke is a well-known brain condition that is accompanied by a decrease in the blood flow to the cerebral area that results in insufficient nutrient replenisher and reduced oxygen delivery. Cerebral stroke is one of the deadliest diseases across the world [1]. Cerebral ischemia can result in a variety of pathological alterations, which include high blood barrier (BBB) permeability, senescence, inflammatory processes, oxidative damage, and mitochondrial dysfunction [2,3]. Cerebellar ischemia has been linked to the concept of age-related decline as well as the pathophysiology of neurological conditions such as stroke [4]. Around 4 out of 5 of stroke incidents are confirmed to be caused by cerebral ischemia. Reperfusion, or blood replenishment, is necessary; otherwise, senescence, necrosis, and programmed cell death will occur. Resuscitation can occur naturally or as a consequence of thrombolytic therapy, surgical removal of a blood clot (thrombectomy) with image-driven device stents to interrupt clots or a combination of these treatments [5]. Immediate reperfusion after cerebral ischemia is crucial. Nevertheless, it has some adverse implications known as "reperfusion injury" [6].

Despite the advantages of oxygen replenishment through reperfusion, fast reperfusion inhibits brain activity, triggering massive pathologies after stroke [7]. Several mechanisms, including oxidative stress and free radical production, are known to play essential roles in the progression of reperfusion injury. Furthermore, reperfusion may result in leukocyte infiltration. Mitochondria may also be involved. It can also cause platelet activation and interrupt the BBB, leading to brain edema or severe bleeding and nerve cell death [5]. The pathogenicity of ischemic stroke (I/R) injury is intimately correlated to inflammatory and oxidative stress via reactive oxygen generation [8]. When ROS levels are too high, they can cause induced oxidative injuries such as DNA strand breaks, protein oxidation, and peroxidation, which can lead to cell apoptotic cell death [8–10]. The inflammatory process is a multifaceted neurochemical reaction involving natural killer (NK) cell types and phagocytic macrophages that are triggered by different molecular signalling via inflammatory cytokines such as tumor necrosis factor (TNF) and nitrous oxide (NO), which are highly toxic to both infective microbes and host cells and can potentially cause cellular injury. Although inflammatory response is an essential defensive measure in the human body, it can also cause health issues if the reactions proceed, likely to result in inflammatory chronic illnesses [11]. The SIRT3 gene resulted in massive inhibition of the mediated antioxidants triggered 5'Amp activated protein kinase (AMPK). and can deacetylate and stimulate LKB1, resulting in AMPK phosphorylation. Moreover, because AMPK is an important modulator of MTOR and Unc-51 autophagy, it is possible to conclude that SIRT3 is a major determinant of signalling via AMPK/mTOR [12] (as illustrated in Figure 1).

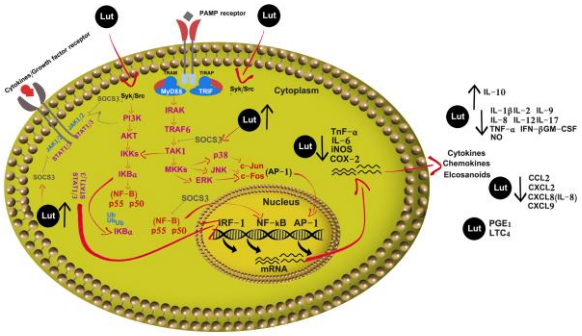

Figure 1. Different schematics of inflammatory signals paths targeted by luteolin.

Toll-like receptors abbreviated TLR's are transmembrane spanning protein receptors (a.k.a G protein-coupled receptors) that identify sustained pathogens or molecules in addition to molecular prototypes associated with intracellular tension or disruption in the immune reaction and initiate provocative inflammatory responses. Toll-like receptors type 2 and 4 (TLR2 and TLR4) act an important function in the progression of ischemic stroke morbidity caused by shortage of blood and oxygen supply (ischemia) and reperfusion injury (reoxygenation injury) [13]. Luteolin was chosen due to its inhibitory activity towards TLR2 and TLR4. It can modify cerebral damage caused by cerebral hypoperfusion and ischemia or reperfusion by suppressing TLR2 and TLR4 interpretation, as well as suppressing the production of the cytokines of the pro-generating reactive molecules NF-κB, iNOS, COX-2, TNF-α and IL-6 [14]. Luteolin is a type of flavonoid (Fig. 2) that has several advantageous effects, such as reduction of oxidative damage, inflammation inhibitory impact, apoptotic cell death

inhibitory effect, and tissue damage reduction [11,12].

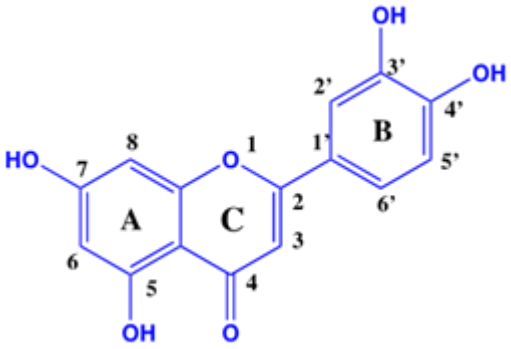

Figure 2. Luteolin structure with four hydroxyl groups linked to the flavone building nuclei at 5-, 7-, 3′-, and 4′-sites.

Besides that, Luteolin enhanced neurological disorders in I/R damage by counteracting pathologies, inhibiting cell death and inflammation, and enhancing the formation of new neurons in the CNS (hippocampal neurogenesis). Apart from improving signalling via AMPK/mTOR, Lutein may also stimulate SIRT3 expression in the cortex and hippocampus after the ischemic stroke, resulting in activation of the downstream opposing forces signalling pathways AMPK/mTOR and, consequently, recovery of cells. However, further study is essential to comprehend the luteolin mechanism to stimulate SIRT3/AMPK/mTOR signal transduction. Since inflammatory response within the brain is a complicated neurological condition that commonly outcomes from unusual interference of the microglia in a provoking path that leads to an efficacious strategy for the treatment of degenerative disorders. It was identified that luteolin suppresses the output of IL-31 and IL-33, and also their release, at the gene expression level. As a result, it is postulated that it is essential for improving neurodegenerative diseases considering IL-31 and IL-33[15]. It was found that anti-inflammatory actions of luteolin are linked to the following aspects; 1) the inhibition of inducible nitric oxide synthase (iNOS) interpretation; 2) Nitrous oxide production; 3) Scavenging of oxygen free radicals and Reactive Oxygen Species (ROS) and inhibition of radical formation; 5) The antioxidant activating capability of the correlated enzymes; 6) Inhibition of the formation of leukotrienes; 7) Proinflammatory cytokine neutralization. In addition, luteolin inhibits the protein kinase B (AKT), the mitogen-activated protein kinase (MAPK). Interestingly, luteolin tends to work partially due to the ATP block of tyrosine-protein kinase enzyme (Syk) or proto-oncogene (c-Src), and the exact mode of action was discovered utilizing molecular modelling experiments [16,17]. Luteolin suppressed pro-inflammatory agent expression and leukocyte infiltration, reducing LPS-induced inflammation significantly. Furthermore, luteolin decreased cytokine-stimulated interleukin-8 (IL-8) and cyclooxygenase-2 (COX-2) levels significantly [18]. Since luteolin suppresses inflammation and protects the hippocampus from AB40-induced injury, it is also useful as a therapy for neurological disorders [19]. Microglial cell activation is reduced significantly by hippocampus inflammatory inhibitors [12]. In addition, shown in Figure 1, it suppressed COX-2 and iNOS, which minimized neuroinflammation after spinal cord injury.

The C6-C3-C6 framework in luteolin is unusual, including two benzene rings linked by a double-bound C2-C3 and an oxygen atom. The therapeutic uses of luteolin and other flavonoids are attributed to the existence of functional OH groups in the two benzene rings at carbons of C3', C4' and C5, C7 as well as the presence of double bonds of carbon-carbon (C=C). The anti-inflammatory effects of luteolin have been linked to interfering isozyme synthase inducible nitric oxide (iNOS), Interpretation and suppression of iNOS. The resonance stability of the phenoxy radical luteolin can easily provide radical species with hydrogen, suppressing chain reaction to free radical generated. The most active functionality in flavonoids is a 3,4-dihydroxy framework in the phenolic B ring (catechol groups), which is essential for their antioxidant property. On the pyrazyl C ring of luteolin, a C2-C3 it's a double connection, in particular, a 1.4 pyrone cluster, together with a 4-oxo characteristic, offers flexible electrons to delocalize around the rings A, B and C, leading to the generation of a much more longstanding phenoxy radical. Luteolin is already a potent inhibitor of 5-LOX, a key regulator in the production of leukotriene B4, which is related to some inflammatory conditions. Luteolin connects to the allosteric iron atom in 5-lipooxygenase (5-LOX) and binds to two amino acids residues to form stable hydrogen bonds, at (His367 and Thre 364) histidine and threonine respectively, according to molecular docking observations [20]. Since cyclooxygenases and lipoxygenases both produce ROS, their inhibition can be related to ROS inhibition. Luteolin is a multi-purpose anti-inflammatory compound, including ROS scavenging and antioxidant activity. Lutein was

also studied in terms of molecular interactions, and it was discovered that it interacts with JNK at the ATP-binding site.

Hytti et al., 2015 reported that flavones have a higher level of suppressive activity in anti JNK3 than p38a [11]. Luteolin-7-O-glucoside, an unusual flavone glycoside that JNK3 is inhibited 35 times more than p38a [21]. The anti-inflammatory activity of luteolin has been shown to rely heavily on ATP sites of Src and Syk kinase [16,17]. The GRID and molecular modelling experimental studies have thus revealed a mechanism for the intervention of Src group kinases in flavonoid inhibitory activity, however, this pathway has been associated with certain flavone constituents such as quercetin, apigenin and catechin. Thus, luteolin like apigenin may be fully bound to the kinase proteins of the Src family. Hence, in this research study, the authors conducted molecular docking studies of luteolin with the inhibitor's interaction of Syk and SOCS3/JAK kinases and compared these theoretical docking experiments with the potent inhibitors of apoptotic and inflammatory aspects in animal models.

2. Experimental

This work was performed under animal protection provisions and health research lab standards, and it was approved by the Institutional Animal Ethics Committee (IACUC) at the University of Alkafeel, College of Pharmacy. Twenty-eight normal healthy mice weighted 20-30 g have been obtained from the University of Kufa's College of Science. Sigma-Aldrich in Germany supplemented the luteolin. More than 98% purity was obtained. Just before the animal model, luteolin was immediately primed by suspending it in the saline solution until fully dissolved. A total of 28 male mice were used in this experiment and assigned at random to one of four groups (7 mice in each): luteolin test group, normal control, control vehicle group, and sham group: the mice were easily accessible to the clinical technique from the vital coronary artery route was not obscured. The molecular modelling experiments were carried out using the Autodock FR. The human protein crystal structure was obtained as PDB files were obtained from the 3d protein data bank portal. with a particular protein code of (PDB ID: 4GL9 and 4fl2), whereas the structure of compound luteolin was acquired as SDF format from PubChem database systems. Following that, the structure's energy was diminished, and a 3D model was created for molecular modelling. This was done with version 19.1.0.8 of the Thermo ChemDraw program, and the Chimera tool was used for the charges, bond visualization, H-bond, and distance measurement. The controlled study (induced ischemia): Mice are subjected to surgery and have their normal carotid artery occluded for 30 min. The vehicle group in charge is: For 30 minutes, mice were given an intraperitoneal (IP) infusion of luteolin saline solvent. A 2-hour reperfusion period was then accompanied [22]. The luteolin research group: Mice were given a 25 mg/kg intraperitoneal injection of luteolin [23].

The mouse model was created by provoking frameworks of middle carotid artery blockages. The mice 'body temperature was maintained constant throughout the procedure at 37°C. Animals were anaesthetized by intraperitoneal injection chloral hydrate of 350 mg/kg from the start of the procedure [22]. They were separated and severed the left common carotid artery. A laser Doppler flowmeter was used to survey the blood perfusion in the brain area [24]. Following that, monofilament nylon has been removed and reperfused for 120 minutes [25]. The BCL-2, caspase-3, IL-1β, MDA, MPO, TLR-2, and TNF-α levels in the brain were limited. However, root tissues were assessed utilizing the ELISA technique the particular methodologies were cautiously selected according to the pack's instructions. In other words, the mice tissues, incubated within a saline solution, were homogenized kept in phosphate buffer containing the protease inhibitor molecules and thrown out the rest of it (i.e. the supernatant). Hematoxylin and eosin (HE) cerebral tissue staining: tiny brain segments were preserved in 10% formaldehyde then were embedded in the paraffin. Then cut 4-8mm slices. Eventually, Hematoxylin and eosin staining was used (H & E) to stain the components to dissect the psychopathic life structures accomplished by the pathological features. Data analysis performed with SPSS version 22-IBM/USA) was used to undertake factual examinations. Information was addressed utilizing means and SD of errors. Within-group variability was evaluated using variance test and LSD post hoc assessments. At 0.05, the P-value was considered relevant.

3. Results and discussion

3.1 Luteolin molecular docking studies

This study shows that the luteolin compound has a representative score function within the proteins shown in figures 3 and 4.

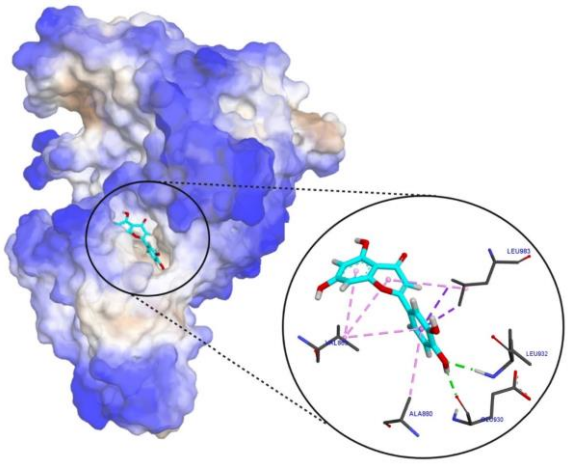

Figure 3. Docking results of luteolin interaction with SOCS3 protein. Luteolin chemical structure is sketched and represented in the stick-model interacting with the active site of SOCS3 protein. The types of interactions explained in Figure S1.

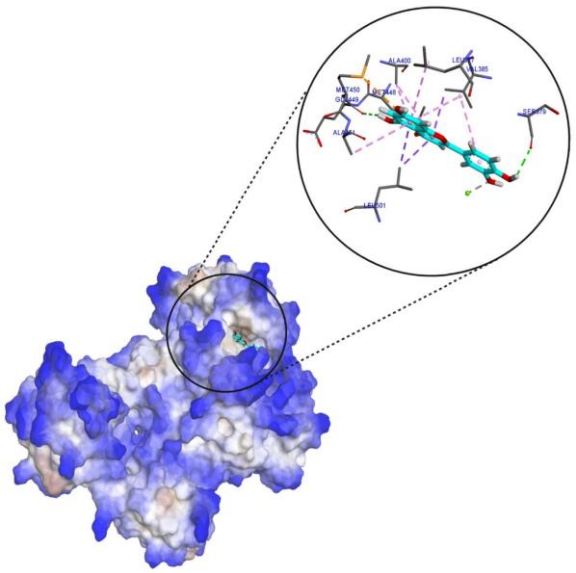

Figure 4. Docking results of luteolin interaction with SyK protein. Luteolin chemical structure is sketched and represented in the stick-model interacting with the active site of SOCS3 protein. The types of interactions explained in Figure S2.

Employing in silico studies, Syk (PDB ID: 4FL2) and SOCS3 (PDB ID: 4GL9) proteins were utilized as a harbour for the luteolin three-dimensional structure. The utilized protein was processed by hydrogen atoms addition and water molecules extraction and adding a Gasteiger charge. Following that, the optimally luteolin conformation was chosen as the potential bind pose for the molecular modelling research (shown in figure 1 and figure 2), with the observed scores of -5.15 Kcal/mol and 5.17 Kcal/mol for the SOCS3-Luteolin and the Syk-luteolin complexes, respectively.

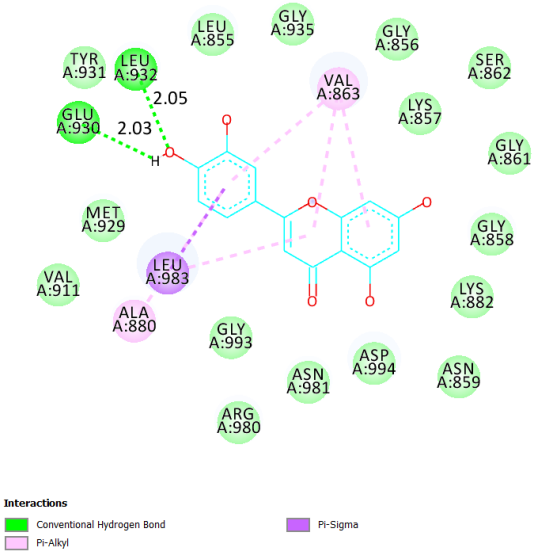

Figure S 1. The 2-dimensional interaction of SOCS3-luteolin complex.

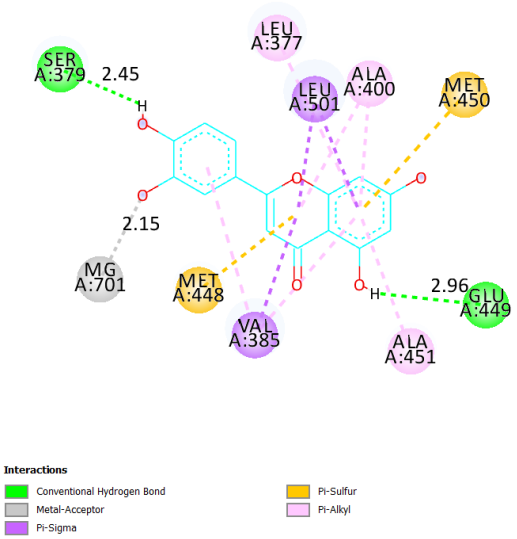

Figure S 2. The 2-dimensional interaction of Syk-luteolin complex.

Regarding the SOCS3-Luteolin complex, the luteolin molecule is capable to form a couple of H-bonding with the residues Glu449O... HNLeu932 distance of 2.05 Aº) and Glu930H...OGlu930

distance of 2.035 Aº) (revealed in fig. S1). In addition, luteolin exhibited lipophilic tendencies toward surrounding residues Leu983, Val863, and Ala880.

Luteolin could establish H-bonding with Glu 449 (H... OLeu932 with 2.96Aº length) and Ser 379 (H... HSer 2.45 Aº distance) of another receptor Sky. Furthermore, Luteolin formed lipophilic interactions considering the nearby amino acid residues, namely; Ala 400, Ala 451, Leu 377, Leu 501, and Val 385. Luteolin also constructed metal-acceptor connections with the cationic Magnesium atom. Met 448 and Met 450 provided a different sort of interaction with luteolin (Pi with Sulfur kind interaction).

3.2 The luteolin effect on proinflammatory cytokines (IL-B, TLR-2, and TNF)

The levels of TNF-α, IL-β and TLR-2, in the brain, were substantially higher in the group of the control, especially when considered in contrast with the animal group of the sham ($P \leq 0.05$). Nevertheless, the levels of cerebral IL-β, TLR-2, and TNF-α were found to be reduced within the group managed with luteolin compared to the control animal group ($P \leq 0.05$), and can be seen in figure 5.

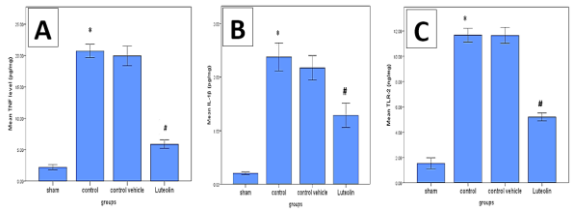

Figure 5. The average of brain concentrations of inflammatory markers: (A) Tumor Necrotic Factor-(TNF-α); (B) Interleukin (IL-1β); and (C) Toll-like Receptor-2 (TLR-2). The four study sessions: Group of the control study, Sham, Group study control vehicle, and a group treated with luteolin. *P* values of ≤0.05 were considered to be significant.

3.3 Luteolin's impact on apoptotic caspase-3 and BCL-2 markers

When compared to a sham study group, the control group's caspase-3 levels were extremely high (shown in Figure 6).

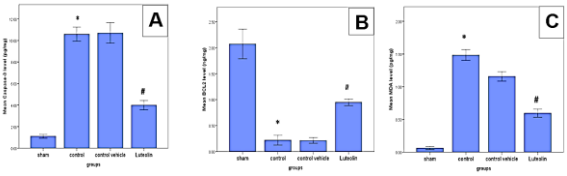

Figure 6. Depicts the average brain levels of apoptotic markers: (a) the caspase-3, (b) the BCL-2, and (c) the malondialdehyde (M D A) in all categories of animal groups; Group of the control study, Sham, Group study control vehicle, and group treated with luteolin. The P value was≤ 0.05, which was considered significant.

In contrast, the control group's Bcl2 threshold was significantly lower., particularly when compared to the sham group (P 0.05).

3.4 Luteolin's effect on oxidative stress markers (MDA)

In the control study group, brains' MDA values have been identified to be considerably elevated for the sham group. Likewise, in comparison to the group of control ($P \leq 0,05$), can be seen in Figure 5, a group of luteolin has significantly higher levels.

3.5 An examination of histopathology

Hemotoxin and eosin were used to stain mouse brain sections (H & E). Groups of vehicle control and control had swelling, whereas the group of Sham Study had normal brain tissue. When compared to the other groups, the group treated with luteolin had significantly less intensity of edema, as shown in Figure 7.

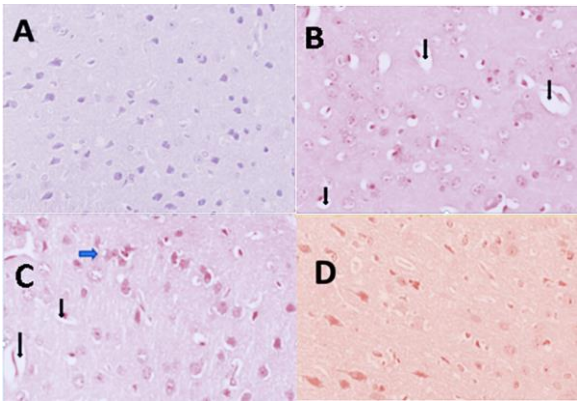

Figure 7. H and E staining of mouse tissue samples of the four research groups: (A) The group of Sham had ordinary brain cells; (B) Group of the control study; (C) Group study control vehicle had substantial swelling, and (D) the group treated with luteolin had lower swelling than the two groups.

There has been observed that substantial growth in the number of inflammatory diseases, accompanied by an increase in TNF-α, IL-β, and TLR-2 in the research group versus the treated controls sham. As a consequence, the research results are consistent with earlier findings [26], which indicate a strong rise in cytokines in hepatic ischemia. Furthermore, the present findings are consistent with those of other studies [27], whereas the existence of Toll-like receptors is critical and causes gastrointestinal and hepatocellular infarction. Moreover, lower cerebellar amounts of TNF-, IL-B, and TLR-2 have been observed in the group treated with luteolin compared to the control group given a vehicle (P 0.05), which is consistent with the findings of another investigator [23] who found that luteolin had such a substantial

preventive role on myocardial ischemia, which may be associated with the dysregulation of TLR4-mediating proteins. The vehicle control group in comparison to the luteolin group had a relatively low concentration of Caspase-3 and a greater elevated value of Bcl2 (P 0.05). These findings are in agreement with other research results [28], as serious alterations in the inflammatory response and a degeneration: cell death often accompanies neuronal enzyme function of the caspase-3 pathway and In mice, Bcl-2 is regulated with ischemic stroke. Consequently, it can be revealed that luteolin can defend the cerebral tissue against damage, most probable via reducing the cell damage associated with oxygen-derived free radicals, apoptosis, and regulating claudin-5 interpretation.

From a histological standpoint, it is evident the rational difference was statistically significant between both the ischemic reperfusion of the control group and that of the sham group, with the cerebral tissue of the control study group showing slight to significant damage [29]. This supports the notion that following ischemic brain damage, a variety of dangerous processes occur, including unnecessary oxidation and disruption of detoxification frameworks. Such advancements disrupt the brain tissue's regular antioxidant defense capacity [30].

4. Conclusion

The current results suggest that luteolin protects mouse brain tissues from ischemic reperfusion injuries. This is due to its antioxidant, anti-inflammatory, and anti-apoptotic properties.

5. Conflicts of interest

“There are no conflicts of interest declared by the authors.”

6. Institutional Review Board Statement

“The research followed the Declaration of Helsinki's protocols and was authorized by Alkafeel University's Institutional Review Board (protocol code/ Ref. No. 414)”

7. Formatting of funding sources

“No external funding was used for this study.”

8. Acknowledgments

The authors express their gratitude to the authorities at the University of Alkafeel, the University of Kerbala, and the University of Kufa for offering their Laboratories to conduct this study.

9. References

[1] Hussien YA, Abdalkadim H, Mahbuba W, Hadi NR, Jamil DA, et al. (2020) The Nephroprotective Effect of Lycopene on Renal Ischemic Reperfusion Injury: A Mouse Model. Indian J Clin Biochem 35: 474–481.

[2] Chen Z, Xu Q, Shan C, Shi Y, Wang Y, et al. (2019) Borneol for regulating the permeability of the blood-brain barrier in experimental ischemic stroke: preclinical evidence and possible mechanism. Oxid Med Cell Longev 2019.

[3] Khoshnam SE, Winlow W, Farzaneh M, Farbood Y, Moghaddam HF (2017) Pathogenic mechanisms following ischemic stroke. Neurol Sci 38: 1167–1186.

[4] Sommer CJ (2017) Ischemic stroke: experimental models and reality. Acta Neuropathol (Berl) 133: 245–261.

[5] Lin L, Wang X, Yu Z (2016) Ischemia-reperfusion injury in the brain: mechanisms and potential therapeutic strategies. Biochem Pharmacol Open Access 5.

[6] Surinkaew P, Sawaddiruk P, Apaijai N, Chattipakorn N, Chattipakorn SC (2018) Role of microglia under cardiac and cerebral ischemia/reperfusion (I/R) injury. Metab Brain Dis 33: 1019–1030.

[7] Levine SR, Khatri P, Broderick JP, Grotta JC, Kasner SE, et al. (2013) Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: part 1: rapidly improving stroke symptoms. Stroke 44: 2500–2505.

[8] Zeng J, Zhu L, Liu J, Zhu T, Xie Z, et al. (2019) Metformin protects against oxidative stress injury induced by ischemia/reperfusion via regulation of the lncRNA-H19/miR-148a-3p/Rock2 axis. Oxid Med Cell Longev 2019.

[9] Wei H, Li Y, Han S, Liu S, Zhang N, et al. (2016) cPKCγ-modulated autophagy in neurons alleviates ischemic injury in brain of mice with ischemic stroke through Akt-mTOR pathway. Transl Stroke Res 7: 497–511.

[10] Huang J, Manaenko A, Ye Z, Sun X, Hu Q (2016) Hypoxia therapy--a new hope for the treatment of mitochondrial dysfunctions. Med Gas Res 6: 174.

[11] Hytti M, Piippo N, Korhonen E, Honkakoski P, Kaarniranta K, et al. (2015) Fisetin and luteolin protect human retinal pigment epithelial cells from oxidative stress-induced cell death and regulate inflammation. Sci Rep 5: 1–13.

[12] Lin TY, Lu CW, Wang SJ (2016) Luteolin protects the hippocampus against neuron impairments induced by kainic acid in rats. Neurotoxicology 55: 48–57.
[13] Wang Y, Ge P, Zhu Y (2013) TLR2 and TLR4 in the brain injury caused by cerebral ischemia and reperfusion. Mediators Inflamm 2013.
[14] Aziz N, Kim M-Y, Cho JY (2018) Anti-inflammatory effects of luteolin: A review of in vitro, in vivo, and in silico studies. J Ethnopharmacol 225: 342–358.
[15] Che DN, Cho BO, Kim J, Shin JY, Kang HJ, et al. (2020) Effect of luteolin and apigenin on the production of IL-31 and IL-33 in lipopolysaccharides-activated microglia cells and their mechanism of action. Nutrients 12: 811.
[16] Lee J-O, Jeong D, Kim M-Y, Cho JY (2015) ATP-binding pocket-targeted suppression of Src and Syk by luteolin contributes to its anti-inflammatory action. Mediators Inflamm 2015.
[17] Lee YS, Kim MS, Lee DH, Kwon TH, Song H-H, et al. (2015) Luteolin 8-C-β-fucopyranoside downregulates IL-6 expression by inhibiting MAPKs and the NF-κB signaling pathway in human monocytic cells. Pharmacol Rep 67: 581–587.
[18] Yao Z-H, Yao X, Zhang Y, Zhang S, Hu J (2018) Luteolin could improve cognitive dysfunction by inhibiting neuroinflammation. Neurochem Res 43: 806–820.
[19] Zhang J-X, Xing J-G, Wang L-L, Jiang H-L, Guo S-L, et al. (2017) Luteolin inhibits fibrillary β-Amyloid1–40-induced inflammation in a human blood-brain barrier model by suppressing the p38 MAPK-mediated NF-κB signaling pathways. Molecules 22: 334.
[20] Kutil Z, Temml V, Maghradze D, Pribylova M, Dvorakova M, et al. (2014) Impact of wines and wine constituents on cyclooxygenase-1, cyclooxygenase-2, and 5-lipoxygenase catalytic activity. Mediators Inflamm 2014.
[21] Goettert M, Schattel V, Koch P, Merfort I, Laufer S (2010) Biological evaluation and structural determinants of p38α mitogen-activated-protein kinase and c-Jun-N-terminal kinase 3 inhibition by flavonoids. Chembiochem 11: 2579–2588.
[22] Hong X, Zhao X, Wang G, Zhang Z, Pei H, et al. (2017) Luteolin treatment protects against renal ischemia-reperfusion injury in rats. Mediators Inflamm 2017.
[23] Qiao H, Dong L, Zhang X, Zhu C, Zhang X, et al. (2012) Protective effect of luteolin in experimental ischemic stroke: upregulated SOD1, CAT, Bcl-2 and claudin-5, down-regulated MDA and Bax expression. Neurochem Res 37: 2014–2024.
[24] Michalinos A, Chatzimarkos M, Arkadopoulos N, Safioleas M, Troupis T (2016) Anatomical considerations on surgical anatomy of the carotid bifurcation. Anat Res Int 2016.
[25] Cheng X, Zhang F, Li J, Wang G (2019) Galuteolin attenuates cerebral ischemia/reperfusion injury in rats via anti-apoptotic, anti-oxidant, and anti-inflammatory mechanisms. Neuropsychiatr Dis Treat 15: 2671.
[26] He X, Zheng Y, Liu S, Shi S, Liu Y, et al. (2018) MiR-146a protects small intestine against ischemia/reperfusion injury by down-regulating TLR4/TRAF6/NF-κB pathway. J Cell Physiol 233: 2476–2488.
[27] Damman J, Daha MR, van Son WJ, Leuvenink HG, Ploeg RJ, et al. (2011) Crosstalk between complement and Toll-like receptor activation in relation to donor brain death and renal ischemia-reperfusion injury. Am J Transplant 11: 660–669.
[28] Erfani S, Khaksari M, Oryan S, Shamsaei N, Aboutaleb N, et al. (2015) Nampt/PBEF/visfatin exerts neuroprotective effects against ischemia/reperfusion injury via modulation of Bax/Bcl-2 ratio and prevention of caspase-3 activation. J Mol Neurosci 56: 237–243.
[29] Li X, Huang L, Liu G, Fan W, Li B, et al. (2020) Ginkgo diterpene lactones inhibit cerebral ischemia/reperfusion induced inflammatory response in astrocytes via TLR4/NF-κB pathway in rats. J Ethnopharmacol 249: 112365.
[30] Noll JM, Li Y, Distel TJ, Ford GD, Ford BD (2019) Neuroprotection by exogenous and endogenous neuregulin-1 in mouse models of focal ischemic stroke. J Mol Neurosci 69: 333–342.