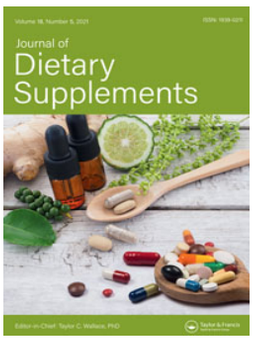

Journal of Dietary Supplements

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijds20

Luteolin Attenuates Glycerol-Induced Acute Renal Failure and Cardiac Complications Through Modulation of Kim-1/NF-κB/Nrf2 Signaling Pathways

Ademola Adetokunbo Oyagbemi, Olumuyiwa Abiola Adejumobi, Temitayo Olabisi Ajibade, Ebunoluwa Racheal Asenuga, Jeremiah Moyinoluwa Afolabi, Blessing Seun Ogunpolu, Olufunke Olubunmi Falayi, Fasilat Oluwakemi Hassan, Enivwenaye Williams Nabofa, Temidayo Olutayo Omobowale, Olufunke Eunice Ola-Davies, Adebowale Benard Saba, Adeolu Alex Adedapo, Oluwafemi Omoniyi Oguntibeju & Momoh Audu Yakubu

To cite this article: Ademola Adetokunbo Oyagbemi, Olumuyiwa Abiola Adejumobi, Temitayo Olabisi Ajibade, Ebunoluwa Racheal Asenuga, Jeremiah Moyinoluwa Afolabi, Blessing Seun Ogunpolu, Olufunke Olubunmi Falayi, Fasilat Oluwakemi Hassan, Enivwenaye Williams Nabofa, Temidayo Olutayo Omobowale, Olufunke Eunice Ola-Davies, Adebowale Benard Saba, Adeolu Alex Adedapo, Oluwafemi Omoniyi Oguntibeju & Momoh Audu Yakubu (2021) Luteolin Attenuates Glycerol-Induced Acute Renal Failure and Cardiac Complications Through Modulation of Kim-1/NF-κB/Nrf2 Signaling Pathways, Journal of Dietary Supplements, 18:5, 543-565, DOI: 10.1080/19390211.2020.1811442

To link to this article: https://doi.org/10.1080/19390211.2020.1811442

JOURNAL OF DIETARY SUPPLEMENTS
2021, VOL. 18, NO. 5, 543–565
https://doi.org/10.1080/19390211.2020.1811442

Taylor & Francis
Taylor & Francis Group

ARTICLE

Luteolin Attenuates Glycerol-Induced Acute Renal Failure and Cardiac Complications Through Modulation of Kim-1/ NF-κB/Nrf2 Signaling Pathways

Ademola Adetokunbo Oyagbemi, DVM, MSc, PhD, FCVSN[a], Olumuyiwa Abiola Adejumobi, DVM, MSc, FCVSN[b], Temitayo Olabisi Ajibade, DVM, MSc, PhD, FCVSN[a], Ebunoluwa Racheal Asenuga, DVM, MSc[c], Jeremiah Moyinoluwa Afolabi, DVM, MSc[b], Blessing Seun Ogunpolu, DVM, MSc[b], Olufunke Olubunmi Falayi, DVM, MSc[d], Fasilat Oluwakemi Hassan, DVM, MSc[a], Enivwenaye Williams Nabofa, PhD[e], Temidayo Olutayo Omobowale, DVM, MSc, PhD, FCVSN[b], Olufunke Eunice Ola-Davies, DVM, MSc, PhD, FCVSN[a], Adebowale Benard Saba, DVM, MSc, PhD[d], Adeolu Alex Adedapo, DVM, MSc, PhD[d], Oluwafemi Omoniyi Oguntibeju, PhD[f], and Momoh Audu Yakubu, PhD[g]

[a]Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria; [b]Department of Veterinary Medicine, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria; [c]Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Benin, Benin City, Nigeria; [d]Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria; [e]Department of Physiology, Ben-Carson (Snr) School of Medicine, Babcock University, Ilishan-Remo, Ogun State, Nigeria; [f]Department of Biomedical Sciences, Faculty of Health and Wellness Sciences, Cape Peninsula University of Technology, Bellville, South Africa; [g]Department of Environmental & Interdisciplinary Sciences, College of Science, Engineering & Technology, Vascular Biology Unit, Center for Cardiovascular Diseases, COPHS, Texas Southern University, Houston, TX, USA

ABSTRACT

Acute renal failure (ARF) has been documented as a life-threatening disease with high morbidity and mortality. We investigated the protective effect of Luteolin against ARF. In this study, forty-male Wistar albino rats were randomly divided into four groups ($n = 10$). Group A received normal saline. Group B received glycerol (10 ml/kg BW, 50% v/v in sterile saline, i.m.). Groups C and D were pretreated with Luteolin 100 and 200 mg/kg for 7 days, and thereafter administered Glycerol (10 ml/kg BW, 50% v/v in sterile saline, i.m.). Administration of glycerol significantly increased systolic blood pressure, diastolic blood pressure and mean arterial pressure. Renal protein carbonyl and xanthine oxidase increased significantly while significant reduction in the activity of renal glutathione peroxidase, glutathione S-transferase and glutathione reductase was observed in the glycerol intoxicated rats. Furthermore, administration of glycerol led to significant increases in serum creatinine and blood urea nitrogen together with reduction in nitric oxide (NO) bioavailability. Immunohistochemistry revealed that glycerol intoxication enhanced expressions of kidney injury molecule 1, nuclear factor kappa beta and cardiac troponin (CTnI). However, Luteolin pretreatment normalized blood pressure, reduced markers of oxidative stress, renal

KEYWORDS

Acute renal failure; glycerol; Luteolin; phytochemicals

CONTACT Ademola Adetokunbo Oyagbemi ademola.oyagbemi778@gmail.com Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria

damage, and improved NO bioavailability. Luteolin also downregulated the expressions of kidney injury molecule 1, nuclear factor kappa beta and cardiac troponin. Together, Luteolin might open a novel therapeutic window for the treatment of acute renal failure and cardiac complication.

Introduction

Acute renal failure (ARF) has been documented as a life-threatening disease with high morbidity and mortality (Kim et al. 2010; Wang et al. 2011; Park et al. 2012; Boozari and Hosseinzadeh 2017) Rhabdomyolysis is a leading cause of acute kidney injury (AKI) and its pathophysiological process has been shown to involve oxidative stress and inflammation (Gu et al. 2014; Xu et al. 2015; Cebi et al. 2016). The clinical syndrome of rhabdomyolysis is caused by injury of skeletal muscles, leading to the release of various intracellular muscle constituents, including severe electrolyte disorders and precipitation of ARF (Polderman 2004). However, oxidative stress has been reported to be involved in the pathogenesis of rhabdomyolysis-induced ARF (Basnakian et al. 2002; Liu et al. 2013). ARF has been reported as one of the most common problems observed in hospitalized critically ill patients with renal failure (Unis 2015). Iron, free radicals and nitric oxide (NO) have also been reported to play a critical role in the pathogenesis of glycerol-induced myoglobinuric ARF (Aydogdu et al. 2006). Despite several years of research, effective treatments have not been identified against ARF-induced pathologies. The herbal medicine and the use of phytochemicals have been introduced as a novel therapeutic agents for prevention of ARF (Unis 2015).

There has been much effort to develop beneficial agents and plant derived products from medicinal plants with the aim of achieving nephroprotective effect. Luteolin (3′,4′,5,7-tetrahydroxyflavone), is a flavonoid that is abundantly present in fruits, vegetables, and medicinal herbs, with various pharmacology and medicinal proprieties for treating various diseases, such as hypertension, inflammatory disorders, and cancer (Chen et al. 2018; Roy and Chakraborty 2018).

Luteolin has been found to protect against myocardial ischemia/reperfusion (I/R) injury and improves cardiac dysfunction (Zhang et al. 2017). The anti-inflammatory and neuroprotective effects of Luteolin has also been reported (Nabavi et al. 2015; Kooti and Daraei 2017). Furthermore, Luteolin has been reported to protect against colistin/cisplatin-induced nephrotoxicity, diabetic nephropathy, and lipopolysaccharide- (LPS-) induced acute renal injury (Kang et al. 2011; Domitrović et al. 2013; Arslan et al. 2016; Xin et al. 2016). Previous studies have demonstrated the antihypertensive and vasorelaxation effects of Luteolin (Qian et al. 2010; Lv et al. 2013; Si et al. 2014; Yang et al. 2017). The global incidence of ARF and hypertension is increasingly becoming worrisome in the last two decades, and this has necessitated the use of phytonutrients as novel therapeutic agents for preventing, ameliorating, mitigating or treating ARF in human (Atwa et al. 2016; Gois et al. 2016; Wu et al. 2017; Yalçınkaya et al. 2018). Recently, luteolin has been suggested as a potential chemopreventive and chemotherapeutic agent against human colon cancer (Chen et al. 2018). In this study, the protective effect of Luteolin against ARF might provide a new insight into the treatment of glycerol-induced rhabdomyolysis-related ARF.

Materials and methods

Chemicals

Luteolin, glycerol, xylenol orange (XO), potassium hydroxide, reduced glutathione (GSH), oxidized glutathione (GSSG), sodium fluoride, thiobarbituric acid (TBA), trichloro acetic acid (TCA), sodium hydroxide, O-dianisidine, hydrogen peroxide (H_2O_2), and 1,2-dichloro-4-nitrobenzene, were purchased from Sigma (St. Louis, MO, USA). Normal goat serum, Biotinylated antibody and Horse Radish Peroxidase (HRP) System were purchased from (KPL, Inc., Gaithersburg, Maryland, USA). The kidney injury molecule I (Kim-1), nuclear factor kappa beta (NF-κB), cardiac troponin I (CTnI) together with nuclear factor erythroid 2-related factor 2 (Nrf2) antibodies were purchased from (Bioss Inc. Woburn, Massachusetts, USA) while 3, 3′-Diaminobenzidine (DAB) tablets were purchased from (AMRESCO LLC. OHio, USA). All other chemicals were of analytical grade.

Experimental animals and design

In the study, forty-male Wistar albino rats were randomly divided into four groups with 10 rats in a group. Group A was administered normal saline, Glycerol-induced acute kidney injury (AKI) in rats was established by the administration of Glycerol (10 ml/kg BW, 50% v/v in sterile saline, i.m.) as described (Cebi et al. 2016) to Group B rats. Rats in Groups C and D were pretreated with Luteolin 100 and 200 mg/kg for 7 days and thereafter administered Glycerol (10 ml/kg BW, 50% v/v in sterile saline, i.m.). The dosage of Luteolin was adopted from our previous study (Oyagbemi et al. 2018). The rats were kept in wire mesh cages under controlled light cycle (12 h light/12 h dark) and fed with commercial rat chow *ad libitum* and liberally supplied with water. The blood of the rats was taken on the 8th day and rats were sacrificed on the 9th day. All the animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" (National Institute of Health, 1996).

Blood pressure measurement

Twenty-four hours after the last administration of Glycerol, blood pressure parameters, including systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures were determined non-invasively in conscious animals by tail plethysmography using an automated blood pressure monitor for rats (CODA S1, Kent Scientific Corporation, Connecticut, USA).

Blood sample collection and plasma preparation

Approximately three milliliters of blood was collected by retro–orbital venous puncture with heparinized capillary tubes into plain bottles and allowed to clot. The clotted blood was then centrifuged at 4, 000 *g* for 10 min. Clear serum was separated with Pasteur pipette into another plain tube and then stored at 4 °C until needed.

Preparation of renal and cardiac homogenates

The organs (kidneys and hearts) excised were rinsed and homogenized with 50 mM Tris-HCl buffer (pH 7.4) containing 1.15% KCl. The resultant homogenates were subjected to cold centrifugation at 4 °C using a speed of 10, 000 *g* for 15 min. The post mitochondrial fractions (PMFs)/cytosolic fractions from cardiac and renal homogenates were used for biochemical assays.

Biochemical assays

Renal and cardiac makers of oxidative stress

Hydrogen peroxide generation was determined according to the method of Wolff (1994). The reaction mixture was subsequently incubated at room temperature for 30 min. The mixtures were read at absorbance of 560 nm and H_2O_2 generated was extrapolated from H_2O_2 standard curve. The malondialdehyde (MDA) content as an index of lipid peroxidation was quantified in the PMFs of cardiac and renal tissue according to the method of Varshney and Kale (1990). The absorbance was measured at 532 nm. Lipid peroxidation was calculated with a molar extinction coefficient of 1.56×10^5/M/cm. Protein carbonyl (PCO) contents in the renal and cardiac tissues were measured using the method of Reznick and Packer (1994). The absorbance of the sample was measured at 370 nm. The renal and cardiac carbonyl content was calculated based on the molar extinction coefficient of DNPH (2.2 10^4 cm^1 M^1) and expressed as nmoles/mg protein while vitamin C contents were measured as earlier described (Jacques-Silva et al. 2001).

Renal and cardiac antioxidants

The superoxide dismutase (SOD) activity was carried out by the method of Misra and Fridovich (1972), with slight modification (Oyagbemi et al. 2015). The increase in absorbance at 480 nm was monitored every 30 s for 150 s. The one unit of SOD activity was given as the amount of SOD necessary to cause 50% inhibition of the auto-oxidation of adrenaline to adrenochrome. The reduced glutathione (GSH) was estimated by the method of Jollow et al. (1974) while catalase (CAT) activity was determined according to the method of Sinha (1972). One unit of CAT activity represents the amount of enzyme required to decompose 1 µmol of H_2O_2/min. Glutathione peroxidase (GPx) activity was also measured according to Beutler et al. (1963). Glutathione S-transferase (GST) was estimated by the method of Habig et al. (1974) using 1-chloro-2, 4-dinitrobenzene as substrate. The activity of glutathione reductase (GRed) was according to the method of Racker (1954). The decrease in absorbance at 340 nm was measured and enzyme activity was calculated with a molar extinction co-efficient of 6.1 mmol/L^{-1} cm. The protein (PSH) and non-protein thiol (NPSH) contents were determined as described by Ellman (1959). Protein concentration was determined by the method of Gornal et al. (1949), using bovine serum albumin (BSA) as standard.

Determination of serum markers of renal damage and hypertension

The serum nitric oxide concentrations were measured spectrophotometrically at 548 nm according to the method of Olaleye et al. (2007). The serum myeloperoxidase (MPO)

activity was determined according to the method of Xia and Zweier (1997). The advanced oxidation protein product (AOPP) contents were determined as described by Kayali et al. (2006). Briefly, 0.4 ml of cardiac and renal PMFs were treated with 0.8 ml phosphate buffer (0.1 M; pH 7.4). The absorbance of the reaction mixture was immediately recorded at 340 nm wavelength. The content of AOPP for each sample was calculated using the extinction coefficient of 261 $cm^{-1} mM^{-1}$ and the results were expressed as μmoles/mg protein. The activity of xanthine oxidase was determined according to the method of Akaike et al. (1990). The blood urea nitrogen (BUN) was determined using Randox kits following manufacturer's instructions.

Histopathology

Small pieces of kidney and heart were fixed in 10% formalin, embedded in paraffin wax, and sections of 5-6 mm in thickness were made and thereafter stained with hematoxylin and eosin for histopathological examination according to the methods as previously described (Drury and Wallington 1976). Thereafter, the sections were examined with light microscopy.

Immunohistochemical staining

The immunolocalization of kidney injury molecule I (Kim-1), nuclear factor kappa beta (NF-κB), cardiac troponin I (CTnI) and nuclear factor erythroid 2-related factor 2 (Nrf2) in the kidney and heart, respectively was determined as earlier reported by Oyagbemi et al. (2017). Fixed tissues (heart and kidney) in 10% buffered formalin were embedded in paraffin and sectioned at a thickness of 5 μm. The immunoreactive positive expressions of Kim-1, NF-κB, Nrf2 and CTnI anti-rabbit intensive regions were viewed starting from low magnification on each slice then with 400× magnifications using a photo microscope (Olympus) and a digital camera (Toupcam®, Touptek Photonics, Zhejiang, China). Immunoreactivity was quantified using Image J software.

Statistical analysis

Data obtained were analyzed with One-way ANOVA with Dunnett's post-test at a 95% confidence limit. All values are expressed as mean ± S.D. The test of significance between two groups was estimated by Student's t test.

Results

From Table 1, the results show that glycerol administration significantly reduced the relative organ weight (kidney and heart) in comparison to the control. Interestingly, pretreatment with Luteolin at 100 and 200 mg/kg significantly increased the relative kidney weight when compared to glycerol alone while no statistically significant changes were observed in the kidney and heart weights (Table 1).

The administration of glycerol significantly ($p < 0.05$) increased cardiac markers of oxidative stress viz: hydrogen peroxide (H_2O_2) generation, (malondialdehyde (MDA)

Table 1. The effect of Glycerol toxicity on organ weight and relative organ weight.

Experimental Groups	Group A (Control)	Group B (Glycerol)	Group C (Glycerol + luteolin 100 mg/kg)	Group D (Glycerol + luteolin 200 mg/kg)
Heart weight (g)	0.46 ± 0.15	0.4 ± 0.05	0.4 ± 0.11	0.37 ± 0.12
Heart/body (g/g)	0.004 ± 0.001	0.003 ± 0.0005[a]	0.004 ± 0.001	0.003 ± 0.0009
Kidney weight (g)	0.74 ± 0.15	0.64 ± 0.15	0.67 ± 0.12	0.71 ± 0.13
Kidney/body (g/g)	0.007 ± 0.002	0.005 ± 0.0007[a]	0.006 ± 0.001[b]	0.0065 ± 0.001[b]

Values are presented as mean ± standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript [a] indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript [b] indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B) in each row. (One-way analysis of variance plus student's t-test was used).

Table 2. Effect of Glycerol on cardiac markers of oxidative stress.

Experimental Groups	Group A (Control)	Group B (Glycerol)	Group C (Glycerol + luteolin 100 mg/kg)	Group D (Glycerol + luteolin 200 mg/kg)
H_2O_2 generated	31.81 ± 0.85	30.17 ± 1.47[a]	29.66 ± 1.38	29.91 ± 1.96
MDA	2.76 ± 0.12	3.38 ± 0.28[a]	3.00 ± 0.81	2.91 ± 0.84
Protein Carbonyl	51.37 ± 6.42	74.86 ± 9.91[a]	66.19 ± 8.99[b]	66.94 ± 7.65[b]
Total thiol	188.44 ± 29.32	177.23 ± 32.10	253.68 ± 31.66 [b]	277.07 ± 29.51[b]
Non-Protein thiol	222.55 ± 32.41	185.71 ± 34.48[a]	231.45 ± 33.97 [b]	203.40 ± 35.74 [b]
GSH	79.94 ± 6.41	77.09 ± 8.55	81.29 ± 6.74	73.29 ± 9.07
Vitamin C	0.38 ± 0.05	0.33 ± 0.10	0.34 ± 0.09	0.30 ± 0.07

Values are presented as mean ± standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript ([a]) indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript ([b]) indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B) in each row. (One-way analysis of variance plus student's t-test was used).

H_2O_2 (hydrogen peroxide generation; μmol/mg protein), MDA (malondialdehyde; μmol of MDA formed/mg protein), GSH (Reduced Glutathione; μmol /mg protein), Protein Thiol (nmol /mg protein); Non-Protein Thiol (nmol /mg protein), Protein Carbonyl (nmol /mg protein), vitamin C (μmol /mg protein). (One-way analysis of variance plus student's t-test was used).

and protein carbonyl (PCO) content) and significantly ($p < 0.05$) reduced cardiac total thiol and non-protein thiol, respectively when compared with the control (Table 2). However, there was no statistically significant difference in the content of cardiac (malondialdehyde (MDA), hydrogen peroxide generated (H_2O_2), reduced glutathione (GSH) and vitamin C of glycerol alone as with Luteolin pretreated rats. In contrast, pretreatment with Luteolin (100 and 200 mg/kg) statistically showed significant ($p < 0.05$) reduction PCO content with concomitant improvement in cardiac total thiol and non-protein thiol vitamin C as indicated in Table 2.

The administration of glycerol alone caused statistically significant ($p < 0.05$) increase in renal hydrogen peroxide (H_2O_2) generation, and protein carbonyl (PCO) content while statistically significant ($p < 0.05$) reduction in reduced glutathione (GSH), non-protein thiol and vitamin C contents were obtained when compared with the control (Table 3). In another experiment, pretreatment with Luteolin at 100 and 200 mg/kg caused significant ($p < 0.05$) reduction in renal markers of oxidative stress (MDA levels, (H_2O_2) generation and PCO content with significant ($p < 0.05$) increase GSH, non-protein thiol and vitamin C with 200 mg/kg of Luteolin showing better protection as indicated in Table 3 when compared with glycerol alone group.

From this study, glycerol alone significantly ($p < 0.05$) increased cardiac glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities together with significant ($p < 0.05$) reduction in the activities of cardiac glutathione S-transferase (GST) and

Table 3. Effect of Glycerol on renal markers of oxidative stress.

Experimental Groups	Group A (Control)	Group B (Glycerol)	Group C (Glycerol + luteolin 100 mg/kg)	Group D (Glycerol + luteolin 200 mg/kg)
H_2O_2 generated	32.09 ± 1.58	34.07 ± 1.95[a]	33.82 ± 1.44	31.94 ± 1.55[b]
MDA	2.34 ± 0.28	2.43 ± 0.35	2.11 ± 0.28[b]	2.36 ± 0.44
Protein Carbonyl	26.95 ± 2.43	32.02 ± 3.39[a]	26.89 ± 6.84[b]	25.42 ± 8.40[b]
Protein thiol	295.40 ± 61.98	294.89 ± 77.12	303.73 ± 88.99	178.28 ± 34.08[b]
Non-Protein thiol	155.01 ± 14.25	103.24 ± 12.04[a]	109.46 ± 18.38	109.13 ± 22.57
GSH	90.65 ± 8.36	93.26 ± 9.82[a]	86.80 ± 11.05[b]	93.35 ± 11.3
Vitamin C	0.24 ± 0.03	0.19 ± 0.02[a]	0.21 ± 0.02[b]	0.22 ± 0.02[b]

Values are presented as mean ± standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript ([a]) indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript ([b]) indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B) in each row. (One-way analysis of variance plus student's t-test was used).

H_2O_2 (hydrogen peroxide generation; μmol/mg protein), MDA (malondialdehyde; μmol of MDA formed/mg protein), GSH (Reduced Glutathione; μmol /mg protein), Protein Thiol (μmol /mg protein); Non-Protein Thiol (μmol /mg protein), Protein Carbonyl (μmol /mg protein), vitamin C (μmol /mg protein). (One-way analysis of variance plus student's t-test was used).

glutathione reductase (GRed) as shown in Table 4 in comparison to the control. However, significant improvement in cardiac GRed activity was obtained in rats pretreated with Luteolin (100 and 200 mg/kg) when compared with glycerol alone (Table 4). The renal GST activity was found to reduce significantly while that of GRed increased in glycerol alone group as compared to the control (Table 5). However, appreciable improvement was noticeable in renal GST activity of rats pretreated with 100 mg/kg of Luteolin when compared with that of rats that received only glycerol (Table 5). This shows that Luteolin antioxidant capacity has more effect on GST and GRed in glycerol-induced ARF.

Again, glycerol administration significantly increased serum xanthine oxidase activity, and at the same time significantly reduced nitric oxide (NO) bioavailability, when compared with the control group (Table 6). The activity of xanthine oxidase further reduced following pretreatment with Luteolin (100 and 200 mg/kg), while significant improvement in serum NO bioavailability was obtained when compared with glycerol alone (Table 6). There was observable statistically significant ($p < 0.05$) increase in the serum advanced oxidative protein product (AOPP), blood urea nitrogen (BUN) and creatinine of glycerol intoxicated rats when compared with the control (Table 6). However, Luteolin pretreatment showed protection against acute renal damage caused by glycerol by significantly lowering the serum creatinine relative to the glycerol alone (Table 6). Furthermore, 200 mg/kg of Luteolin pretreatment was able to significantly reduce the high values of AOPP in comparison to the glycerol alone as indicated in Table 6.

The administration of glycerol alone caused statistically significant increases in systolic, diastolic and mean arterial blood pressure when compared with the control (Figure 1). However, pretreatment with Luteolin (100 and 200 mg/kg), dose-dependently and significantly reduced the blood pressure parameters when compared to glycerol alone (Figure 1). It is worthy to note that 200 mg/kg Luteolin showed better antihypertensive action against glycerol induced hypertension. The histopathology of the kidney of rats administered only glycerol revealed disseminated glomerular hyperplasia and a focal area of interstitial infiltration by inflammatory cells and necrosis (Figure 2). Furthermore, focal area of congestion and mild area of cellular infiltration were

Table 4. Effect of Glycerol on cardiac antioxidant enzymes.

Experimental Groups	Group A (Control)	Group B (Glycerol)	Group C (Glycerol + luteolin 100 mg/kg)	Group D (Glycerol + luteolin 200 mg/kg)
GPx	120.80 ± 8.59	149.63 ± 8.28[a]	154.19 ± 7.29	126.80 ± 6.00[b]
SOD	43.11 ± 2.69	48.12 ± 7.24[a]	53.19 ± 4.80	48.78 ± 7.9
GST	0.14 ± 0.04	0.10 ± 0.02[a]	0.03 ± 0.01[b]	0.04 ± 0.02[b]
G.Red	0.36 ± 0.01	1.16 ± 0.35[a]	3.16 ± 0.35[b]	2.31 ± 0.62[b]

Values are presented as mean ± standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript ([a]) indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript ([b]) indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B) in each row. (One-way analysis of variance plus student's t-test was used).

GPx (Glutathione Peroxidase; units/mg protein); SOD (Superoxide Dismutase; units/mg protein); GST (Glutathione-S-transferase; mmole1- Chloro-2, 4-dinitrobenzene-GSH complex formed/min/mg protein); G.Red (Glutathione reductase; (units/min/mg protein^{-1}). (One-way analysis of variance plus student's t-test was used).

Table 5. Effect of Glycerol on renal antioxidant enzymes.

Experimental Groups	Group A (Control)	Group B (Glycerol)	Group C (Glycerol + luteolin 100 mg/kg)	Group D (Glycerol + luteolin 200 mg/kg)
GPx	77.63 ± 11.22	72.99 ± 5.08	77.14 ± 5.95	75.96 ± 7.82
SOD	27.29 ± 3.44	25.72 ± 1.41	27.17 ± 1.68	26.40 ± 2.41
GST	0.15 ± 0.06	0.10 ± 0.03[a]	0.62 ± 0.09[b]	0.11 ± 0.03
G.Red	0.72 ± 0.15	1.37 ± 0.30[a]	1.27 ± 0.09	1.52 ± 0.29

Values are presented as mean ± standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript ([a]) indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript ([b]) indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B) in each row. (One-way analysis of variance plus student's t-test was used).

GPx (Glutathione Peroxidase; units/mg protein); SOD (Superoxide Dismutase; units/mg protein); GST (Glutathione-S-transferase; mmole1- Chloro-2, 4-dinitrobenzene-GSH complex formed/min/mg protein); G.Red (Glutathione reductase; (units/min/mg protein^{-1}). (One-way analysis of variance plus student's t-test was used).

Table 6. Effect of Glycerol on serum markers of oxidative stress, inflammation and renal damage.

Experimental Groups	Group A (Control)	Group B (Glycerol)	Group C (Glycerol + luteolin 100 mg/kg)	Group D (Glycerol + luteolin 200 mg/kg)
AOPP	126.41 ± 16.83	140.05 ± 23.42	133.74 ± 13.29	111.77 ± 12.29[b]
Xanthine oxidase	0.12 ± 0.02	0.14 ± 0.03[a]	0.04 ± 0.02[b]	0.06 ± 0.03[b]
Nitric oxide	10.29 ± 1.25	9.06 ± 0.81[a]	7.44 ± 1.02 [b]	8.37 ± 1.55[b]
Urea	0.49 ± 0.13	0.55 ± 0.12 [a]	0.48 ± 0.14	0.51 ± 0.15
Creatinine	43.86 ± 5.54	48.85 ± 8.44 [a]	40.31 ± 2.12[b]	44.27 ± 8.52

Values are presented as mean ± standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript ([a]) indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript ([b]) indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B) in each row. (One-way analysis of variance plus student's t-test was used).

AOPP (nmoles/mg protein); Xanthine Oxidase (Units/min/mg protein), Nitric oxide (μmol/mg protein); Urea (μmol/L); Creatinine Urea (μmol/L). (One-way analysis of variance plus student's t-test was used).

observed in rats pretreated with Luteolin (100 and 200 mg/kg) compared with glycerol alone (Figure 2).

The immunohistochemistry of kidney injury molecule 1 (Kim-1) showed higher expressions of Kim-1 in glycerol treated rats relative to the control (Figure 3). However, lower expressions of Kim-1 were observed in kidney of rats pretreated with Luteolin at 100 and 200 mg/kg, respectively (Figure 4). Further, higher immune-positive expressions of nuclear factor kappa beta (NF-κB) were observed in glycerol treated rats relative to the control and statistically significant lower expressions of NF-κB were observed in glycerol + 200 mg/kg of Luteolin as shown in Figure 4. In another experiment, higher

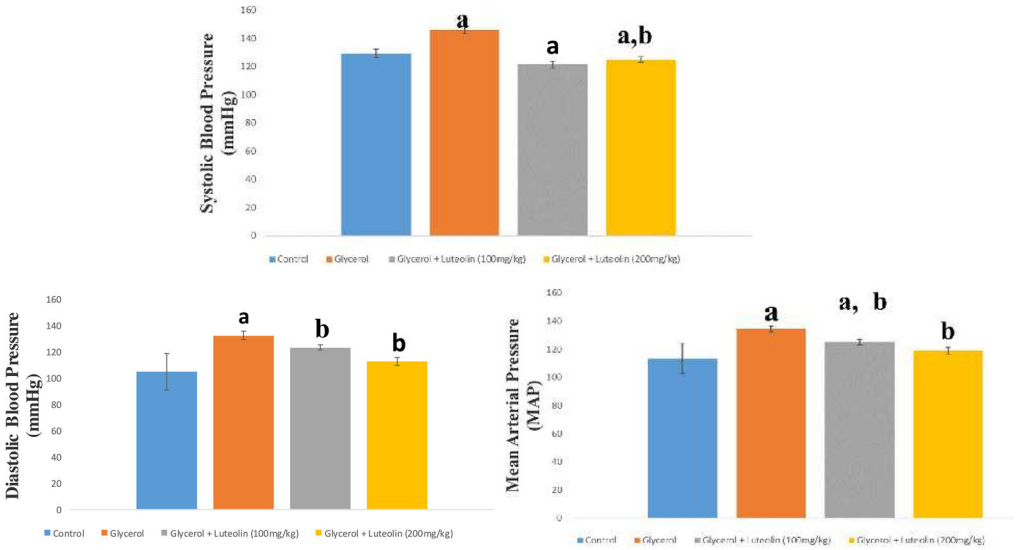

Figure 1. The effect of Glycerol on Mean arterial pressure. Values are presented as mean + standard deviation. Group A (Control), Group B (Glycerol), Group C (Glycerol + Luteolin 100 mg/kg), Group D (Glycerol + Luteolin 200 mg/kg). Superscript ([a]) indicates significant difference at $p < 0.05$ (Group B compared with group A) and superscript ([b]) indicates significant difference at $p < 0.05$ compared (groups C, D are compared with group B). (One-way analysis of variance plus student's t-test was used).

expressions of Nrf2 were observed in glycerol alone treated rats while lower expressions of nuclear factor erythroid 2-related factor 2 (Nrf2) were recorded in rats pretreated with Luteolin (100 and 200 mg/kg) compared with Glycerol alone, but lower expressions when compared to the glycerol alone (Figure 5). We also observed that glycerol administration caused higher immune-positive expressions of cardiac troponin I (CTnI). This is indicative of cardiac damage accompanying renal damage and hypertension. Interestingly, Luteolin pretreatment (100 and 200 mg/kg) caused statistically significant reduction in the expressions of CTnI relative to glycerol alone (Figure 6). This might be indicative of cardioprotective effect of Luteolin in glycerol-induced ARF and cardiac complication.

Discussion

Myoglobinuric acute kidney injury is a uremic syndrome that develops due to damage of skeletal muscle (Yalçınkaya et al. 2018). Free radical generation and production of nitric oxide have been shown to play a critical role in the pathogenesis of myoglobinuric acute kidney injury (Singh et al. 2012; Yalçınkaya et al. 2018). Acute renal failure (ARF) has been reported as a life-threatening disease with high mortality mediated by inflammation and oxidative stress as mechanism of action (Boozari and Hosseinzadeh 2017). Recently, the association between renal failure and hypertension was reported (Di Nicolò 2018). From the present study, glycerol administration caused a significant increase in systolic, diastolic and mean arterial pressure which was indicative of hypertension. The mechanism of glycerol-induced ARF and its association with hypertension

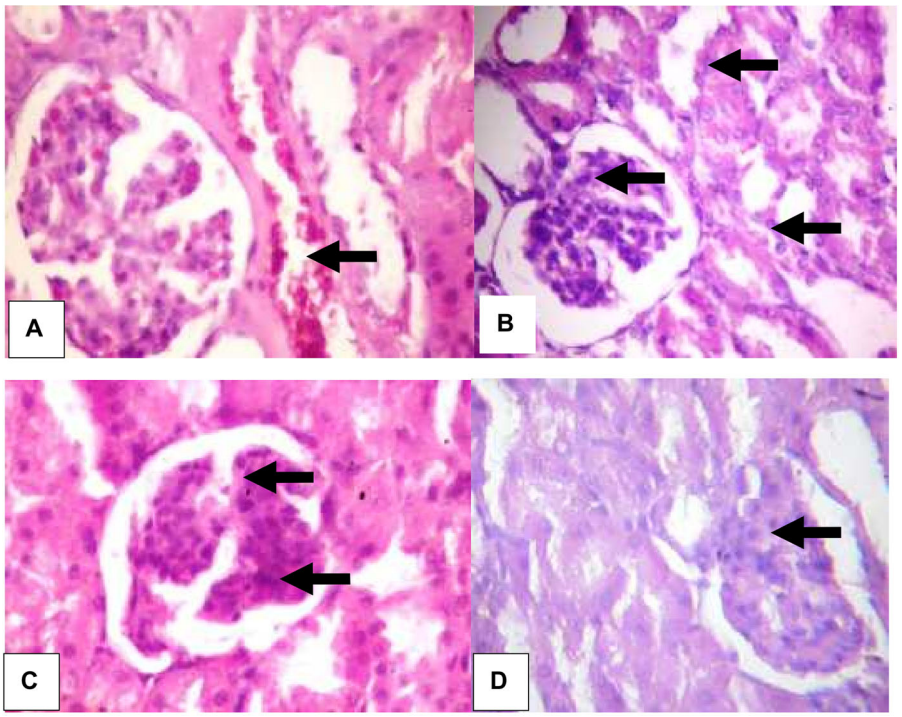

Figure 2. Photomicrograh showing kidney of rats (Group A)-Control: mild rea area of congestion and inflammation; (Group B) administered with (Glycerol; 8 ml/Kg) shows disseminated glomerular hyperplasia and a focal area of interstitial infiltration by inflammatory cells and necrosis (black arrow); (Group C: Glycerol; 8 ml/Kg + Luteolin 100 mg/kg) mild area of cellular infiltration and congestion, (Group D: Glycerol; 8 ml/Kg + Luteolin 200 mg/kg) focal area of congestion and mild area of cellular infiltration. Plates are stained with H and E stains and viewed with X 400 objectives.

has been reported elsewhere (Tsai et al. 2017). It was remarkable to note that the administration of Luteolin was able to reduce the high blood pressure parameters better than the values obtained for glycerol alone-induced hypertension. Our study therefore supports earlier reports on the use of Luteolin as anti-hypertensive and vasorelaxation effect (Jiang et al. 2005; Lv et al. 2013).

Oxidative stress can be defined as imbalance between reactive oxygen species (ROS) and antioxidant defence system with a shift more toward production of ROS. The MDA is a by-product of lipid peroxidation of polyunsaturated fatty acid and a marker of oxidative stress (Benoist d'Azy et al. 2016; Tsikas 2017). Hence, oxidative stress has been identified as a major player in the pathogenesis of ARF and hypertension (Pouvreau et al. 2018). Luteolin pretreatment prevented glycerol-induced ARF and hypertension and this demonstrated the antioxidant and antihypertensive effect of Luteolin. Protein carbonyl is another marker of nitrosative stress, and there is a causal link between hypertension and nitrosative stress (Gaikwad et al. 2017; Mozos and Luca 2017). The ability of glycerol to cause lipid peroxidation was demonstrated by excessive production of MDA, PCO and H_2O_2 in cardiac while exaggerated production of PCO and H_2O_2 was observed in renal tissues. The significant reduction in renal non-enzymic antioxidant such as GSH, vitamin C and non-protein thiol (NPSH) by glycerol toxicity was an

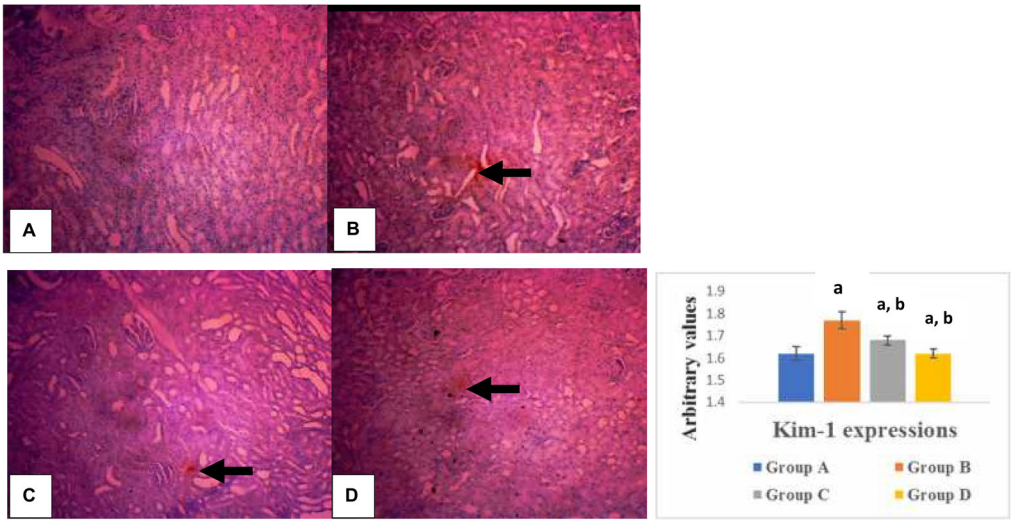

Figure 3. Immunohistochemistry of Kim-1 of rats. A — Control: There is lower immune-positive expressions of Kim-1. Group B (Glycerol; 8 ml/Kg) shows higher immune-positive expressions of Kim-l when compared to the control. (Group C); Glycerol; 8 ml/Kg + Luteolin100 mg/kg) shows lower expressions of Kim-1 when compared with the Glycerol only treated group (black arrow) and (Group D) administered Glycerol; 8 ml/Kg + Luteolin 200 mg/kg; also shows lower expressions of Kim-1 when compared with the Glycerol only treated group (black arrow). The slides were counterstained with high definition hematoxylin and viewed x 100 objectives.

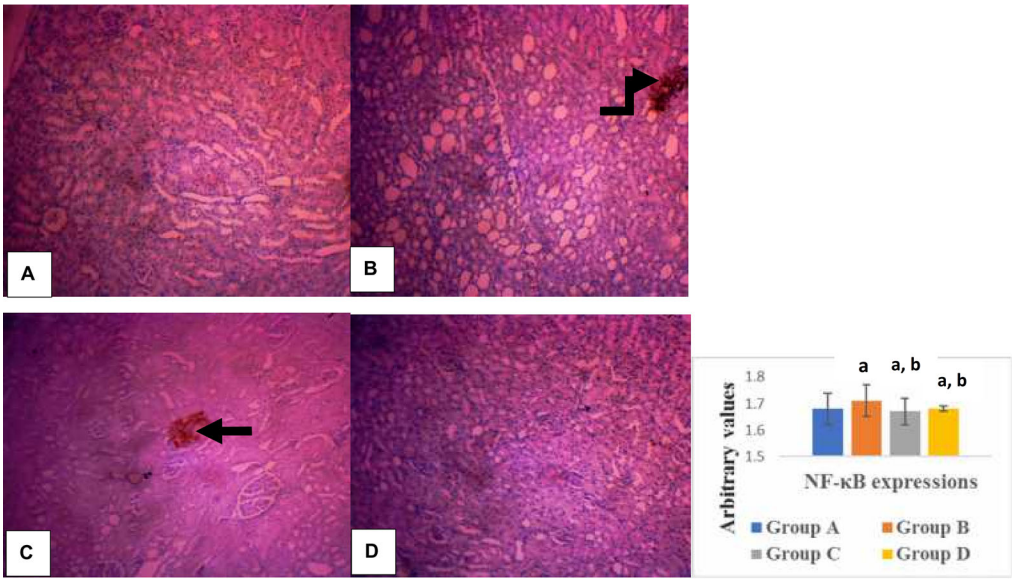

Figure 4. Immunohistochemistry of NF-«B in kidney of rats. A — Control: There is lower immune-positive expressions of NF-KB. Group B (Glycerol; 8 ml/Kg) shows higher immune-positive expressions of NF-kB when compared to the control. (Group C); Glycerol; 8 ml/Kg + Luteolinl00O mg/kg) shows lower expressions of NF-kB when compared with the Glycerol only treated group (black arrow) and (Group D) administered Glycerol; 8 ml/Kg + Luteolin 200 mg/kg; also shows lower expressions of NF-kB when compared with the Glycerol only treated eroup (black arrow). The slides were counterstained with high definition hematoxylin and viewed x 100 objectives.

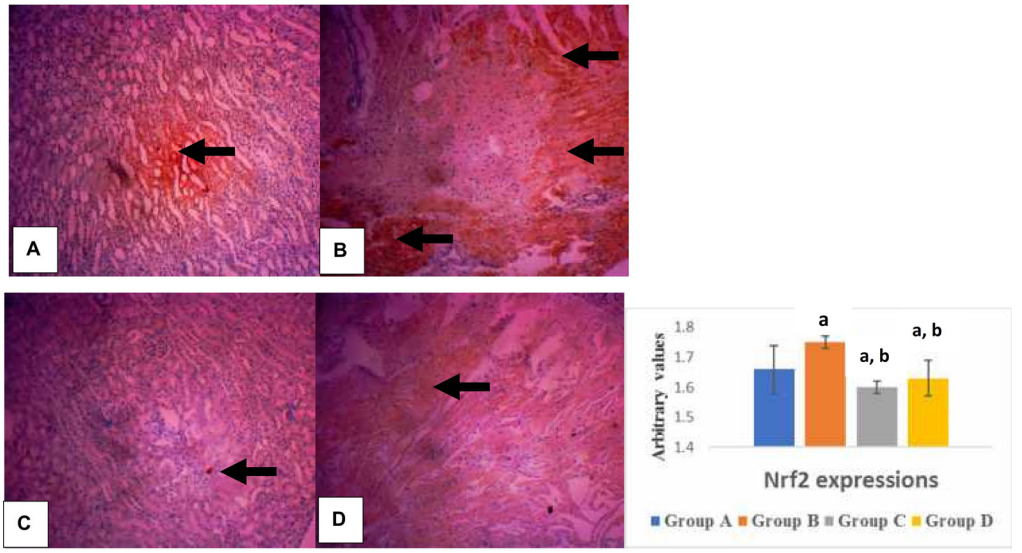

Figure 5. Immunohistochemistry of Nrf2 of Kidney of rats. A — Control: There is lower immune-positive expressions of Nrf2. Group B (Glycerol; 8 ml/Kg) shows higher immune-positive expressions of Nrf2 when compared to the control. (Group C); Glycerol; 8 ml/Kg + Luteolin 100 mg/kg) shows higher expressions of Nrf2 when compared with the Glycerol only treated group (black arrow) and (Group D) administered Glycerol; 8 ml/Kg + Luteolin 200 mg/kg; also shows lower expressions of Nrf2 when compared with the Glycerol only treated group (black arrow). The slides were counterstained with high definition hematoxylin and viewed x 100 objectives.

indication of oxidative stress. The non-enzymic antioxidants are known to complement the enzymic antioxidants to quench and scavenge free radicals and reactive oxygen species (ROS), thereby attenuating oxidative stress. But we observed significant improvement in renal GSH (100 mg/kg Luteolin), vitamin C contents in rats pretreated with 200 mg/kg of Luteolin, indicating importance of nutraceutical such as Luteolin as antioxidant in mitigating oxidative stress. On the other hand, glycerol intoxication precipitated reduction in cardiac GSH, vitamin C, and protein thiol (PSH) though, not statistically significant. However, significant reduction in cardiac non-protein thiol (NPSH) in glycerol alone treated rats was observed when compared to the control. Going forward, the administration of glycerol alone caused severe oxidative stress which was indicated with significant increases in renal hydrogen peroxide (H_2O_2) generation, protein carbonyl (PCO) contents together with significant decreases in non-protein thiol (NPSH), reduced glutathione (GSH) and vitamin C content, respectively. However, cardiac oxidative stress was indicated with statistically significant increase in cardiac MDA, PCO and H_2O_2 generation, indicating complication arising from glycerol-induced ARF. Further, mitigation of cardiac oxidative stress was more pronounced in cardiac total thiol at 100 and 200 mg/kg while 100 mg/kg of Luteolin was able to cause noticeable improvement in cardiac antioxidant capacity. Hence, Luteolin pretreatment was able to offer better protection against nephrotoxicity than cardiotoxicity caused by glycerol intoxication.

Apart from the aforementioned markers of oxidative stress; advanced oxidative protein products (AOPPs) contents, and xanthine oxidase activities were significantly

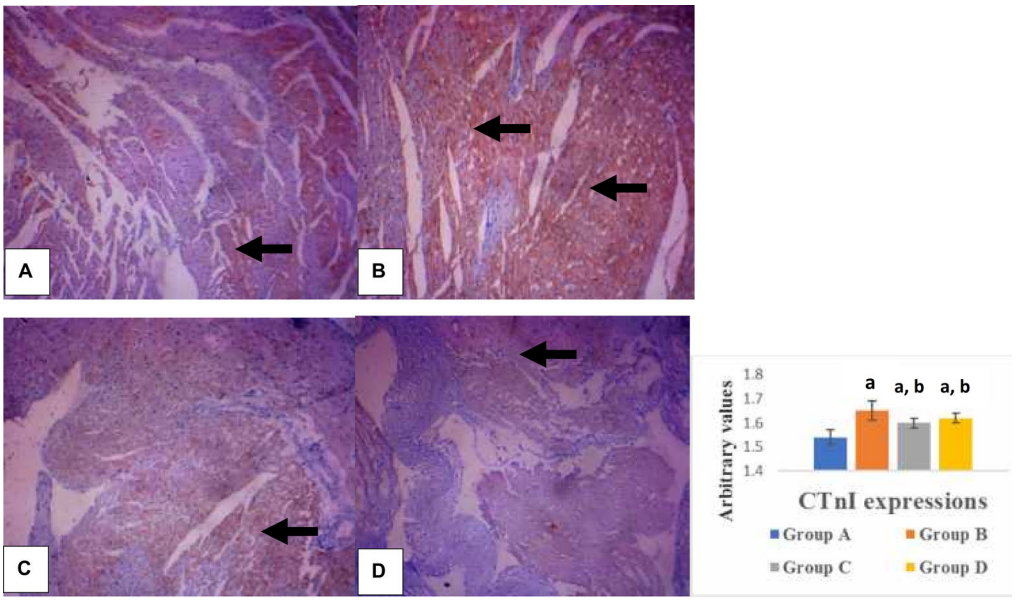

Figure 6. Immunohistochemistry of cardiac troponin (CTnI) of rat's heart. A — Control: There is lower immune-positive expressions of CTnI. Group B (Glycerol; 8 ml/Kg) shows higher immune-positive expressions of CTnI when compared to the control. (Group C); Glycerol; 8 ml/Kg + Luteolin 100 mg/kg) shows lower expressions of CTnI when compared with the Glycerol only treated group (black arrow) and (Group D) administered Glycerol; 8 ml/Kg + Luteolin 200 mg/kg; also shows lower expressions of CTnI when compared with the Glycerol only treated eroup (black arrow). The slides were counter-stained with high definition hematoxylin and viewed x 100 objectives.

increased in the serum of rats administered only glycerol. More so, that increase in AOPP and xanthine oxidase has been linked to oxidative stress, inflammation and renal damage (Zhang et al. 2010; Su et al. 2018). Additionally, high levels of serum AOOP and xanthine oxidase have been directly related to renal damage while xanthine oxidase activity has been positively correlated, thereby directly proportional to uric acid production (Park et al. 2014; Perez Gutierrez & de Jesus Martinez Ortiz 2014). Hence, dysregulation in the xanthine oxidase activity in the present study might contribute to endothelial dysfunction, reduced glomerular filtration and ultimately renal failure. Since, nitric oxide (NO) helps in the maintenance of vascular tone and blood pressure, therefore, the beneficial effects of Luteolin was observed as it improved NO bioavailability, and that also attests to the anti-hypertensive effect of Luteolin. Myeloperoxidase (MPO) has been documented elsewhere to participate in inflammation, oxidative, cardiac and renal damage (Dkhil et al. 2018; Pan et al. 2018; Rodrigues de Carvalho *et al.*, 2018). In this study, glycerol administration was able to cause increase in the activity of MPO which concomitantly precipitated inflammation, oxidative stress, and ARF. However, pretreatment with Luteolin prior to the administration of glycerol mitigated the activity of MPO; this also, might be responsible for the anti-inflammatory and renoprotective effect of Luteolin in glycerol-induced ARF. The renoprotective effect of Luteolin was also demonstrated by reduction in the serum creatinine and blood urea nitrogen levels compared to values obtained for glycerol alone.

The administration of glycerol significantly reduced the activities of renal glutathione S-transferase (GST) and glutathione reductase (GRed). On the contrary, statistically significant increase in cardiac glutathione peroxidase (GPx), superoxide dismutase (SOD) and glutathione reductase (GRed) together with statistically significant decrease in cardiac glutathione S-transferase (GST) was observed. This possibly implies that renal tissues are more prone to glycerol toxicity than the cardiac tissues. Also, the increase in the activity of SOD, GPx and GRed could be hypothesized as adaptive response from glycerol toxicity. Together, oxidative stress was more pronounced in the kidney and this might also be responsible and accountable for the pathophysiology and pathogenesis of glycerol-induced ARF.

The SOD is the first line of defence against oxidative stress while the GPx and CAT participate in the final detoxification of H_2O_2 to H_2O and O_2. During oxidative stress, the inhibition or inactivation of SOD, GPx and CAT will allow O_2- and H_2O_2 to accumulate, thereby causing peroxidation of polyunsaturated fatty in the biological membranes. The formation of peroxynitrite (ONOO-) from O_2- and NO has been reported to contribute to arterial stiffness, endothelial dysfunction and hypertension (Khan et al. 2018; Malakul et al. 2018). The formation of ONOO- also facilitates the uncoupling of endothelial nitric oxide synthase (eNOS), reduction in NO bioavailability with resultant formation of clinical hypertension (Kröller-Schön et al. 2018). Histopathology revealed disseminated glomerular hyperplasia and a focal area of interstitial infiltration by inflammatory cells and necrosis in rats administered only glycerol while pretreatment with Luteolin almost restored the observed histopathological changes as evidenced by mild area of cellular infiltration and congestion of the renal tissues. Kidney injury molecule 1 (Kim-1) is one of the recent markers of acute kidney injury (Wanigasuriya et al. 2017; Beker et al. 2018; Kim et al. 2018). From the present study, the level of Kim-1 correlated with the level of damage induced by glycerol administration. The immunohistochemistry revealed higher expressions of Kim-1 in glycerol alone treated rats while the expresssions of Kim-1 were lowered relative to the control and groups pretreated with Luteolin. The higher expressions of Kim-1 was also proportional to the histopathological lesions in the kidney of glycerol intoxicated rats. Hence, administration of Luteolin provided a meaningful protective effect against glycerol-induced ARF. We therefore infer that Luteolin is a potential drug candidate and a novel strategy for the prevention of glycerol-induced ARF. We therefore suggest that patients with renal injury can take more fruits and vegetables that are rich in Luteolin for the tretment of ARF.

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor which plays a leading role in oxidative stress, apoptosis, cytokine production and arrays of disease conditions such as hypertension and ARF (Fattori et al. 2017; Tomar et al. 2017; Chen et al. 2018). The activation of NF-κB has been reported in cisplatin and diclofenac-induced acute kidney injury (Fattori et al. 2017; Humanes et al. 2017). Pretreatment of Luteolin prior to the administration of glycerol reduced the expressions of renal NF-κB, this is indicative of anti-inflammatory and renoprotective effects of Luteolin. This observation is consistent with the anti-inflammatory and nephroprotective effects of Luteolin as previously described (Abu-Elsaad and El-Karef 2018; Kim et al. 2018). The nuclear factor-erythroid-2-related factor 2 (Nrf2), has been

described as a redox-sensitive master regulator of oxidative stress (Arafa Keshk et al. 2017). Surprisingly, glycerol administration caused over expressions of Nrf2 relative to the control and that Nrf2 expressions in rats pretreated with Luteolin were less compared to that of glycerol alone. Over expressions of Nrf2 have been reported in conditions associated with oxidative stress signifying adaptive response (Hu et al. 2013; Zheng et al. 2015; Jeddi et al. 2018). The observed over expressions of Nrf2 is reported for the first time in glycerol-induced ARF. Hence, results from the present study as indicated with increase cardiac SOD and GPx could align with the observed over expressions of NrF2, confirming the aforementioned adaptive response. Cardiac complications of glycerol toxicity were also assessed in this study. The immunohistochemistry of cardiac troponin I (CTnI) was assessed, and glycerol administration caused higher expressions of CTnI. This observation could therefore be extrapolated that cardiac complication could arise from glycerol toxicity. The elevated CTnI might suggest rhabdomyolysis which was responsible for the observed ARF, and thereafter, account for the pathophysiology of glycerol-induced renal failure. The cardio and reno-protective effect of Luteolin might be ascribed to the ability of Luteolin to suppress myoglobinuric acute kidney injury which was characterized by inflammation, oxidative stress and hypertension.

Conclusion

Taken together, Luteolin pretreatment reduced high blood pressure and ameliorated acute renal failure caused by the administration of glycerol. Luteolin administration also reduced markers of oxidative stress, inflammation and renal damage, improved nitric oxide bioavailability, suppressed the expressions of kidney injury molecule 1, nuclear factor kappa beta, cardiac troponin I and nuclear factor erythroid 2-related factor 2 in the kidney and heart, respectively. Hence, Luteolin is a drug candidate for patients with kidney injury and associated cardiovascular complications. The mechanism of renoprotective effect of Luteolin might be through modulation of Kim-1/NF-κB/Nrf2 signaling pathways.

Declartion of interest

The authors declare no conflict of interest whatsoever.

Funding

This study was supported with a grant (TETFUND/DESS/NRF/UI IBADAN/STI/VOL. 1/B2.20.11) received from the National Research Foundation of the Tertiary Education Trust Fund (TETFUND), Nigeria.

About the Authors

Ademola Adetokunbo Oyagbemi is a Senior Lecturer at the Department of Veterinary Physiology and Biochemistry, and a Consultant to the Veterinary Teaching Hospital, Faculty of Veterinary Medicine, University of Ibadan, Nigeria. He has Doctor of Veterinary Medicine with master's degrees in both Pharmacology and Biochemistry, and Ph.D. in Biochemistry. In addition, He is a

Fellow of College of Veterinary Surgeons, Nigeria (FCVSN). His research interest focuses on the Cardiovascular Pharmacology, Neuropharmacology and Toxicology. In his laboratory, he explores the use of medicinal plants and phytochemicals/ nutraceuticals in ameliorating, mitigating or reversing cardiovascular diseases such as hypertension, diabetes, neurodegenerative conditions including Parkinson disease e.t.c. Over the years, he has attempted to explore canonical and non-canonical pathways associated with inflammation, cell survival, apoptosis, and antioxidant defence system both *in vitro* and *in vivo*. From these past studies, has used different signaling pathways as molecular tools and therapeutic targets in the treatment or modulation of different cardiovascular and neurodegenerative conditions. Some of these signaling pathways he has explored include mineralocorticoid receptor, angiotensin converting enzyme, kidney injury molecule, glial fibrillary acidic protein (GFAP), nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor kappa beta, p38MAPK,COX-2/Bax, HSP70, ERK, and PPARγ.

Dr. Olumuyiwa Abiola Adejumobi is a veterinarian and researcher in the University of Ibadan. He is a member of Cardio-renal laboratory, University of Ibadan. He joined the service of the University of Ibadan as Veterinary Registrar in the Veterinary Teaching Hospital (November 2011- November 2012) and later as the Academic staff and Registrar in Small Animal and Laboratory Animals Unit of the Department of Veterinary Medicine, University of Ibadan (2012 till date). He became a Fellow of the College of Veterinary Surgeons (FCVSN), Nigeria in 2018. He belongs to national and international societies including American Society of Pharmacology and Experimental Therapeutics (ASPET), USA, Physiological society (PHYSOC), UK, Society of Medicinal Plants for Economic Development (SOMPED), Africa, Society of Toxicology (SOT), USA. He has publications in local and international peer-reviewed journals. His research interest focuses on cardiovascular pharmacology and internal medicine using medicinal plants and phytochemicals as novel therapeutic agents and their molecular mechanisms of action.

Dr. Temitayo Olabisi Ajibade DVM, with Ph.D. in Veterinary Physiology, and Fellow of the College of Veterinary Surgeons (FCVSN). He teaches veterinary Physiology to undergraduate veterinary students at the Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Ibadan. He is Registrar at the Veterinary Teaching Hospital (VTH) and Sub-dean Undergraduate, Faculty of Veterinary Medicine, University of Ibadan. He belongs to national and international societies including American Society of Medicinal Plants for Economic Development (SOMPED), Africa, Society of Toxicology (SOT), USA, America Physiological Society (APS), USA, Physiological society (PHYSOC), UK. He has publications in highly-rated international peer-reviewed journals. Dr Ajibade's research interest is in the areas of Cardiovascular and Reproductive Physiology.

Ebunoluwa Racheal Asenuga holds Doctor of Veterinary Medicine and MSc (Biochemistry) degrees. She is a Lecturer at the Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Benin, Benin City, Nigeria. Most of her research activities focus on environmental toxicology, where she looks at the effect of environment toxicants on some systems of the body such as the cardiovascular system, reproductive system e.t.c., as well as using nutraceuticals and medicinal plants to prevent or alleviate the detrimental effects of these environmental toxicants. Recently, she has been looking into the world of endocrine disruptors, their effect in the aquatic environment and the possibilities of bioremediation as a technique to clean up the aquatic bodies.

Jeremiah Afolabi is a pre-doctoral fellow in the Molecular and Translational Physiology Ph.D. track at the University of Tennessee Health Science center, Memphis, USA. He holds DVM and MVSc. degrees from the University of Ibadan, Nigeria. His current research focuses on the mechanisms that underlie acute and chronic kidney disease using small and large preclinical animal models.

Blessing Seun ogunpolu is a veterinary surgeon with a passion for translational biomedical research. She works as a Research Assistant at the Cardio-renal research group, Faculty of Veterinary Medicine, University of Ibadan. Dr. Ogunpolu won 2020 International Travel Award

to present her research findings at ASPET conference, USA. An avid birdwatcher with interest in ecosystem conservation.

Olufunke Olubunmi Falayi is a graduate student in the Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary medicine, University of Ibadan, Nigeria. She holds a Doctor of Veterinary Medicine and a Masters' degree in Veterinary Pharmacology and Toxicology, both from the University of Ibadan, Nigeria. She works as a Research Assistant at the Cardiorenal Laboratory, a biomedical laboratory that focuses on non-infectious diseases of various body systems including the cardiovascular, renal and nervous systems. She utilizes techniques such as redox and inflammation-based assays, immunohistochemistry and immuno-blotting and has collaborated on several projects in drug discovery, development and innovation against hypertension and related cardiovascular and renal diseases. Using animal models, she has explored the therapeutic effects of various medicinal plants, plant-derived products and phytochemicals on diseases such as hypertension, myocardial infarction, diabetes, acute renal injury among others, and the signaling pathways involved in the pathogenesis and amelioration of these diseases.

Fasilat Oluwakemi Hassan is a graduate of Veterinary Medicine (DVM) from the University of Ibadan, I earned a Master's degree in Veterinary Biochemistry also from the prestigious university of Ibadan. She is a Research Assistant at the cardio-Renal Research Laboratory, University of Ibadan, and also an aspiring Ph.D. candidate. She has been involved with research activities, deciphering certain mechanisms involved in disease progression especially those associated with the cardiovascular system including hypertension, cardiac arrhythmia, heart failure, and other disease conditions affecting the nervous system. She has been carrying out research to understand the signaling pathways through which Extracellular Regulated Kinase (ERK), Caspase 3 and 9, nuclear erythroid factor related-factor 2 (Nrf2), nuclear factor Kappa beta (NF-κB) activities involved in various disease conditions. She is a member of Society of Toxicology (SOT), USA, Physiological society (PHYSOC), UK, American Society of Pharmacology and Experimental Therapeutics (ASPET), USA, Society of Medicinal Plants for Economic Development (SOMPED), Africa. She desires to dedicate her lifelong research career for development of more effective therapeutics for human and animal healthcare.

Enivwenaye E.W. Nabofa, BSc. MSc., PhD, is an early career scientist. He presently serves as a faculty at the Physiology Department, School of Basic Medical Sciences, Benjamin S. Carson College of Medicine, Babcock University, Ogun State, Nigeria. He is a cardiovascular physiologist with research interest in cardiovascular and metabolic studies, using nanotechnology and plant cyclotides in the possible treatment and or prevention of cardiovascular and metabolic disorders. He is a member of several learned associations such as Physiological Society of Nigeria (PSN), Physiological Society of UK (PHYSOC), British Pharmacology Society (BPS), Society for Endocrinology (SfE), Society for Medicinal Plants and Economic Development (SOMPED).

Dr. Temidayo Olutayo Omobowale holds D.V.M (1995), M.Vet.Sci (2003), and Ph.D. (2011) from the University of Ibadan, and FCVSN (2013). He is a Senior Lecturer and currently the head of department of Veterinary Medicine, Department of Veterinary Medicine at the University of Ibadan, Nigeria with focus on Veterinary Internal Medicine. Also, he is consultant to the Veterinary Teaching Hospital, University of Ibadan, Nigeria. He is a member of several professional and scientific organizations including the Nigerian Veterinary Medical Association, The Physiological Society, the Society of Toxicology and the British Small Animal Veterinary Association. Dr. Omobowale and his research team have been working on the use of natural products commonly available in Nigeria for the management of cardiovascular, renal and metabolic diseases using experimental models. He is a member of Society of Toxicology (SOT), USA, Physiological society (PHYSOC), UK, American Society of Pharmacology and Experimental Therapeutics (ASPET), USA.

Olufunke Eunice Ola-Davies is a Professor of Veterinary Biochemistry in the Environmental Toxicology, Phytomedicine and Cancer Research Unit. She obtained Doctor of Veterinary

Medicine degree, Master's Degrees in Veterinary Parasitology and Biochemistry, and a doctoral degree in Biochemistry. Professor Ola-Davies is one of the leading scientists of toxicology in the University of Ibadan, and in recognition of her active role in this field, she was honored with the Global Senior Scholar exchange programme award (GSSEP) of the Society of Toxicology, USA (2017). She is the recipient of many national and international awards amongst which are Postgraduate Training Fellowship of the Third World Organization for Women in Science (2002), Norman E. Borlaug Fellowship (USA), John D. and Catherine T. MacArthur Foundation Overseas Training Research Fellowship (USA), IUTOX/AstraZeneca/SOT Endowment Fund award (2014), World Academy of Science -UNESCO (2015-2018) e.t.c. She is a fellow of the College of Veterinary Surgeons Nigeria (FCVSN). Prof Olufunke Ola-Davies is a visiting professor at Oregon State University, USA, University of Forte Hare, Alice, South Africa and Norwegian University of Science and Technology (NTNU), Trondheim. She is currently an external examiner in some Universities within and outside Nigeria and a member of Senate of the University of Ibadan.

Adebowale Bernard Saba is a Doctor of Veterinary Medicine, with Masters and Ph.D. degrees in Veterinary Pharmacology and Toxicology. He is a Professor of Veterinary Pharmacology and Toxicology. He teaches veterinary pharmacology and toxicology to undergraduate and postgraduate students. He is also currently the Chair of the department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Ibadan. His research focus has been on the toxicology of various drugs, heavy metals, environmental pollutants/toxicant and plants that are of medicinal use. He has investigated the antioxidant, anti-inflammatory, analgesic, antihypertensive effects of various medicinal plants and phytochemicals, together with the elucidation of mechanism(s) of action. He is a member of various professional bodies including society of toxicology (SOT), USA, Forum of Nigeria Toxicologists (FONTOX), Toxicology of African origin (TAO), West Africa Society of Pharmacology, among others.

Professor Adeolu Alex Adedapo, DVM, MSc, PhD FIIA FACN is of the Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Ibadan, Nigeria. He has additional specialist training in the role of biotechnology in Medicinal Plants at the International Institute of Tropical Agriculture, Ibadan, Nigeria (2003), Advanced Leadership Training at the Haggai Institute of Leadership, Singapore (2007, Advanced Training in Renal pathophysiology techniques at the Center of Cardiovascular Diseases, Texas Southern University, Houston, TX, USA (2009-2010) and IUTOX training on environmental risk analysis with focus on water, air quality and hazardous chemical wastes in 2012. He has published in both national and international journals with over 180 publications to his credit. He is a recipient of Bassir-Thomas Biomedical Foundation award (1998); OMPADEC postgraduate award (2000); National Research Foundation of South Africa (2006-2007); UNESCO award (2008); Senior Fulbright Scholarship (2009-2010); International Union of Toxicology award (2012); University revitalization grant (2015); TETFUND NRF (2015) and many national and global conference travel supports.

Oluwafemi Omoniyi Oguntibeju is Professor of Biomedical Science and Group Leader (Phytomedicine & Phytochemistry Group), Department of Biomedical Sciences, Cape Peninsula University of Technology, Bellville, Cape Town, South Africa. Over the years, He has been involved in the field of HIV/AIDS and related- public health issues but later on natural products and health (Phytomedicine). He has successfully supervised 20 honours' projects, 25 masters and 7 doctoral students, 3 postdoctoral research fellows and currently supervising 6 doctoral and 6 masters' students at various stages of their programmes. He has published over 160 scientific articles in peer-review journals, 20 chapters in books, editor of three books on diabetes, presented over 70 papers at international and national conferences. He is a member of editorial board of various scientific journals and reviews manuscripts for various scientific journals. Professor Oguntibeju has received various awards such as the Gold and Platinum Research Excellence Awards at his current university. He is a National Research Foundation (NRF) C-rated researcher and hold Postgraduate Diploma (FIMLS) of the Institute of Medical Laboratory Science, Nigeria

in Clinical Biochemistry, MSc degree in Biochemistry from the University of Ibadan and doctoral degree in Biomedical Science, Central University of Technology, Free State (2005), South Africa.

Momoh Audu Yakubu, PhD, Tenured Professor of Pharmacology and Environmental Toxicology in the Department of Environmental and Interdisciplinary Sciences, a Senior Scientist and Head of Vascular Biology Unit of the Center for Cardiovascular Diseases, Professor of Pharmaceutical & Environmental Health Sciences, College of Pharmacy and Health Sciences, Texas Southern University, Houston - Texas. Dr. Yakubu employs interdisciplinary research approach integrating environmental, biological, pharmacological and toxicological analysis to meet the challenges of integrated medical and environmental concerns. His research is synergized by integrated analysis using of instruments such as – **Seahorse XFp** for evaluation of energy metabolism and regulation of variety of cellular and physiological processes in metabolic dysfunction/ or reprogramming of cells. Profiling and analysis of emerging contaminants; Analysis and Molecular consequences of exposure to complex chemical mixtures; Profiling of gut and saliva of *trypanosomes'* infected *tsetse fly* for differentially regulated proteins, peptides, and lipids, the role of gasotransmitters – NO, CO, and H_2S as neuroprotectants in stroke or traumatic brain injury. **Funding:** Dr. Yakubu's research had attracted funding from Carnegie Foundation, NIH, AHA, and others with a recent collaborative (with mentees from the University of Ibadan) award from UK based - World Small Animal Veterinary Association.

ORCID

Ademola Adetokunbo Oyagbemi, DVM, MSc, PhD, FCVSN http://orcid.org/0000-0002-8996-8610
Temidayo Olutayo Omobowale, DVM, MSc, PhD, FCVSN http://orcid.org/0000-0002-9486-2861
Adeolu Alex Adedapo, DVM, MSc, PhD http://orcid.org/0000-0003-3003-7579
Momoh Audu Yakubu, PhD http://orcid.org/0000-0002-6072-2473

References

Abu-Elsaad N, El-Karef A. 2018. The Falconoid luteolin mitigates the myocardial inflammatory response induced by high-carbohydrate/high-fat diet in wistar rats. Inflammation. 41(1): 221–231. doi:10.1007/s10753-017-0680-8.

Akaike T, Ando M, Oda T, Doi T, Ijiri S, Araki S, Maeda H. 1990. Dependence on O_2- generation by xanthine oxidase of pathogenesis of influenza virus infection in mice. J Clin Invest. 85(3):739–745. doi:10.1172/JCI114499.

Arafa Keshk W, Zahran SM, Katary MA, Abd-Elaziz Ali D. 2017. Modulatory effect of silymarin on nuclear factor-erythroid-2-related factor 2 regulated redox status, nuclear factor-κB mediated inflammation and apoptosis in experimental gastric ulcer. Chem Biol Interact. 273: 266–272. doi:10.1016/j.cbi.2017.06.022.

Arslan BY, Arslan F, Erkalp K, Alagöl A, Sevdi MS, Yıldız G, Küçük SH, Altınay S. 2016. Luteolin ameliorates colistin-induced nephrotoxicity in the rat models. Ren Fail. 38(10): 1735–1740. doi:10.1080/0886022X.2016.1229995.

Atwa A, Hegazy R, Shaffie N, Yassin N, Kenawy S. 2016. Protective effects of vasodilatory βeta-blockers carvedilol and nebivolol against glycerol model of rhabdomyolysis-induced acute renal failure in rats, maced. Open Access Maced J Med Sci. 4(3):329–336. doi:10.3889/oamjms.2016.082.

Aydogdu N, Atmaca G, Yalcin O, Taskiran R, Tastekin E, Kaymak K. 2006. Protective effects of L-carnitine on myoglobinuric acute renal failure in rats. Clin Exp Pharmacol Physiol. 33(1-2): 119–124. doi:10.1111/j.1440-1681.2006.04336.x.

Basnakian AG, Kaushal GP, Shah SV. 2002. Apoptotic pathways of oxidative damage to renal tubular epithelial cells. Antioxid Redox Signal. 4(6):915–924. doi:10.1089/152308602762197452.

Beker BM, Corleto MG, Fieiras C, Musso CG. 2018. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. Int Urol Nephrol. 50, 705–713 doi:10.1007/s11255-017-1781-x..

Benoist d'Azy C, Pereira B, Chiambaretta F, Dutheil F. 2016. Oxidative and anti-oxidative stress markers in chronic glaucoma: a systematic review and meta-analysis. PLoS One. 11(12): e0166915. doi:10.1371/journal.pone.0166915.

Beutler E, Duron O, Kelly BM. 1963. Improved method for the determination of blood glutathione. J Lab Clin Med. 61:882–888.

Boozari M, Hosseinzadeh H. 2017. Natural medicines for acute renal failure: a review. Phytother Res. 31(12):1824–1835. doi:10.1002/ptr.5943.

Cebi G, Yildiz S, Uzun G, Oztas Y, Sabuncuoglu S, Kutlu A, Ilgaz Y, Karatop-Cesur I, Dogan E, Oztas E. 2016. The effect of hyperbaric oxygen therapy on rhabdomyolysis-induced myoglobinuric acute renal failure in rats. Ren Fail. 38(9):1554–1559. doi:10.1080/0886022X.2016.1227925.

Chen X, Yu W, Li W, Zhang H, Huang W, Wang J, Zhu W, Fang Q, Chen C, Li X, et al. 2018. Liang G An anti-inflammatory chalcone derivative prevents heart and kidney from hyperlipidemia-induced injuries by attenuating inflammation. Toxicol Appl Pharmacol. 338:43–53. doi:10.1016/j.taap.2017.11.003.

Di Nicolò P. 2018. The dark side of the kidney in cardio-renal syndrome: renal venous hypertension and congestive kidney failure. Heart Fail Rev. 23 (2):291–302. doi:10.1007/s10741-018-9673-4.

Dkhil MA, Kassab RB, Al-Quraishy S, Abdel-Daim MM, Zrieq R, Abdel Moneim AE. 2018. Ziziphus spina-christi (L.) leaf extract alleviates myocardial and renal dysfunction associated with sepsis in mice. Biomed Pharmacother. 102:64–75. doi:10.1016/j.biopha.2018.03.032.

Domitrović R, Cvijanović O, Pugel EP, Zagorac GB, Mahmutefendić H, Škoda M. 2013. Luteolin ameliorates cisplatin-induced nephrotoxicity in mice through inhibition of platinum accumulation, inflammation and apoptosis in the kidney. Toxicology. 310:115–123. doi:10.1016/j.tox.2013.05.015.

Drury RA, Wallington EA. Editors. 1976. Carlton's histopathological techniques. 4th ed. London: Oxford University Press; p. 139–142.

Ellman GL. 1959. Tissue sulfhydryl groups. Arc Biochem Biophy. 82(1):70–77. doi:10.1016/0003-9861(59)90090-6.

Fattori V, Borghi SM, Guazelli CFS, Giroldo AC, Crespigio J, Bussmann AJC, Coelho-Silva L, Ludwig NG, Mazzuco TL, Casagrande R, et al. 2017. Vinpocetine reduces diclofenac-induced acute kidney injury through inhibition of oxidative stress, apoptosis, cytokine production, and NF-κB activation in mice. Pharmacol Res. 120:10–22. doi:10.1016/j.phrs.2016.12.039.

Gaikwad KB, Joshi NG, Selkar SP. 2017. Study of nitrosative stress in 'pregnancy induced hypertension. J Clin Diagn Res. 11(3):BC06–BC08.

Gois PHF, Canale D, Volpini RA, Ferreira D, Veras MM, Andrade-Oliveira V, Câmara NOS, Shimizu MHM, Seguro AC. 2016. Allopurinol attenuates rhabdomyolysis-associated acute kidney injury: Renal and muscular protection. Free Radic Biol Med. 101:176–189. doi:10.1016/j.freeradbiomed.2016.10.012.

Gornal AG, Bardawill JC, David MM. 1949. Determination of serum proteins by means of biuret reaction. J Biol Chem. 177(2):751–766.

Gu V, Yang M, Zhao X, Zhao B, Sun X, Gao V. 2014. Pretreatment with hydrogen-rich saline reduces the damage caused by glycerol-induced rhabdomyolysis and acute kidney injury in rats. J Surg Res. 188(1):243–249. doi:10.1016/j.jss.2013.12.007.

Habig WH, Pabst MJ, Jakoby WB. 1974. Glutathione-S-transferases. The first enzymatic step in mercapturic acid formation. J Bio Chem. 249(22):7130–7139.

Hu XF, Yao J, Gao SG, Wang XS, Peng XQ, Yang YT, Feng XS. 2013. Nrf2 overexpression predicts prognosis and 5-FU resistance in gastric cancer. Asian Pac J Cancer Prev. 14(9): 5231–5235. doi:10.7314/APJCP.2013.14.9.5231.

Humanes B, Camaño S, Lara JM, Sabbisetti V, González-Nicolás MA, Bonventre JV, Tejedor A, Lázaro A. 2017. Cisplatin-induced renal inflammation is ameliorated by cilastatin nephroprotection. Nephrol Dial Transplant. 32(10):1645–1655. doi:10.1093/ndt/gfx005.

Jacques-Silva MC, Nogueira CW, Broch LC, Flores EMM, Rocha JBT. 2001. Diphenyl diselenide and ascorbic acid changes deposition of selenium and ascorbic acid in liver and brain of mice. Pharmacol Toxicol. 88(3):119–125. doi:10.1034/j.1600-0773.2001.d01-92.x.

Jeddi F, Soozangar N, Sadeghi MR, Somi MH, Shirmohamadi M, Eftekhar-Sadat AT, Samadi N. 2018. Nrf2 overexpression is associated with P-glycoprotein upregulation in gastric cancer. Biomed Pharmacother. 97:286–292. doi:10.1016/j.biopha.2017.10.129.

Jiang H, Xia Q, Wang X, Song J, Bruce IC. 2005. Luteolin induces vasorelaxion in rat thoracic aorta via calcium and potassium channels. Pharmazie. 60(6):444–447.

Jollow DJ, Mitchell JR, Zampaglione N, Gillette JR. 1974. Bromobenzene-induced liver necrosis. Protective role of glutathione and evidence for 3,4-bromobenzene oxide as the hepatotoxic metabolite. Pharmacology. 11(3):151–169. doi:10.1159/000136485.

Kang KP, Park SK, Kim DH, Sung MJ, Jung YJ, Lee AS, Lee JE, Ramkumar KM, Lee S, Park MH, et al. 2011. Luteolin ameliorates cisplatin-induced acute kidney injury in mice by regulation of p53-dependent renal tubular apoptosis. Nephrol Dial Transplant. 26 (3):814–822. doi:10.1093/ndt/gfq528.

Kayali R, Cakatay U, Akçay T, Altuğ T. 2006. Effect of alpha-lipoic acid supplementation on markers of protein oxidation in post-mitotic tissues of ageing rat. Cell Biochem Funct. 24(1):79–85. doi:10.1002/cbf.1190.

Khan A, Dawoud H, Malinski T. 2018. Nanomedical studies of the restoration of nitric oxide/peroxynitrite balance in dysfunctional endothelium by 1,25-dihydroxy vitamin D3 - clinical implications for cardiovascular diseases. Int J Nanomedicine. 13:455–466. doi:10.2147/IJN.S152822.

Kim JH, Lee SS, Jung MH, Yeo HD, Kim HJ, Yang JI, Roh GS, Chang SH, Park DJ. 2010. N-acetylcysteine attenuates glycerol-induced acute kidney injury by regulating MAPKs and Bcl-2 family proteins. Nephrol Dial Transplant. 25(5):1435–1443. doi:10.1093/ndt/gfp659.

Kim KS, Lim HJ, Lim JS, Son JY, Lee J, Lee BM, Chang SC, Kim HS. 2018. Curcumin ameliorates cadmium-induced nephrotoxicity in Sprague-Dawley rats. Food Chem Toxicol. 114:34–40. doi:10.1016/j.fct.2018.02.007.

Kooti W, Daraei N. 2017. A Review of the Antioxidant Activity of Celery (*Apium graveolens* L). J Evid Based Complementary Altern Med. 22(4):1029–1034. doi:10.1177/2156587217717415.

Kröller-Schön S, Daiber A, Schulz E. 2018. Modulation of Vascular Function by AMPK: Assessment of NO Bioavailability and Surrogates of Oxidative Stress. Methods Mol Biol. 1732:495–506. doi:10.1007/978-1-4939-7598-3_31.

Liu Y, Fu X, Gou L, Li S, Lan N, Zheng Y, Yin X. 2013. L-citrulline protects against glycerol-induced acute renal failure in rats. Ren Fail. 35(3):367–373. doi:10.3109/0886022X.2012.760408.

Lv GY, Zhang YP, Gao JL, Yu JJ, Lei J, Zhang ZR, Li B, Zhan RJ, Chen SH. 2013. Combined antihypertensive effect of luteolin and buddleoside enriched extracts in spontaneously hypertensive rats. J Ethnopharmacol. 150(2):507–513. doi:10.1016/j.jep.2013.08.058.

Malakul W, Pengnet S, Kumchoom C, Tunsophon S. 2018. Naringin ameliorates endothelial dysfunction in fructose-fed rats. Exp Ther Med. 15(3):3140–3146. doi:10.3892/etm.2018.5759.

Misra HP, Fridovich I. 1972. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem. 247(10):3170–3175.

Mozos I, Luca CT. 2017. Crosstalk between Oxidative and Nitrosative Stress and Arterial Stiffness. Curr Vasc Pharmacol. 15(5):446–456. doi:10.2174/1570161115666170201115428.

Nabavi SF, Braidy N, Gortzi O, Sobarzo-Sanchez E, Daglia M, Skalicka-Woźniak K, Nabavi SM. 2015. Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. Brain Res Bull. 119 (Pt A):1–11. doi:10.1016/j.brainresbull.2015.09.002.

Olaleye SB, Adaramoye OA, Erigbali PP, Adeniyi OS. 2007. Lead exposure increases oxidative stress in the gastric mucosa of HCl/ethanol-exposed rats. WJG. 13(38):5121–5126. doi:10.3748/wjg.v13.i38.5121.

Oyagbemi AA, Omobowale TO, Akinrinde AS, Saba AB, Ogunpolu BS, Daramola O. 2015. Lack of reversal of oxidative damage in renal tissues of lead acetate-treated rats. Environ Toxicol. 30(11):1235–1243. doi:10.1002/tox.21994.

Oyagbemi AA, Omobowale TO, Asenuga ER, Adejumobi AO, Ajibade TO, Ige TM, Ogunpolu BS, Adedapo AA, Yakubu MA. 2017. Sodium fluoride induces hypertension and cardiac complications through generation of reactive oxygen species and activation of nuclear factor kappa beta. Environ Toxicol. 32(4):1089–1101. doi:10.1002/tox.22306.

Oyagbemi AA, Omobowale TO, Ola-Davies OE, Asenuga ER, Ajibade TO, Adejumobi OA, Afolabi JM, Ogunpolu BS, Falayi OO, Saba AB, Adedapo AA, Yakubu MA. 2018. Luteolin-mediated Kim-1/NF-kB/Nrf2 signaling pathways protects sodium fluoride-induced hypertension and cardiovascular complications. Biofactors. 44(6):518–531. doi:10.1002/biof.1449.

Pan GJ, Rayner BS, Zhang Y, van Reyk DM, Hawkins CL. 2018. A pivotal role for NF-κB in the macrophage inflammatory response to the myeloperoxidase oxidant hypothiocyanous acid. Arch Biochem Biophys. 642:23–30. doi:10.1016/j.abb.2018.01.016.

Park CH, Tanaka T, Cho EJ, Park JC, Shibahara N, Yokozawa T. 2012. Glycerol-induced renal damage improved by 7-O-galloyl-D-sedoheptulose treatment through attenuating oxidative stress. Biol Pharm Bull. 35(1):34–41. doi:10.1248/bpb.35.34.

Park CH, Yokozawa T, Noh JS. 2014. Oligonol, a low-molecular-weight polyphenol derived from lychee fruit, attenuates diabetes-induced renal damage through the advanced glycation end product-related pathway in db/db mice. J. Nutr. 144(8):1150–1157. doi:10.3945/jn.114.193961.

Perez Gutierrez RM, de Jesus Martinez Ortiz M. 2014. Beneficial effect of *Azadirachta indica* on advanced glycation end-product in streptozotocin-diabetic rat. Pharm Biol. 52(11):1435–1444. doi:10.3109/13880209.2014.895389.

Polderman KH. 2004. Acute renal failure and rhabdomyolysis. Int J Artif Organs. 27(12): 1030–1033. doi:10.1177/039139880402701204.

Pouvreau C, Dayre A, Butkowski EG, de Jong B, Jelinek HF. 2018. Inflammation and oxidative stress markers in diabetes and hypertension. JIR. Volume 11:61–68. doi:10.2147/JIR.S148911.

Qian LB, Wang HP, Chen Y, Chen FX, Ma YY, Bruce IC, Xia Q. 2010. Luteolin reduces high glucose-mediated impairment of endothelium-dependent relaxation in rat aorta by reducing oxidative stress. Pharmacol Res. 61(4):281–287. doi:10.1016/j.phrs.2009.10.004.

Racker E. 1954. Glutathione reductase from bakers' yeast and beef liver. J Biol Chem. 217: 855–865.

Reznick AZ, Packer L. 1994. Oxidative damage to proteins: spectrophotometric method for carbonyl assay. Meth Enzymol. 233:357–363. doi:10.1016/s0076-6879(94)33041-7.

Rodrigues de Carvalho L, de Brito TV, Simião da C Júnior J, José Dias Júnior G, de Aguiar Magalhães D, Guimarães Sousa S, Oliveira Silva R, Rodolfo Pereira da Silva F, Fernando Pereira Vasconcelos D, Maria Costa Véras L, et al. 2018. Epiisopiloturine, an imidazole alkaloid, reverses inflammation and lipid peroxidation parameters in the Crohn disease model induced by trinitrobenzenosulfonic acid in Wistar rats. Biomed Pharmacother. 102:278–285. doi:10.1016/j.biopha.2018.03.090.

Roy S, Chakraborty T. 2018. Deciphering the molecular mechanism and apoptosis underlying the in-vitro and in-vivo chemotherapeutic efficacy of vanadium luteolin complex in colon cancer. Cell Biochem Funct. 36(3):116–128. doi:10.1002/cbf.3322.

Si H, Wyeth RP, Liu D. 2014. The flavonoid luteolin induces nitric oxide production and arterial relaxation. Eur J Nutr. 53(1):269–275. doi:10.1007/s00394-013-0525-7.

Singh AP, Junemann A, Muthuraman A, Jaggi AS, Singh N, Grover K, Dhawan R. 2012. Animal models of acute renal failure. Pharmacol Rep. 64(1):31–44. doi:10.1016/S1734-1140(12)70728-4.

Sinha KA. 1972. Colorimetric assay of catalase. Anal Biochem. 47(2):389–394. doi:10.1016/0003-2697(72)90132-7.

Su Q, Su H, Nong Z, Li D, Wang L, Chu S, Liao L, Zhao J, Zeng X, Ya Q, et al. 2018. Hypouricemic and Nephroprotective Effects of an Active Fraction from Polyrhachis Vicina Roger On Potassium Oxonate-Induced Hyperuricemia in Rats. Kidney Blood Press Res. 43(1): 220–233. doi:10.1159/000487675.

Tomar A, Vasisth S, Khan SI, Malik S, Nag TC, Arya DS, Bhatia J. 2017. Galangin ameliorates cisplatin induced nephrotoxicity in vivo by modulation of oxidative stress, apoptosis and inflammation through interplay of MAPK signaling cascade. Phytomedicine. 34:154–161. doi:10.1016/j.phymed.2017.05.007.

Tsai JP, Lee CJ, Subeq YM, Lee RP, Hsu BG. 2017. Acute Alcohol Intoxication Exacerbates Rhabdomyolysis-Induced Acute Renal Failure in Rats. Int J Med Sci. 14(7):680–689. doi:10.7150/ijms.19479.

Tsikas D. 2017. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. Anal Biochem. 524:13–30. doi:10.1016/j.ab.2016.10.021.

Unis A. 2015. Açai berry extract attenuates glycerol-induced acute renal failure in rats. Ren Fail. 37(2):310–317. doi:10.3109/0886022X.2014.991262.

Varshney R, Kale RK. 1990. Effect of calmodulin antagonists on radiation induced lipid peroxidation in microsomes. Int J Radiat Biol. 58(5):733–743. doi:10.1080/09553009014552121.

Wang YD, Zhang L, Cai GY, Zhang XG, Lv Y, Hong Q, Shi SZ, Yin Z, Liu XF, Chen XM. 2011. Fasudil ameliorates rhabdomyolysis-induced acute kidney injury via inhibition of apoptosis. Ren Fail. 33(8):811–818. doi:10.3109/0886022X.2011.601830.

Wanigasuriya K, Jayawardene I, Amarasiriwardena C, Wickremasinghe R. 2017. Novel urinary biomarkers and their association with urinary heavy metals in chronic kidney disease of unknown aetiology in Sri Lanka: a pilot study. Ceylon Med J. 62(4):210–217. doi:10.4038/cmj.v62i4.8568.

Wolff SF. 1994. Ferrous ion oxidation in the presence of ferric ion indicator xylenol orange for measurement of hydrogen peroxides. Methods Enzymol. 233:182–189.

Wu J, Pan X, Fu H, Zheng Y, Dai Y, Yin Y, Chen Q, Hao Q, Bao D, Hou D. 2017. Effect of curcumin on glycerol-induced acute kidney injury in rats. Sci Rep. 7(1):10114doi:10.1038/s41598-017-10693-4.

Xia Y, Zweier JL. 1997. Measurement of myeloperoxidase in leukocyte-containing tissues. Anal Biochem. 245(1):93–96.

Xin SB, Yan H, Ma J, Sun Q, Shen L. 2016. Protective Effects of Luteolin on Lipopolysaccharide-Induced Acute Renal Injury in Mice. Med Sci Monit. 22:5173–5180. doi:10.12659/MSM.898177.

Xu Y, Zhang J, Liu J, Li S, Li C, Wang W, Ma R, Liu Y. 2015. Luteolin attenuate the D-galactose-induced renal damage by attenuation of oxidative stress and inflammation. Nat Prod Res. 29(11):1078–1082. doi:10.1080/14786419.2014.981181.

Yalçınkaya OY, Aydoğdu N, Taştekin E, Süt N. 2018. The Effects of Baicalin on Myoglobinuric Acute Renal Failure in Rats. Balkan Med J. 35(1):68–76. doi:10.4274/balkanmedj.2017.0040.

Yang Y, Chen B, Liang KL, Su J, Chen SH, Lv GY. 2017. [Relaxation effect of buddleoside combined with luteolin on isolated vessels in vivo and its mechanism]. Zhongguo Zhong Yao Za Zhi. 42(7):1370–1375. doi:10.19540/j.cnki.cjcmm.20170222.011.

Zhang JW, Lv GC, Zhao Y. 2010. The significance of the measurement of serum xanthine oxidase and oxidation markers in patients with acute organophosphorus pesticide poisoning. J Int Med Res. 38(2):458–465. doi:10.1177/147323001003800209.

Zhang X, Du Q, Yang Y, Wang J, Dou S, Liu C, Duan J. 2017. The protective effect of luteolin on myocardial ischemia/reperfusion (I/R) injury through TLR4/NF-κB/NLRP3 inflammasome pathway. Biomed Pharmacother. 91:1042–1052. doi:10.1016/j.biopha.2017.05.033.

Zheng H, Nong Z, Lu G. 2015. Correlation between nuclear factor E2-related factor 2 expression and gastric cancer progression. Med Sci Monit. 21:2893–2899. doi:10.12659/MSM.894467.