ORIGINAL ARTICLE

CONTENTS

Tangeretin ameliorates renal ischemia reperfusion injury *via* regulating oxidative stress and Notch1/Jagged1 signaling in male rats

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ABSTRACT

Aim: This study was performed to investigate the potential nephroprotective effect of Tangeretin on bilateral renal I/R injury in male rats.

Materials and Methods: Forty male rats were split into four groups of ten (sham, control, DMSO, and Tangeretin). The sham group underwent a median laparotomy under anaesthesia without inducing ischemia/reperfusion; the control group underwent clamping for thirty minutes on the bilateral renal artery, followed by two hours of reperfusion; the vehicle group received DMSO one hour before induction of ischemia; and the Tangeretin group received 5 mg/kg of Tangeretin one hour before ischemia. Biochemical parameters (KIM1, IL-1β, and TNF-α, F2-isoprostane, GSH, and caspase-3) were measured using an ELISA approach. Furthermore, histological alterations were examined, and the Notch/Jagged1 signalling pathway was assessed using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR).

Results: Tangeretin pre-treatment reduced kidney damage molecules (KIM1, IL-1β, and TNF-α, F2-isoprostane, GSH, and caspase-3) while increasing antioxidant indicators and decreasing inflammatory and apoptotic markers. Improving histological outcomes and significantly decreasing Notch1 and Jagged-1 gene expression in kidney tissues during renal ischemia/reperfusion injury.

Conclusions: Tangeretin has significant nephroprotective advantages in renal IRI by decreasing the Notch pathway and exhibiting anti-apoptotic, antioxidant, and anti-inflammatory properties.

KEY WORDS: renal IRI, Tangeretin, inflammation, oxidative stress, Notch1, Jagged-1, apoptosis and nephroprotection

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ABBREVIATIONS

IRI: Renal Ischemia-reperfusion Injury
AKI: Acute Kidney Injury
mPTP: mitochondrial Permeability Transition Pore
NICD: Notch Intracellular Domain
KIM: Kidney Function Measures

INTRODUCTION

Renal I/R injury results from a sudden, brief disruption of the kidney's blood supply, which is followed by the blood returning to normal and reoxygenation the tissue. This leads to several pathological changes, including glomerular damage and significant tubular damage, which is shown by nuclear sequestration, tubular dilatation, brush border defects, tubular formation, interstitial oedema, medullary congestion, and necrosis. Overproduction of (ROS) from broken tissue during I/R results in oxidative stress, and blood flow during reperfusion produces oxygen free radicals that cause apoptosis through lipid peroxidation and oxidative damage to proteins and DNA, which ultimately causes damage to kidney tissue [1-2]. Following an ischaemic insult, a considerable drop in mitochondrial ATP production, membrane potential, and the subsequent opening of the mitochondrial permeability transition pore (mPTP) [3]. The levels of ATP in proximal tubule cells fall to a trough within minutes of ischemia [4]. Furthermore, the drop in ATP levels may restrict the action of Na+/K+-ATPase, resulting in intracellular Na+ build-up and subsequent Ca2+ influx, leading to accumulation in mitochondrial. Following reperfusion, large increases in ROS and Ca2+ levels inside the mitochondria which cause mitochondrial dysfunction [5]. Reactive oxygen species, such as the hydroxyl radical, interact with DNA and damage the ribose-phosphate backbone. Furthermore, reactive oxygen species' interactions with lipid bilayers remove hydrogen atoms from unsaturated fatty acids attached to phospholipid; this process is called lipid peroxidation, which leads to the reduction of the integrity and functionality of cellular membranes [6]. As a result, the mPTP releases cytochrome C, which initiates the caspase

cascade and the mitochondrial death pathway [7]. Notch signalling pathway; mammals possess Notch ligands such as Jagged-1, Jagged-2, Delta-like 1 (DLL1), DLL3, and DLL4, as well as four Notch receptors (Notch1-4). The receptor and its ligands are transmembrane proteins that have many extracellular domains [8]. The interaction with ligand cause modulation of the receptor which lead to stimulating two proteolytic processes. The extracellular region sheds as a result of primary cleavage, which is carried out by metalloproteases from the ADAM family. The γ-secretase complex catalyses the second cleavage, which takes place within the membrane domain. The Notch intracellular domain (NICD) is then cleaved and transported to the nucleus, where it forms a transactivation complex [9]. This approach eliminates co-repressing complexes via co-activators, resulting in the transcription of Notch target genes, which comprise two families of transcriptional factors: hairy/enhancer-of-split linked with YRPWmotif (Hey) (HEY1 and HEY2) and hairy-enhancer of split (Hes) (HES1 and HES5) [10-13]. Furthermore, during ischemia reperfusion, the activation of the Notch pathway by ROS leads to the activation of metalloproteases (ADAM17), which indirectly triggers the discharge of NICD. NICD translocate to the nuclease and promotes transcription of its target genes, causing the development of fibrosis [14]. Tangeretin, a natural bioactive compound known as (5,6,7, 8,4-pentamethoxyflavone), which is a member of polyethoxylated flavones [15-16]. It is located evidently in citrus fruit peels and dried tangerine peels [17]. It exhibits different effects, which include antioxidant, anti-inflammatory, antidiabetic, anticancer, and neuroprotective results [18-20], moreover, Tangeretin exhibits neuroprotective consequences against ischemic stroke by increase the activity of superoxide dismutase and the survival of endothelial cells of human brain micro vascular. This action affects in reduced level of reactive (ROS) and malondialdehyde (MDA), which decrease apoptosis and subsequently reduce brain injury [21-22]. In kidney tissue, Tangeretin significantly decreased inflammatory cytokines and lipid peroxides with the improving the levels of both enzymatic and nonenzymatic antioxidants [23]. This normalization included antioxidant enzymes which include Catalase (CAT), Superoxide dismutase (SOD), Glutathione reductase (GR), and Glutathione peroxidase (GPx) in diabetic rats [24].

MATERIALS AND METHODS

PREPARATION OF ANIMALS

We obtained 40 male Wistar albino rats aged 8 to 12 weeks from the University of Kufa's Faculty of Science, each weighing 200 to 300 g. The rats lived at Kufa University's Faculty of Science Animal Facility. The animals were housed in cages with a 12-hour light/dark cycle, a temperature of 22 ± 2°C, and humidity levels ranging from 60–65%. The rats were given a typical meal that included commercial ordinary chow pellets and tab water. All experimental methods at the University of Kufa followed Institutional Animal Care and Use Committee (IACUC) guidelines.

STUDY DESIGN

Forty male Wistar albino rats were randomly assigned to four groups of ten each: sham, control, DMSO, and Tangeretin. The sham group underwent a median laparotomy under anaesthesia with no ischemia or reperfusion in the kidneys. While the IRI group (control group) underwent clamping in bilateral renal arteries for thirty minutes, followed by two hours of reperfusion, the vehicle group received DMSO intraperitoneally one hour before the induction of ischemia [25-26]. In the Tangeretin group, all ten rats were pre-treated with Tangeretin 5 mg/kg [27] and for anaesthesia during the procedure, the rats received an intraperitoneal injection of 10 mg/kg xylazine and 100 mg/kg ketamine [28].

SAMPLING TECHNIQUES

TISSUE SAMPLING FOR BIOCHEMICAL ANALYSIS

The kidney tissues were stored at -80°C until homogenised with a high-intensity ultrasonic liquid processor in 1:10 W/V phosphate buffered saline with 1% Triton X-100 and a protease inhibitor cocktail. The homogenate samples were centrifuged at 4°C for 15 minutes at 14000 rpm [29-30], then we analysed the supernatants for kidney injury markers (KIM, TNF-α, IL-1β, F2-isoprostane, GSH, and caspase-3).

TISSUE SAMPLING FOR IMMUNOHISTOCHEMISTRY

This approach makes use of formalin-fixed, paraffin-embedded slides. Primary antibodies target particular antigens, while labelled secondary antibodies assess target protein expression. The antigen-antibody combination is detected using a labelling approach that is either fluorescent or enzymatic. IHC analysis is based on the labelled streptavidin-biotin staining technique (LSAB).

ANALYSIS OF NOTCH SIGNALING PATHWAY BY QRT-PCR.

Notch-1 and Jagged-1 expression levels in the kidney were determined using qRT-PCR. We extracted around 50-100 mg of kidney tissue using the Easy-spin™ (DNA-

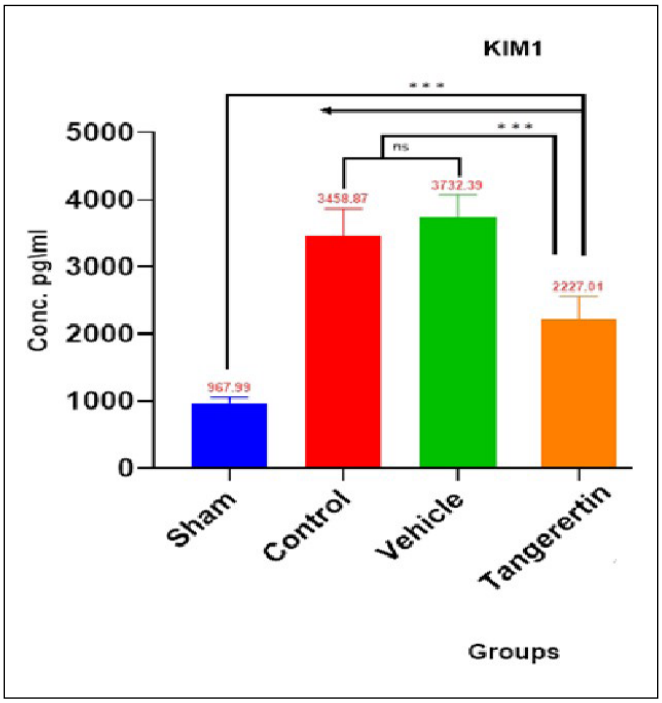

Fig. 1. Impact of Tangeretin on levels following renal IR, tissue KIMI (pg/ml) among groups, Mean ± SD, n=10
***p≤0.001 *vs.* sham; ***p≤0.001 *vs.* control/vehicle
Source: Own materials

free) total RNA extraction Kit (Intron/Korea) according to the manufacturer's procedure. cDNA was synthesised using reverse transcription using the Add Script cDNA Synthesis Kit according to the manufacturer's instructions. PCR was carried out in accordance with the GoTaq® RT-qPCR System instructions. The sequences of the primer for Jagged1 (F) AACTGGTACCGGTGCGAA (R) TGATGCAAGATCTCCCTGAAAC; Notch1 (F) CACCCATGACCACTACCCAGTT (R) CCTCGGACCAATCAGAGATGTT [31] and for GAPDH (F) ATGACTCTACCCACGGCAAG [32] for specific gene amplification. The 2-ΔΔCt method was used to measure fold changes in gene expression. Gene expression is measured as a relative fold change from GADPH, an internal control reference gene.

INVESTIGATIONS

BIOCHEMICAL MARKERS ANALYSIS

By using Elisa kits from SunLong Biotech Co.LTD, China, to evaluate the levels of KIM1, IL-1β, and TNF-α, F2-isoprostane, GSH, and caspase-3.

STATISTICAL ANALYSIS

The statistical analysis for this study was carried out using Graph Pad Prism version 8 software. After determining the normal distribution of data. To make numerous comparisons across groups, the one-way ANOVA test was utilised using parametric variables, and the Bonferroni procedure was chosen for the Post Hoc test. P-values less than 0.001 were deemed statistically significant in all tests, all data are presented as mean ± SD.

RESULTS

The ischemia lasted 30 minutes, with two hours of reperfusion. Prior to one hour of ischemia, the rats received DMSO, Tangeretin (5 mg/kg), or were left untreated (sham and control groups). Several biochemical indicators were used to assess the degree of kidney injury.

IMPACT ON KIDNEY INJURY MOLECULE (KIM1 1)

Following renal I/R, the IRI (control) group had significantly greater tissue KIM1 levels than the Sham group. Tangeretin treatment resulted in a significant decline in KIM 1 levels in tissues (Fig. 1)

IMPACT ON KIDNEY TISSUE INFLAMMATORY MARKERS

The IRI group showed significantly higher levels of TNF-α and IL-1β in their tissues than the sham group. The Tangeretin group dramatically reduced tissue inflammatory parameters (IL-1β and TNF-α) (Fig. 2 A-B).

IMPACT ON OXIDATIVE AND APOPTOTIC MARKERS

F2-isoprostane, GSH, and caspase-3 levels in rat kidney tissue were significantly increased in the IRI group compared to the Sham group. Tangeretin treatment increased antioxidant marker (GSH) levels in renal tissue while reduced apoptotic marker (Caspase-3) levels when compared to the control group (IRI) (Fig. 3 A-C).

HISTOPATHOLOGICAL FINDINGS

The Sham group reported much lower damage estimates than the other groups (***, p < 0.001 vs. Sham). Tangeretin showed much less damage than the control and DMSO groups (***p < 0.001 vs. induced groups), indicating a nephroprotective effect (Fig. 4).

The control group had a significant abnormality in renal structure, with severe renal tissue architecture changes such as tubular increased cytoplasmic eosin-

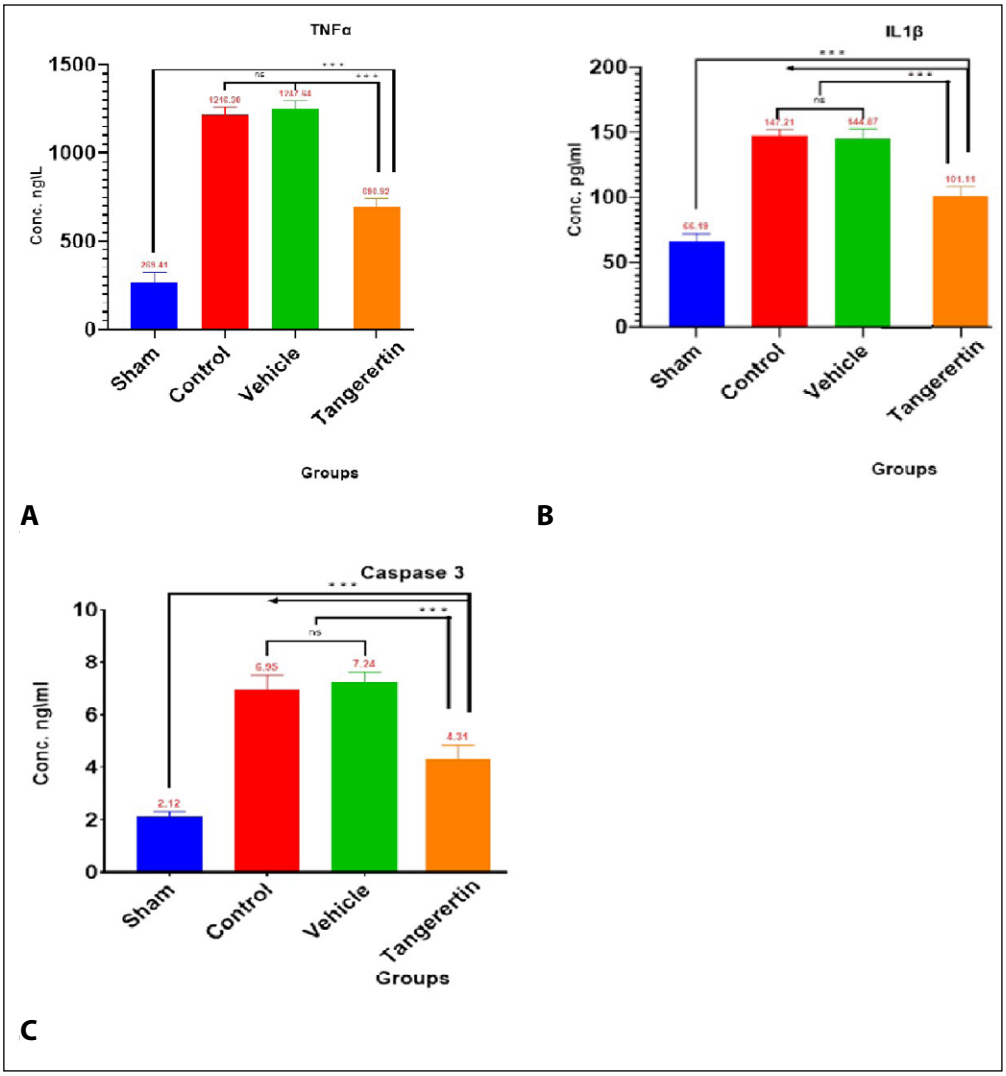

Fig. 2. Effect of Tangeretin on TNF-α (A) and IL-1β (B) levels after renal IR, including tissue TNF-α (ng/L) and IL-1β (pg/ml) between groups, n = 10, mean ± SD
***p≤0.001 *vs*. sham;
***p≤0.001 compared control/ vehicle
Source: Own materials

ophilia, cellular swelling, tubular epithelium degeneration, vascular congestion, eosinophilic cast, and cytoplasmic vacuoles (score = 4 and representing > 75% of damage). The group that got DMSO exhibited comparable pathology to the IRI group. The Tangeretin group showed moderate alterations in renal architecture (scoring = 2) (Fig. 5A-F).

The Sham group had a normal morphological appearance tissue without histological change while control and vehicle groups had severe morphological change in renal tubules include increased cytoplasmic eosinophilia, eosinophilic cast, cytoplasmic vacuoles and cytoplasmic swelling. Tangeretin pre-treated group the renal tubules damage with score 2 characterized by involving 30% of the examined damaged tubules.

IMPACT ON NOTCH1 AND JAGGED1 M RNA EXPRESSION

Notch1 and Jagged-1 expression levels in renal tissue were significantly greater in the control and vehicle groups compared to the sham group ($p<0.001$). However, there was no significant difference between the vehicle and control groups. Tangeretin showed significantly lower levels ($p<0.001$) compared to the sham, control, and vehicle groups (Fig. 6).

DISCUSSION

Ischemia is a quick transitory drop in blood flow to the organ and subsequent reoxygenation, which is followed by a severe oxidative stress and inflammatory response to hypoxia and reperfusion, disrupting organ function [33] cause exacerbation in tubular and glomerular damage due to strong inflammatory response, called "reperfusion injury" [34]. This research aims to explain the nephroprotective impact of Tangeretin in the kidneys through decrease inflammation, oxidative stress, and apoptotic pathway. The current investigation found that renal IRI raised tissue levels of KIM1, IL-1β, and TNF-α, F2-isoprostane, and caspase-3 with decreased GSH in kidneys of rats. Interestingly, pre-treated with Tangeretin

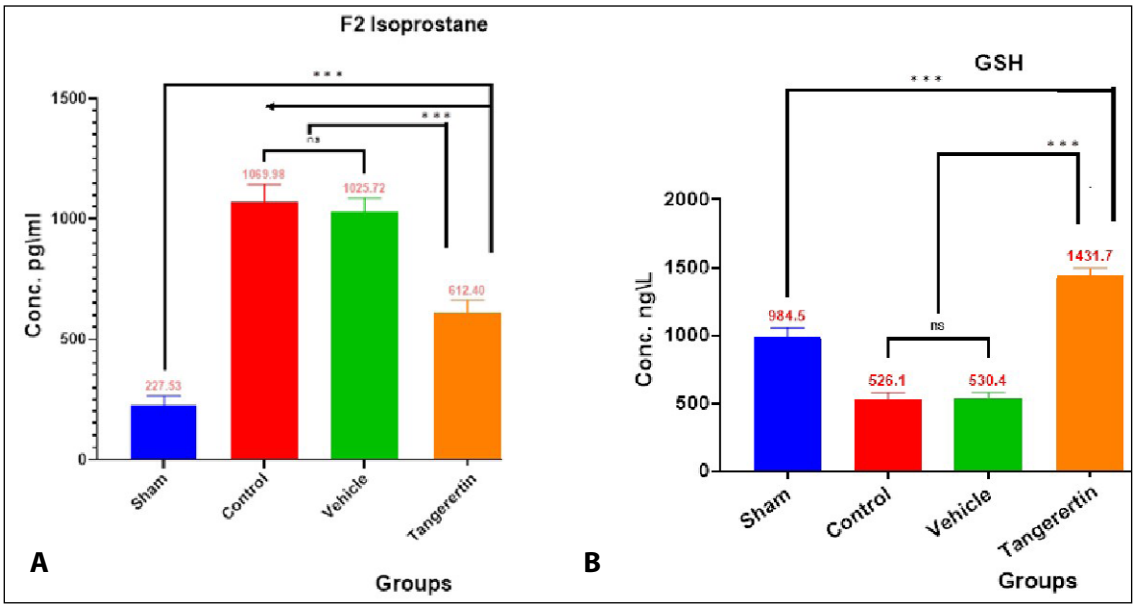

Fig. 3. Effect of Tangeretin on levels F2-isoprostane, GSH, and caspase-3 following renal IR, tissue F2-isoprostane (pg/ml), GSH (ng/L) and caspase-3(ng/ml) between groups, Mean ± SD, n=10,
***p≤0.001 *vs.* sham; ***p≤0.001 *vs.* control and vehicle
Source: Own materials

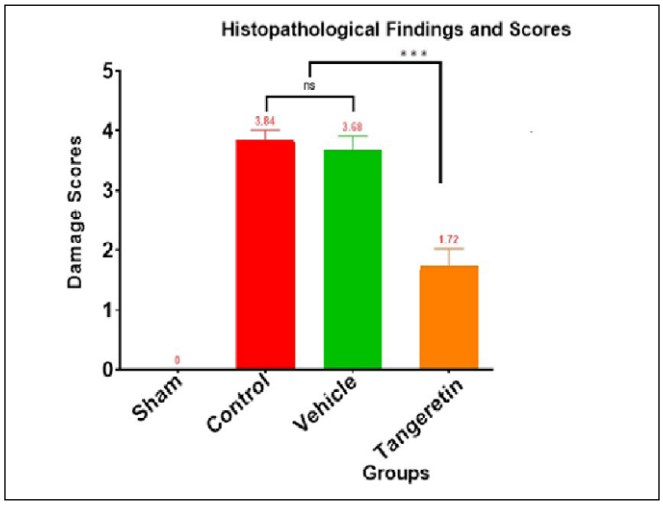

Fig. 4. Mean of Histopathological kidney injury score
***p < 0.001 vs. control & vehicle groups, the Kruskal-Wallis test was used for analysis, data are expressed as mean ± SD
Source: Own materials

increased the level of antioxidant (GSH) with reduced levels of KIM1, oxidative stress marker (F2-isoprostane), apoptotic marker (Caspase-3), and inflammatory markers (IL-1β, TNF-α). According to [35], increasing the level of KIM-1 in the proximal tubule in early kidney damage has the advantage of being a sensitive, specific, and ideal biomarker marker for early diagnosis of kidney injury, including acute kidney injury (AKI), as well as a prognostic predictor. The results indicate that Tangeretin has a protective effect on kidney function measures (KIM) after renal IRI. The [36] found that Tangeretin reduce significantly renal tissue levels of KIM-1 in cisplatin induced nephrotoxicity of rats kidney tissue which reflects amelioration in the kidney functions. The important parameters for detection of inflammation in RIRI are (TNF-α, IL-1β). This result agreement with [37] which shown that the level of TNF-α was increased after 30 minutes of ischemia followed by 2 hours of reperfusion in a rat model. The reference [38] demonstrated that elevation of the inflammatory cytokines (IL-1β and TNF-α) as a result of hypoxia due to decreased in renal supply which cause infiltrate of different inflammatory cells into the injured tissue. Pre-treatment with Tangeretin significantly suppresses production of inflammatory markers TNFα and IL-1β. This consistent with a study by [36] revealed that Tangeretin decreases NF-κB activity lead to significantly decline in TNF-α and IL-1ß protein levels in kidney tissue which alleviates oxidative stress and renal inflammation in cisplatin-induced nephrotoxic rats and enhancement of renal protective mechanisms of renal tubular cell injuries. The research showed significant elevation in F2 Isoprostane in renal tissue of the IRI group, that mean there is increase in the level of ROS formation due to oxidative stress which consist with study by [39] have established that during IRI, inflammation and tubular cell injury can be caused by a burst of (ROS); hence, lowering oxidative stress can prevent damage in IRI by assessing F2-isoprostane. The pre-treatment group with Tangeretin exhibited a substantial decrease in the level of F2 Isoprostane, and no prior study has demonstrated the effect of Tangeretin on (F2) in RIRI damage in a rat animal model. The reference [40] demonstrated that

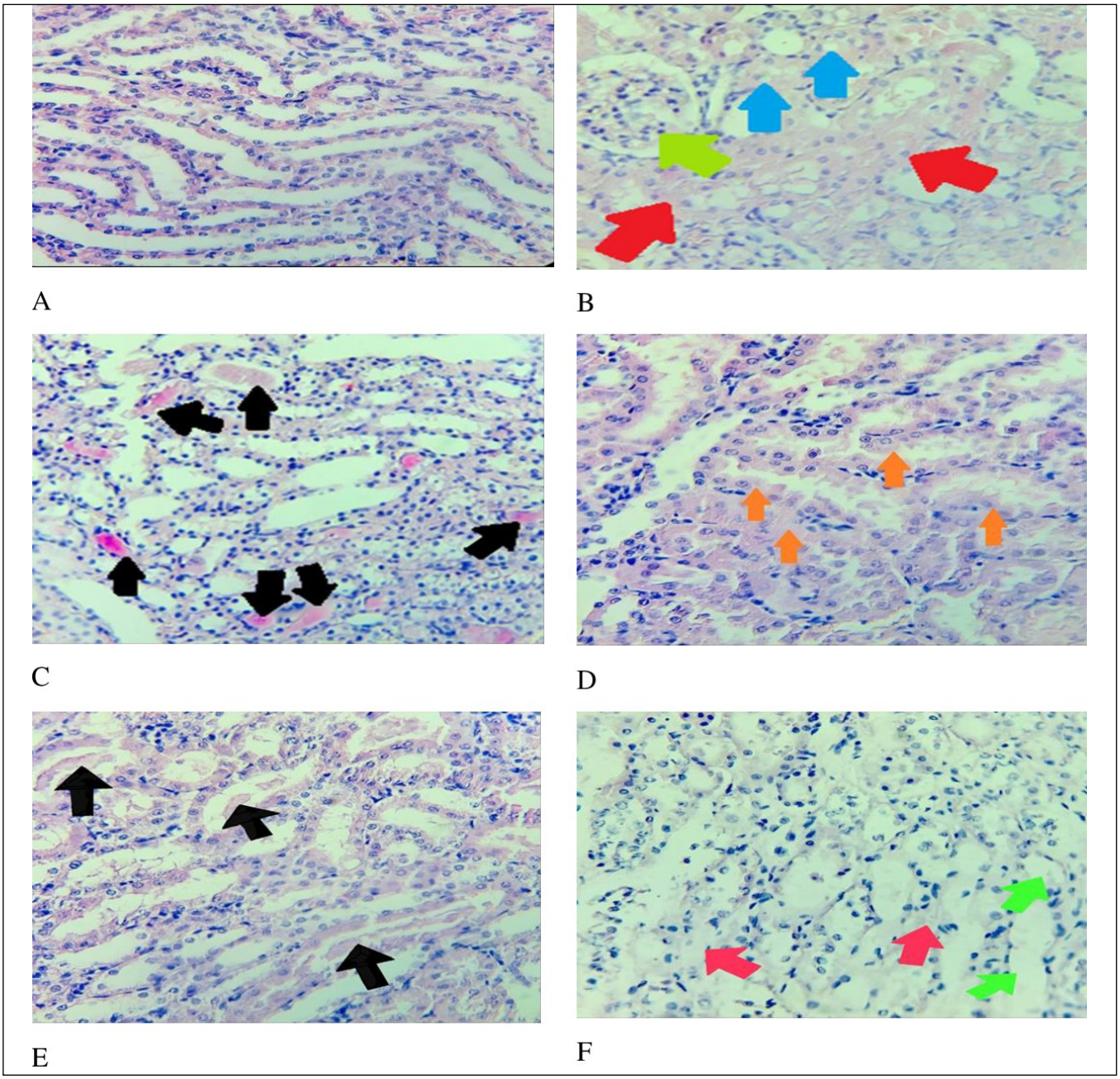

Fig. 5. Histopathological analysis of renal tissues, (A) Sham group has normal renal tubules, (B, C) Control group, renal tubules with score 4 damage, cytoplasmic swelling and increased cytoplasmic eosinophilia (red arrows), cytoplasmic vacuoles (blue arrows), eosinophilic cast (black arrows), normal glomerulus (green arrow), (D, E) Vehicle group, renal tubules with score 4 damage, Cytoplasmic swelling and increased cytoplasmic eosinophilia (red arrows), eosinophilic cast (black arrows), vascular congestion (orange arrow), (F) Tangeretin group renal tubules with score 2 damage, damaged tubules (red arrows), normal tubules (green arrows), H&E. X400
Source: Own materials

Tangeretin downstream the protein expression of nitric oxide (NO)in renal tissues, which cause attenuating renal oxidative stress and inflammation therefore have protective actions against cisplatin-induced renal injury in rats. The research showed significant reduction in Glutathione (GSH) in renal tissue of IRI group, this result agreement with [41] which indicated that GSH levels were considerably lower in the renal IRI and vehicle groups as compared to the sham group in response to renal ischemia reperfusion, indicating that this is due to a decline in the kidney's capacity to serve as an antioxidant. The significantly higher the level of (GSH) in renal ischemic tissues of group that pre-treated with Tangeretin, [36] shown that Tangeretin pre-treatment group significant increased the levels of CAT, GSH and concentrations of SOD in renal tissues which alleviates renal oxidative stress and inflammation, these effects reduces renal nitric oxide (NO) and malondialdehyde

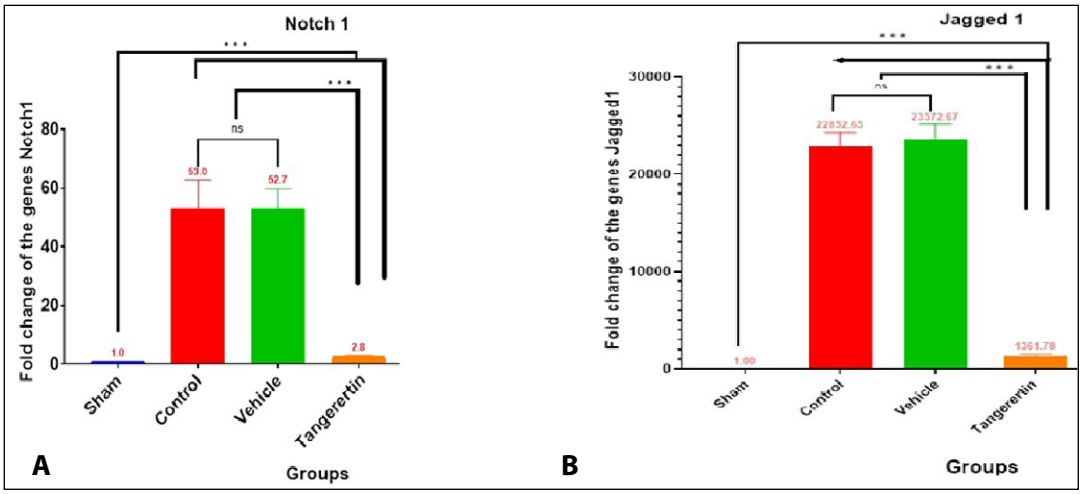

Fig. 6. (A) The bar graph Notch gene expression, (B) The bar graph Jagged-1 gene expression, All data were expressed as mean ± SD (n = 10), Sham group *vs.* vehicle & control groups ***p < 0.001, Tangeretin treated group *vs.* vehicle & control groups, ***p < 0.001.
Source: Own materials

1(MDA) levels with concomitantly increases GSH concentrations which ameliorative nephrotoxic effect by cisplatin in the renal tissue and improve renal function. The significant increase of Caspase-3 in current study agreement with [42] shown that after thirty minutes of renal ischemia after that two hours of reperfusion in rats model the significant increase in Caspase-3 level with a significant decrease in Bcl-2, which explain the results that apoptosis is a conclusive process in renal IRI and the stimulation of caspase-3 have an important role for programmed cell death because the equilibrium between antiapoptotic (Bcl-2) proteins and pro-apoptotic (Bax) is essential for the survival of cells, the disruption. The significant decreased in Caspase-3 level in Tangeretin pre-treated group shown the nephroprotective effect of Tangeretin after renal IRI, the research by [43] revealed that the pre-treated group with Tangeretin can attenuate cisplatin induced apoptosis in hepatic injury tissues in rats model which inhibited the apoptotic markers Bax and caspase with increased the anti-apoptotic Bcl-2 with suppression of TNF-α and oxidative stress cause attenuation of hepatic tissue apoptosis. Furthermore, histological examinations confirmed Tangeretin have protective properties in kidney injury. These examinations demonstrated a significant reduction in renal tissue damage, including decrease in infiltration of inflammatory cells, and damage of renal tubules in rats treated with Tangeretin compared to control and vehicle groups, there has been no research to determine the effect of Tangeretin on reducing tissue damage in unilateral or bilateral renal ischemia/reperfusion injury models in rats or mice. The findings in the current study were parallel to the histopathological results through the ability of Tangeretin to decrease oxidative and the inflammatory markers and the results agreement with study by [36] which showed that Tangeretin pre-treatments groups markedly improved histological changes in the kidneys against oxidative stress and inflammations induced by cisplatin through reduced serum levels of blood urea nitrogen (BUN) and creatinine with declined renal levels of the inflammatory cells into the perivascular and sub vascular areas. Moreover, in the present study the level of Notch gene expression in renal tissue of IRI group significantly greater than sham group, this finding is consistent with [44] that show there was a significant upregulation of Notch expression in the endothelial cells and increased cleaved Notch1 was found in all parts of the post ischemic kidney with strongest signal intensity in proximal tubules. The reference [45] revealed that Notch signaling plays a key role in the developing kidney by regulation of ontogenetic nephron segmentation which strongly reduced in the adult kidney but reactivation of Notch has been appeared in chronic and acute kidney injury. The level of Notch1 pathway gene expression was significantly lower in Tangeretin treated group than IRI control group, there is no previous study demonstrate the effect of Tangeretin on Notch1 Jagged1 gene expression in renal ischemia reperfusion injury in an animal model. The reference [46] demonstrated that Tangeretin could specifically inhibit the expression of Notch1 and Jagged1 in CD4 + T cells which can mitigate allergic rhinitis by inhibiting the expression of Notch1 and Jagged1.

The data in the present study adds novel insights about the effects of Tangeretin to protect the tissue damage due to ischemia/reperfusion in kidney as show by [40] that Tangeretin markedly attenuates cisplatin-induced histopathological alterations in renal tissues and preserved the renal architecture with mitigation of renal leukocyte recruitment, the changes in renal tissues due to free radical generation along with lowering of cellular anti-oxidants enhanced renal cellular damage, tangeretin which have antioxidant action reversed the generation of lipid peroxides and NO with augmented the cellular GSH and GPx.

CONCLUSIONS

Tangeretin shown a nephroprotective effect due to ischemia/reperfusion (I/R). Tangeretin exhibited anti-apoptotic, antioxidant, and anti-inflammatory characteristics by significant decreased in inflammatory, oxidative apoptotic markers and Notch1 and Jagged-1 expression in kidney tissues after renal ischemia/reperfusion damage. Therefore it may be a promising treatment people with RIRI.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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