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Tideglusib Reduces kidney damage in renal ischemia –reperfusion injury through wnt activation in male rats

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ABSTRACT

Background: Renal ischemia-reperfusion injury (RIRI) is a serious complication associated with kidney surgery, transplantation, and conditions impairing renal perfusion. Its pathogenesis involves oxidative stress, inflammation, and cell death pathways. Developing effective therapeutic strategies requires targeting these mechanisms. This study evaluated the protective effect of Tideglusib, a selective glycogen synthase kinase 3β inhibitor that activates the Wnt/β-catenin signaling pathway, in an experimental rat model of RIRI. Rats were divided into six groups: sham, untreated RIRI control, vehicle groups for QS11 and Tideglusib, and treatment groups receiving QS11 or Tideglusib. **Aim of study:** The objective of this research was to evaluate the renoprotective effects of Tideglusib through the activation of the Wnt/β-catenin signaling pathway in a rat model exhibiting acute kidney injury induced by ischemia-reperfusion. **Methodology:** An experimental rat model of renal ischemia-reperfusion injury was established by clamping the renal pedicles for 30 minutes, followed by 90 minutes of reperfusion. Renal function was evaluated by measuring kidney injury molecule-1 (KIM-1). Apoptotic markers (Bax, Bcl-2), inflammatory mediators (TNF-α, IL-1, IL-6), and antioxidant proteins (Nrf2, HO-1) were quantified using ELISA. **Result:** The capacity of Tideglusib to enhance the wnt β-catenin signaling pathway has been demonstrated to substantially mitigate renal ischemia-reperfusion injury (RIRI) in comparison to the control cohort. Nevertheless, this pharmacological agent (Tideglusib) demonstrated a protective role against apoptosis, or programmed cell death. When juxtaposed with the control group exhibiting RIRI, the sham group displayed reduced levels of Bax, a pro-apoptotic mediator and elevated Bcl2. Additionally, the Tideglusib-treated cohort presented lower concentrations of both Bax,NFkB and elevated Bcl2 in comparison to the control group with RIRI.

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1. Introduction

Acute kidney injury (AKI), formerly termed acute renal failure, is a major clinical problem and a frequent cause of hospitalization. Over the past 15 years, its incidence has risen significantly, yet the associated morbidity and mortality rates have shown little improvement despite considerable advancements in medical technology and supportive therapies.

Renal ischemia-reperfusion (RIR) injury represents one of the principal causes of AKI, leading to a rapid decline in renal function and elevated serum creatinine levels. The pathophysiology of RIR-induced damage is multifactorial, involving apoptosis, excessive production of reactive oxygen species (ROS), activation of neutrophils, and the release of pro-inflammatory mediators such as adhesion molecules and cytokines. These complex and interconnected pathways contribute to progressive renal parenchymal injury, often resulting in sub-lethal damage to kidney cells and impaired tissue repair.

Understanding these underlying mechanisms is essential for developing effective therapeutic strategies to mitigate renal ischemia-reperfusion injury and improve clinical outcomes in patients at risk of AKI.

The route of Wnt-βcatenin:

Canonical and noncanonical Wnt signaling pathways are the two varieties. Noncanonical Wnt pathways that are independent of β-catenin-Tcell factor/lymphoid enhancer-binding factor (TCF/LEF) include the Wnt/Ca2+ pathway and noncanonical Wnt planar cell polarity (3).

Mechanisms of the Wnt-catenin pathway:

The Wnt/β-catenin pathway may be caused by inactivation of Wnt signaling: When Wnt signaling is absent, β-catenin is broken down by protein complexes like AXIN, APC, serine/threonine kinase GSK-3, CK1, and E3 ubiquitin ligase β-trcp. AXIN binds to phosphorylated lipoprotein receptor-related protein (LRP) when it binds to its receptor, activating Wnt signaling. After the destruction complex is broken, β-catenin stabilizes and binds to TCF in the nucleus to regulate the target gene. APC adenomatous polyposis coli, TCF T cell factor, LEF lymphocyte enhancer factor-1, GSK-3 glycogen synthase kinase-3, AXIN axis inhibition protein, and CK1 casein kinase 1 (4).

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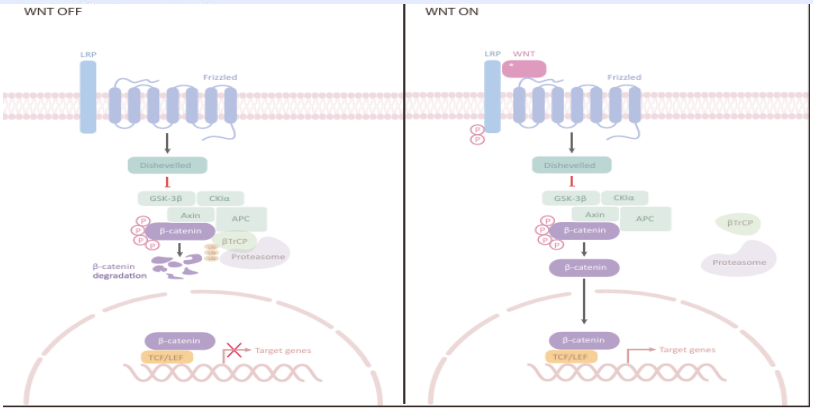

Figure (1) wnt βcatenin pathway mechanisms **(4)**

2. The function of Wnt signaling in acute kidney damage:

Acute injury to the kidneys damages and kills tubular epithelial cells. These damaged cells release pro-inflammatory cytokines and Wnts, which draw macrophages and trigger the Wnt pathway. Wnt/β-catenin signaling activation in tubular epithelium has many downstream effects, the primary ones being proliferation or inhibition of apoptosis. Apoptosis is prevented by inhibiting pro-apoptotic Bax (B-cell lymphoma-2(Bcl-2)associated X protein), which is achieved by p53 suppression and/or β-catenin-dependent activation of Akt (protein kinase B). (5)Additionally, Wnt/β-catenin signaling promotes the expression of survivin, which aids in cell survival. Wnt/β-catenin signaling promotes target genes, including the pro-proliferative proteins cyclin D and cMyc. Healing is the outcome of these damaged cells differentiating, and proliferation helps to replenish cells lost due to injury. (5)

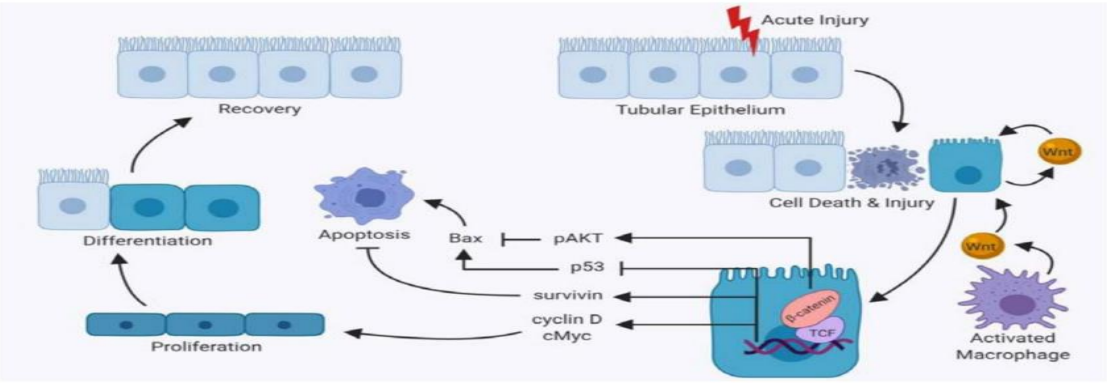

Figure (2) Effect of Wnt signaling in acute kidney injury. **(5)**

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Glycogen synthase kinase-3 (GSK-3)

A serine/threonine protein kinase with two functionally different isoforms, α and β, was found in the context of glycogen metabolism and emerged as a ubiquitous regulator of numerous signaling pathways (Figure 3).(6) Phosphorylation of tyrosine 216 and serine 9 prepares the GSK-3 beta (GSK-3β) enzyme to either activate or inhibit its kinase capabilities, respectively.(7)About 100 proteins have been identified as phosphorylation targets of GSK-3β.8 GSK-3β can act as a tumor suppressor by preparing oncogene products for degradation by the proteasome, or it can act as a pro-oncogene, mostly through pathways that promote cell growth, including Wnt/β-catenin(.9) Recent studies have connected GSK-3 to higher levels of programmed cell death-1 (PD-1) expression, and stopping GSK-3 made T-cells respond better.(10)

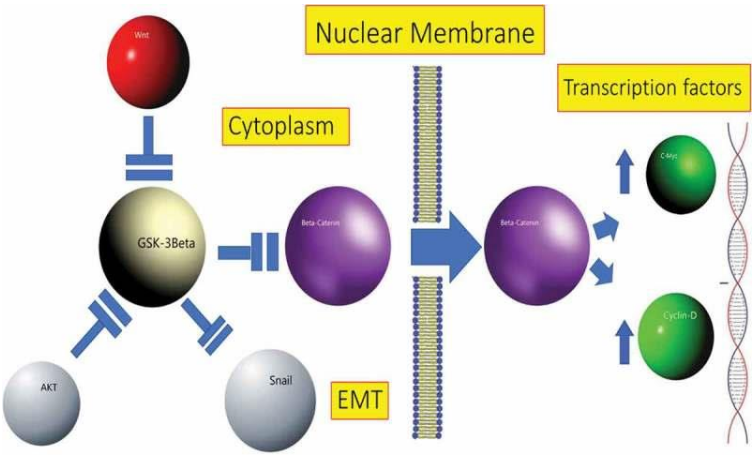

Figure 3 the pathway of GSK3β(6)

Tideglusib (GSK3β inhibitor):

Small –molecule of the thiadiazolidinone ,The proline/serine protein kinase GSK-3 is a well-known protein that is involved in several cellular signaling pathways. It has many different jobs, but it is very important in Alzheimer's disease. This function is linked to tau and β-amyloid pathology. Some people think that aberrant Wnt or insulin signaling causes GSK-3 to work better. This kinase interacts with γ-secretase, which causes senile plaques, neurofibrillary tangles, and tau hyperphosphorylation.3. Tideglusib inhibits GSK-3 permanently by acting as a non-competitive inhibitor of ATP. The motif including Cys199.4 seems to be directly associated with tideglusib binding.(11)

Materials and methods

Animal Preparation :

The Wistar Albino rats in this study weighed between 300 and 350 grams and came from the

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Animal Resources Center at Duhok University's College of Veterinary Medicine. The animals lived at Kufa University in an animal housing that had a 12-hour light-dark cycle and a temperature range of 24 ± 2°C.
The rats were given a normal diet of food and water. The experiments started after two weeks of getting used to the quarantine chamber. maintaining the rats in the study after the University of Kufa's Animal Care and Research Committee has accepted them and the necessary forms have been sent in.

Preparation of Tideglusib

The dose TDS of each rat 33.23mg/kg after the coversion the dose in mouse of TDS into the dose in rat by using the equition

Dose in rat = dose in mouse *(wt of rat /wt of mouse)^0.75**(12).**

The solubility 109.69mg of TDS disolve in 6ml of 0.9% saline containing 5% DMSO and 5% Tween-80. The Rat dose 33.23mg/kg were injected with tideglusib or vehicle solution intraperitoneally (i.p.) 20 min prior to surgery **(13)**

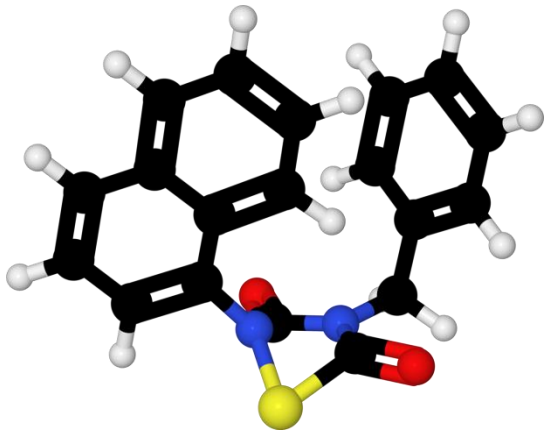

Figure 4 structure of Tideglusib (Wikipedia)

The study design:
Sixty mature male rats, weighing between 300 and 350 grams, are given free access to water and regular rat food. Every study is carried out with Kufa University's Ethical Committee's consent. The six groups (n = 10) of rats are as follows:
1. **IRI-free sham group**: rats received the same anesthetic and surgical treatments with the exception of ischemia induction.
2. Ischemia reperfusion damage was modeled by the control group (NO treatment IRI) (12),(13)

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3. The Control Vehicle 1 group (vehicle1 + IRI)
4. QS11group's Wnt-catenin activator (QS11+ IRI)
5-Control Vehicle 2 group (vehicle2 +IRI):
6. The group known as "tediglusib+IRI" is an inhibitor of glycogen synthase kinase (GSK)3β.
Twenty minutes before surgery, rats receiving a dose of 33.23 mg/kg were given an intraperitoneal (i.p.) injection of either tideglusib or a vehicle solution **(13).**
In this investigation, groups **2 and 6** were used as test groups.

RIRI experimental model: RIRI experimental model: To put rats to sleep, xylazine hydrochloride (10 mg/kg) and ketamine hydrochloride (100 mg/kg) were given intraperitoneally **(14).** To make sure the rats would stay still during the process, they were laid on their backs and made immobile by sticking stickers to their legs and tails. After the men's hair was cut off, their skin was washed. Putting pressure on the back and tail of the feet during the reflex test showed how well the anesthetic worked. After making a midline laparotomy cut in the abdomen, the intestines were pulled back to show the renal pedicles. A midline cut was made to get to the abdominal region. After making a cut in the middle to get to the abdomen, the renal arteries on both sides were revealed and freed by blunt dissection. A microvascular clamp was used to stop the renal pedicle and limit blood flow. Rats were kept in a 37 °C room and had their core temperatures checked often. After 30 minutes, the clamp was taken off to let blood flow back to the kidney **(15).** After the clamp was taken off, the kidney's color changed from dark blue to rich red, which meant that reperfusion had been successful. After the cut from the surgery was fixed, the animals were put back in their cages and given 90 minutes of rest to allow for reperfusion **(16).** have time to rest and recover, and they can eat and drink whatever they want. Rats were put to sleep and then killed after the time of resuscitation. After the kidneys were taken out and split in half, blood samples were taken directly from the heart. One part was preserved in tissue for histology study, and the other was preserved in 10% formalin.

Sample Preparation

Sampling of Blood: A gel tube was used to remove roughly 1 cc of cardiac blood following the procedure. Blood samples were centrifuged at 4000 revolutions per minute (rpm) for 10 minutes. The serum component was then isolated, and its kim levels were assessed.

Preparing Tissue for TNF, IL1B, HO-1, Nrf2, and IL6 Measurements.

After being cleaned in cold saline to eliminate red blood cells and clots, the kidneys were homogenized using a high intensity ultrasonic liquid processor in a solution of 1:10 (w/v) 0.1 M (PBS) phosphate buffered saline (pH 7.4) containing 1% Triton-X-100 and a protease inhibitor cocktail **(17).**
The 10% homogenates were centrifuged at 10,000 rpm for 10 minutes at 4°C in order to measure IL-1, TNFα, IL6, HO-1, and Nrf2. The supernatants were then gathered.

Table (1): Measurement of Study Parameters

Type of kit	application

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Rat Heme oxygenase 1(HO-1) Tissue ELISA Kit/ Solarbio China	
Rat Nuclear factor erythroid 2-related factor 2 (Nrf Tissue ELISA KIT/ Solarbio China	
Rat Kidney injury molecule (KIM -1)) Serum ELISA Kit/ Solarbio China	Every kit is used for the quantitative determination
Rat tumor necrosis factor(TNFα) Tissue ELISA Kit/ Solarbio China	of the concentration of the analyte in the animal sample
Rat interleukin-1(IL-1) Tissue ELISA Kit/ Solarbio China	
Rat interleukin-6(IL-6) Tissue ELISA Kit/ Solarbio China	
Immunohistochemistry kits for NFkb,caspase 3	use of antibodies to identify proteins in cells and tissues and offer data that is semi quantitative in nature on the expression, distribution, and localization of target proteins.

Analysis of Histopathology

The kidney parts of the dead rat were put in a 10% formaldehyde solution right away so they could be studied by pathologists. The pelvis and renal cortex were part of the macroscopic pieces that were made after the tissues were further processed to make paraffin tissue blocks. Hematoxylin-eosin dye was used to color the thin, 5 µm-thick pieces that were cut from the formalin-fixed, paraffin-embedded block. We used the methods described by to look at the changes in the histology, which included cell death, tubule growth, cast formation, and brush boundary loss. Tissue injury was evaluated without giving the judges any specific information so that they could judge the damage based on the amount of tubule damage. (18) Say the damage was broken down into four groups: mild damage (less than 25% damage score), moderate

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damage (25 to 50% damage score 2), serious damage (50 percent or more damage score), and no damage score. The histological study was done with a light microscope that was first enlarged 40 times.(19)

Analysis of Statistics

The number of studies (n) is written in the text of each figure, and the results are shown as mean ± standard error of mean (SEM). The statistical study of the data is also talked about in the ends of the legs. Graphpad Prism version 9 (Graphpad software Inc., San Diego, USA) was used to look at the data and figure out what it all meant. Using the Shapiro-Wilk test to see if our data was normally distributed, we looked into the differences between the medicines and the controls. The control group and the treated group were compared using a One Way ANOVA with the TUKYS multiple comparison test. There is statistical significance in the data if the p-value is less than 0.05. Kruskal-Wallis post hoc tests were done after a non-parametric statistical analysis for histological scoring.

3. Results

Kidney function parameter (Kidney injury molecule, or KIM) is affected by RIRI.

In comparison to the sham group, KIM significantly increased ($p < 0.0001$) in both the control and control vehicle groups. There were no notable changes that observed in comparison to the control /vehicle groups. The groups who received Tideglusib showed a significant reduction in renal damage molecule levels as compared to the control groups. Furthermore, the two treated groups do not differ significantly from one another. The Figure (5) provide a summary of the variations observed in levels of KIM

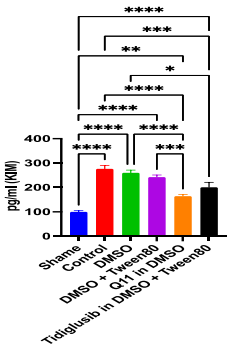

Figure5: **Serum level of kim (pg/ml) of the 6 experimental groups at the end of the experiment, mean ±SEM**

Effect of RIRI on Inflammatory Mediator in Different Study groups
Impact of RIRI on renal TNFα,IL1β,IL6 :

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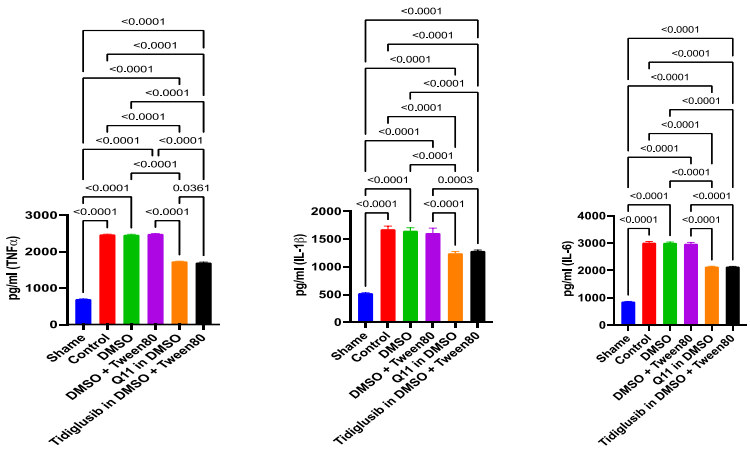
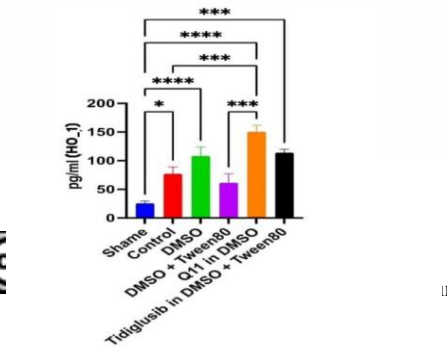
The renal concentration of TNF-a,IL1β,IL6 showed a statistically significant rise ($p < 0.0001$) in both the control and control vehicle groups compared to the sham group.No significant difference was seen between the control group and the .control vehicle group.
There was a significant decrease in renal TNF-a,IL1β,IL6 levels observed in the groups treated with Tideglusib in comparison to the control .

TheFigures (6),(7) , (8) provide a summary of the variations observed in renal levelof TNF-a,IL1β,IL6



How RIRI Affects Renal Antioxidant Mediators in Various Research Groups: RIRI's Effect on Renal HO-1, Nrf2: When compared to the sham group, the renal concentration of HO-1,Nrf2 decreased statistically significantly ($p < 0.0001$) in both the control and control vehicle groups.The control group and the control vehicle group did not differ significantly.
When comparing the QS11-treated groups to the control, a notable increase in kidney HO-1,Nrf2 levels was noted.



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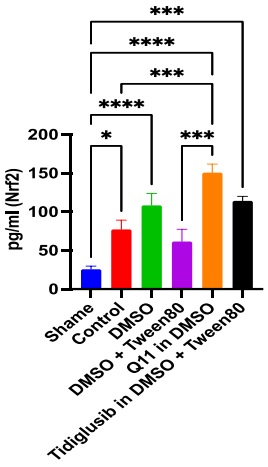

Figure 9 the renal level of Nrf2

Figure10 the renal level of HO-1

Impact of RIRI on Pro-apoptotic Mediators (Caspase 3):

The renal expression level of caspase 3, significantly increased ($p < 0.0001$) in both the control and control vehicle groups compared to the sham group. No significant difference was seen between the control group and the control vehicle group

The renal caspase3 levels in the Tideglusib groups exhibited a significant decrease ($p<0.0001$) in comparison to the control group.

The Figure **(11)** provide a summary of the variations observed in renal levels of Caspase 3

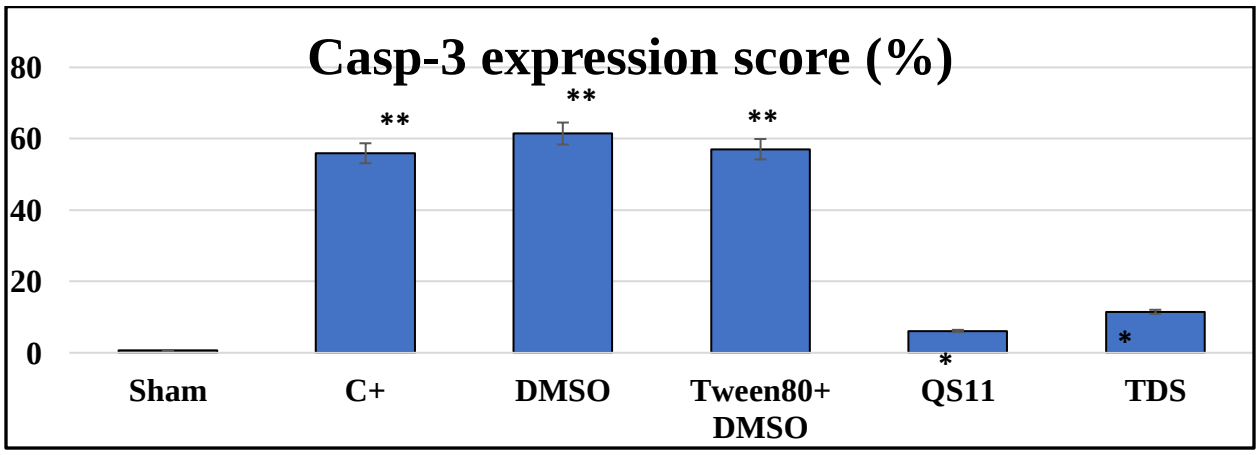

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Figure 11 renal levels of caspase 3

Impact on Renal NF-kB Level

The renal level of NF-kB exhibited a statistically significant increase ($p<0.0001$)

in both the control and control vehicle groups as compared to the sham group.

No significant difference was seen between the control group and the control vehicle group

There was a significant decrease in renal NF-kB levels observed in the group

treated with Tideglusib , in comparison to the control group .**The figure(12) provide a summary of the variations observed in renal levels of NF-kB,**

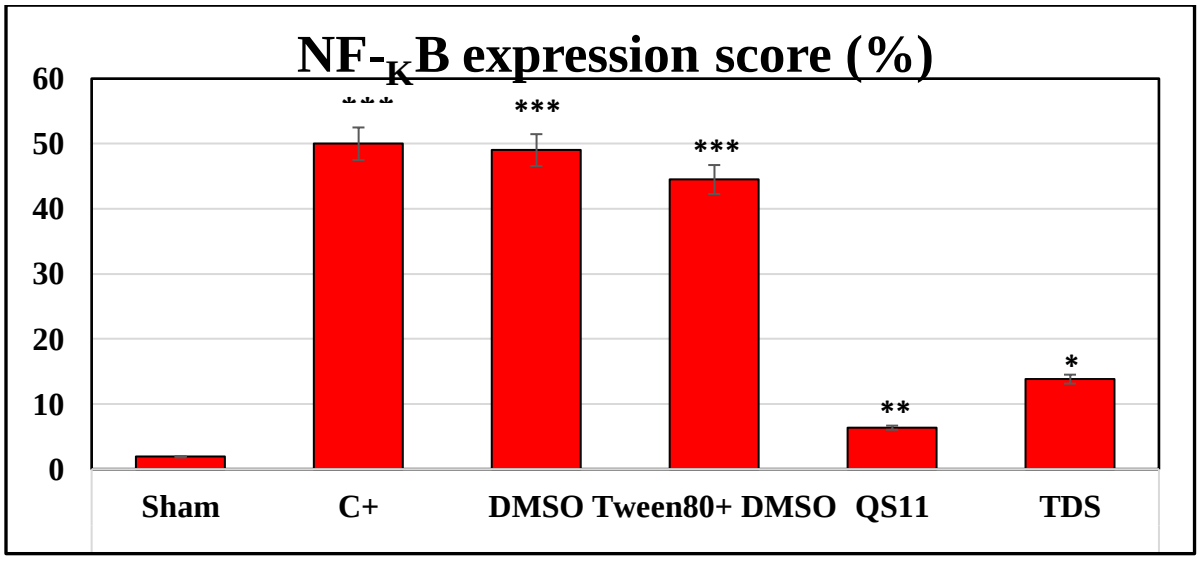

Figure 12 renal levels of NF-kB

Histopathological Finding :
At the end of the trial, the renal rats in the six experimental groups were tested for acute kidney injury. The results are as follows:
Sham group

The sham renal rats exhibited a normal renal morphology in cross-section. Figure (13) shows that the kidneys of every rat in this group were entirely normal. The cross-section of the kidney shows a glomerulus that is practically normal and a renal tubule that is completely normal and almost typical.

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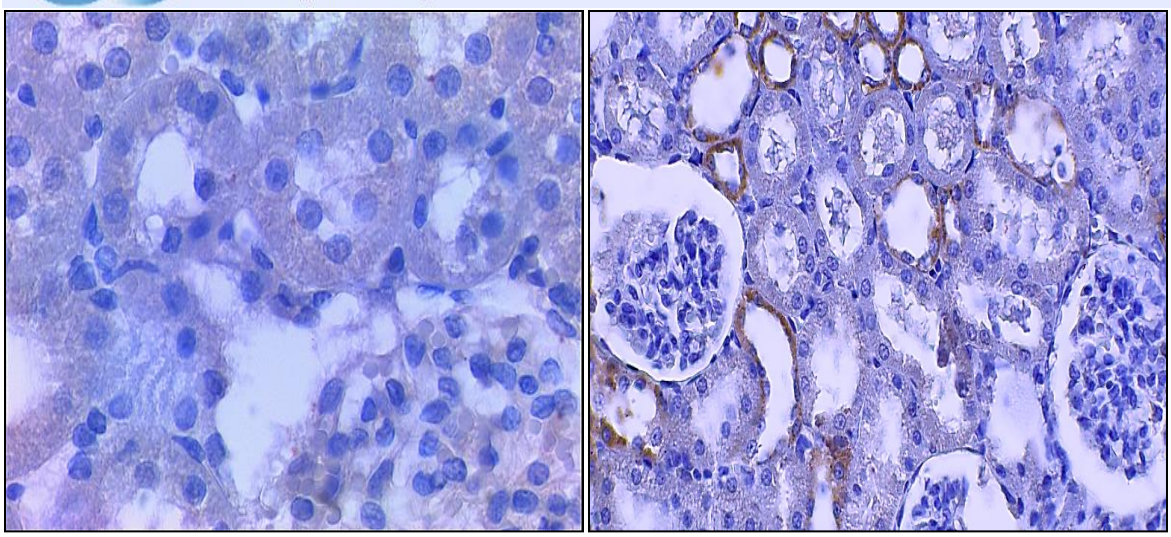
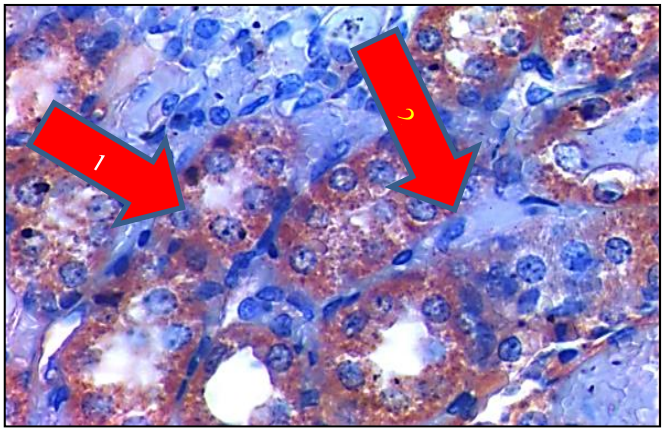
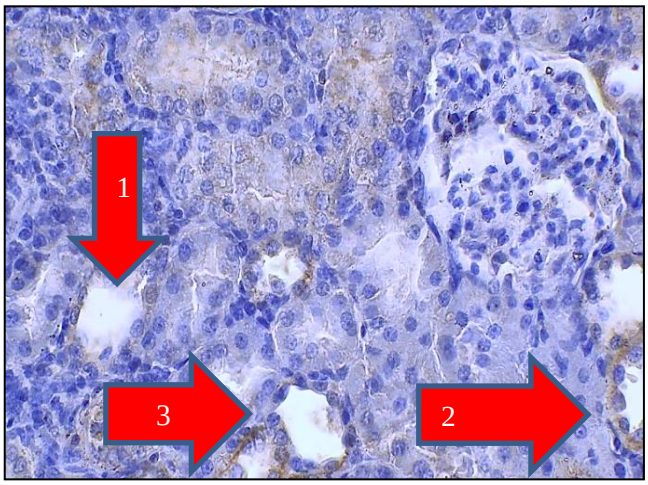


Figure 13 the shame group

2- Control group :The control group demonstrated that 70% of tissues within this cohort sustained damage, whereas 30% had mild renal impairment, as illustrated in the Figure 14





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Drug group (Tideglusib):

The treatment of rats with Tideglusib enhanced renal injury compared to the control groups, with 70% exhibiting substantial injury and 30% exhibiting mild renal impairment, as illustrated in **Figure 15**

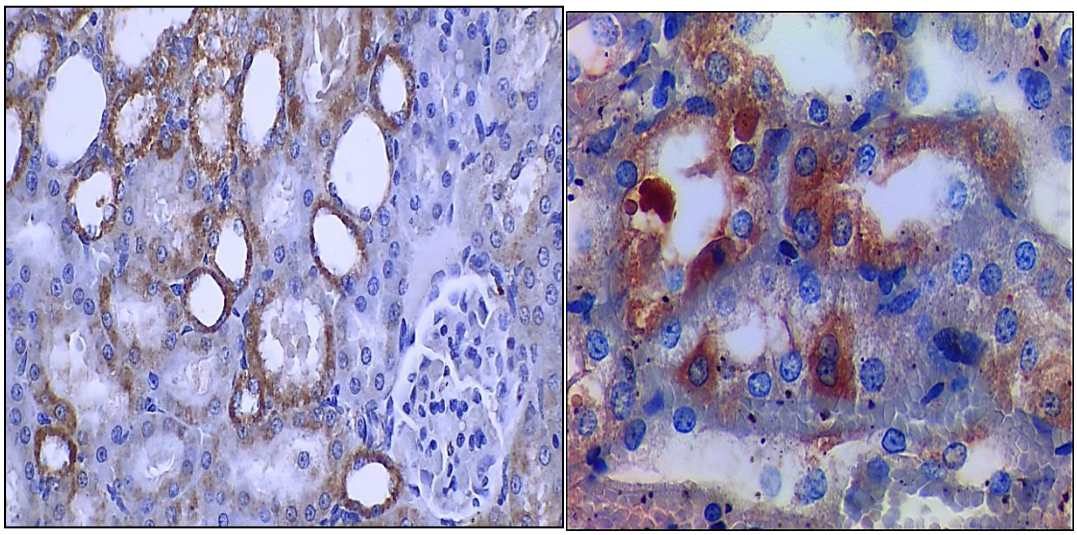

Figure 15 the tideglusib group

4. Discussion

Ischemic-reperfusion injury puts a lot of stress on healthy kidney cells. When there isn't enough air and nutrients, this happens. This starts a chain of inflammatory reactions that can hurt both systemic and local tissues very badly. Acute kidney damage (AKI) is mostly caused by the two steps of damage that happen during renal ischemia-reperfusion injury (RIRI). It's strange that when blood flow returns to the kidneys, ischemia makes the damage done by the shock worse, even though this seems like a good thing. When blood flow slows down, the kidneys lose oxygen and nutrients, which can lead to ischemia. It has a big effect on the tubules that secrete and reabsorb water. RIRI sets off a chain reaction of inflammatory responses, but reperfusion starts a chain reaction of oxidative stress, inflammation, and microvascular dysfunction **(20)**

How Renal I/R changes a kidney function measure (the KIM-1 molecule): Rats that were given RIRI had a lot more KIM 1 in their kidney cells. There was a strong positive relationship between KIM-1 and both creatinine and urea. KIM-1 is a new biomarker that can accurately and sensitively show damage to the proximal tubules of the kidneys. It also does a better job than blood urea and creatinine of predicting changes in the RIRI's histology in reaction to different medical conditions or toxins.After kidney damage, the mRNA levels of this protein rise more than those of any other gene**.(21)**The study showed that both the cotrol group and the vehicle group had much higher amounts of kim-1, a molecule that causes kidney damage.

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What Tideglusib does to kidney function factors (kidney injury molecule (KIM-1)); Even though there haven't been any direct studies, if Tideglusib were to protect the kidneys in a rat model of kidney damage, it would likely do so through the following pathways: Getting rid of inflammation: Tideglusib might be able to lower KIM-1 expression, which goes up during inflammation, by blocking GSK-3β. This could change the inflammatory processes that cause kidney damage. lowering oxidative stress: If tideglusib is an antioxidant, it may be able to protect kidney cells from oxidative harm. This might lower the stress on cells that causes KIM-1 to be turned on. Pro-survival pathways have been linked to GSK-3β reduction, which helps cells stay alive and heal. Since KIM-1 is a sign of damage, tideglusib may lower KIM-1 levels indirectly if it keeps kidney tubular cells healthy or helps them grow back**.(22)**

What effect does RIRI have on cytokines that cause inflammation (TNF-α, IL1β, and IL-6)? This study found that inflammatory markers (TNF-α, IL-1, and IL-6) were higher in the control and control vehicle groups compared to the sham group (P 0.05). High amounts of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6) have been found in the blood of rats that have had ischemia reperfusion injury **(23).** IRI-caused kidney damage is mostly caused by pro-inflammatory cytokines like interleukin 6 (IL6), IL-1, and TNFα**(24)**

Tideglusib's effect on cytokines that cause inflammation (TNF-α, IL1β, and IL-6): According to study, tideglusib may stop the production and release of cytokines that cause inflammation, like TNF-α, IL-1β, and IL-6.**(25)**
In general, it works like this: It has to do with inflammation. IL-1β, IL-6, and TNF-α are some of the inflammatory chemicals that are made when GSK-3 signaling is activated and the transcription factor NFκB is active. A drug called Tideglusib stops GSK-3 from working, which blocks this pathway and lowers NFκB activity. This stops the production of cytokines that cause inflammation**.(25)**

What RIRI does to antioxidant intermediaries (Nrf2, HO-1): The levels of Nrf2, HO-1 drop after RIRI because too many ROS are made in this study.During the first steps of ischemia and then reperfusion, Nrf2 and HO-1 interact in a complex way: To begin with The Nrf2 pathway may be set off by the reactive stress that is created during reperfusion. To fight the higher ROS levels, the cell's defense system increases the production of HO-1**.(26).** Some other research has found that Nrf2 activation and the subsequent induction of HO-1 are generally linked to a protective effect against RIRI. Animals used in experiments that had higher Nrf2 signals or overexpressed HO-1 showed this by having less tissue damage, less inflammation, and better kidney function.(**27)**.

Effect of Tideglusib on Antioxidant Mediators (Nrf2,HO-1): The glycogen synthase kinase-3 beta (GSK-3β) inhibitor tideglusib has been shown to protect neurons. One important way it does this is by affecting antioxidant mediators like Nrf2 and HO-1**.(28)**
Tideglusib and the Expression of HO-1: Because tideglusib turns on Nrf2, it greatly raises the production of heme oxygenase-1 (HO-1). HO-1 is an important Nrf2-regulated cytoprotective enzyme. It turns heme into carbon monoxide, ferrous iron, and biliverdin, which is then changed into bilirubin. Because they fight inflammation and free radicals so well, these breakdown products protect cells from oxidative damage**.(29)**

What RIRI does to caspase 3, a pro-apoptotic mediator:Renal ischemia/reperfusion injury (RIRI) is one of the main causes of acute kidney damage (AKI). It is linked to a rise in pro-

apoptotic molecules, especially caspase-3.RIRI has a big effect on pro-apoptotic mediators **(30),** and a noticeable and long-lasting rise in Caspase-3 shows that the damage has been done. Caspase-3 activity directly causes the kidney damage and cell death seen in RIRI, so this is an important area of study for understanding how the disease works and coming up with ways to stop it**.(31)**

Effect of Tideglusib on pro-apoptotic mediator (Caspase 3): A study found that Tideglusib usually lowers the cleavage and activation of Caspase-3. This has neuroprotective and anti-apoptotic effects on the pro-apoptotic mediator Caspase-3 in rats**.(32)** Haitao **(32)** found that Tideglusib reduced the cleavage of pro-apoptotic signal caspase proteins, like caspase-3 and caspase-9, after hypoxic-ischemic brain injury in neonatal mice, which are often used as a model for perinatal brain injury. Because some mechanisms are the same in different species, results from this study can often be carefully applied to models of rats that are similar. In this case, this means that tideglusib may help protect neurons in part by stopping the apoptotic process.

What RIRI does to the kidneys Mediator of NF-KB: Activation of NF-κB: The NF-κB signaling mechanism in the kidneys is greatly boosted by RIRI. This action is a main part of the inflammatory response that makes kidney damage worse. Some of the things that help turn on NF-κB during reperfusion are toll-like receptors (TLRs), cytokines (like TNF-α and IL-6), and pattern recognition receptors (PRRs)**.(33)**

Effect of Tideglusib on renal NFkB : Tideglusib's Inhibition of GSK-3: Tideglusib possesses the potential to modulate the activity of the NF-κB signaling pathway indirectly through the inhibition of GSK-3β. The inhibition of GSK-3 has been substantiated in various contexts to mitigate inflammatory responses and safeguard against tissue injury. The suppression of GSK-3 activity by Tideglusib may lead to a reduction in NF-κB-mediated inflammatory responses within the renal system, given that NF-κB plays a crucial role in the induction of pro-inflammatory chemokines and cytokines. **(34)**

5. Conclusions

1. Tideglusib showed apossible protective effect againist RIRI

2. According to our research, Tideglusib might have nephroprotective properties. This protective effect may be explained by the medicines' ability to activate the Wnt β catenin signaling pathway, which lowers inflammatory markers like IL-6, TNF-α, and IL1B, suppresses KIM activation, decrease NfkB and lowers apoptosis by decrease pro apoptotic mediators(caspase -3)

Disclosure

The authors declared no conflicts of interest.

References

1- HAN, S. J. & LEE, H. T. 2019. Mechanisms and therapeutic targets of ischemic acute kidney injury.Kidney research and clinical practice, 38, 427-440.
2- BARROSO, L. C., SILVEIRA, K. D., LIMA, C. X., BORGES, V., BADER, M., RACHID, M., SANTOS, R. A. S., SOUZA, D. G., SIMõES E SILVA, A. C. & TEIXEIRA, M. M. 2012. Renoprotective effect of AVE0991, a nonpeptide Mas receptor agonist, in experimental acute renal injury. International journal of hypertension, 2012.
3- Niehrs, C. The complex world of WNT receptor signalling. Nat. Rev. Mol. Cell Biol.13, 767–779 (2012).-Jiaqi Liu , Qing Xiao , Jiani Xiao , Chenxi Niu , Yuanyuan Li , Xiaojun Zhang , Zhengwei Zhou , Guang Shuand Gang Yin, Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities Signal Transduction and Targeted Therapy (2022) 7:3
4- Huffstater, W. David Merryman, Leslie S. Gewin, MD,Semin Nephrol. (2020) March ; 40(2): 126–137. doi:10.1016/j.semnephrol.2020.01.004
5- Woodgett JR. Molecular cloning and expression of glycogen synthase kinase-3/factor A. EMBO J. 1990;9:2431–2438.
6- Patel P, Woodgett JR. Glycogen synthase kinase 3: a kinase for all pathways? Curr Top Dev Biol. 2017;123:277–302. doi: 10.1016/bs.ctdb.2016.11.011.
7- Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. Pharmacol Ther. 2015;148:114–131. doi: 10.1016/j.pharmthera.2014.11.016
8- Walz A, Ugolkov A, Chandra S, Kozikowski A, Carneiro BA, O'Halloran TV, Giles FJ, Billadeau DD, Mazar AP. Molecular pathways: revisiting glycogen synthase Kinase-3beta as a target for the treatment of cancer. Clin Cancer Res. 2017;23:1891–1897. doi: 10.1158/1078-0432.CCR-15-2240.
9- Taylor A, Harker JA, Chanthong K, Stevenson PG, Zuniga EI, Rudd CE. Glycogen synthase kinase 3 inactivation drives t-bet-mediated downregulation of co-receptor PD-1 to enhance CD8(+) cytolytic T cell responses. Immunity. 2016;44:274–286. doi: 10.1016/j.immuni.2016.01.018.
10- Dominguez JM, Fuertes A, Orozco L, del Monte-Millan M, Delgado E, Medina M: Evidence for irreversible inhibition of glycogen synthase kinase-3beta by tideglusib. J Biol Chem. 2012 Jan 6;287(2):893-904. doi: 10.1074/jbc.M111.306472. Epub 2011 Nov 18.
11- Nair, A. B., & Jacob, S. (2016). A simple practice guide for dose conversion between animals and human. Journal of Basic and Clinical Pharmacy, 7(2), 27-31.
12- Haitao Wang, Sammen Huang, Kuipo Yan, Xiaoyan Fang, Ahmed Abussaud, Ana Martinez, Hong-Shuo Sun, Zhong-Ping Feng, Tideglusib, a chem ical inhibitor of GSK3β, attenuates hypoxic-ischemic brain injury in neonatal mice, BBA- General Subjects (2016)
13- Celestine Okwudili, U., Athanasius Chinedu, E., & Jonas Anayo, O. (2014). Biochemical Effects of Xylazine, Propofol, and Ketamine in West African Dwarf Goats. Journal of Veterinary Medicine, 2014, Article ID 758581, 6 pages. doi: 10.1155/2014/758581
14- Hussien, Y. A., Abdalkadim, H., Mahbuba, W., Hadi, N. R., Jamil, D. A., & Al-Aubaidy, H. A. (2020). The Nephroprotective Effect of Lycopene on Renal Ischemic Reperfusion Injury: A Mouse Model. Indian Journal of Clinical Biochemistry, 35(4), 474-481.
15- Güzel, A., Özorak, A., Oksay, T., Öztürk, S. A., Bozkurt, K. K., Yunusoğlu, S., Uz, E., Uğuz, A. C., & Koşar, P. A. (2022). The efficiency of oxerutin on apoptosis and kidney function in rats with renal ischemia reperfusion injury. Ulusal Travma ve Acil Cerrahi Dergisi, 28(3), 344351.

16- AL-Sheibani, B. I. M. et al. (2014) 'Effect of ferulic acid on Myocardial Ischemia/Reperfusion Injury In Male Mice.', Kufa Journal For Veterinary Medical Sciences, 5(2).
17- Jiang, M., Liu, K., Luo, J., & Dong, Z. (2010). Autophagy is a renoprotective mechanism during in vitro hypoxia and in vivo ischemia-reperfusion injury American Journal of Pathology, 176(3), 1181–1192.
18- HU, L., YANG, C., ZHAO, T., XU, M., TANG, Q., YANG, B., RONG, R. & ZHU, T.(2012). Erythropoietin ameliorates renal ischemia and reperfusion injury via inhibiting tubulointerstitial inflammation. Journal of Surgical Research, 176, 260 266.
19- X-D Ying 1, G. W. H. A. (n.d.). Sodium butyrate relieves lung ischemia-reperfusion injury by inhibiting NF-κB and JAK2/STAT3 signaling pathways. Eur Rev Med Pharmacol Sci. 2021 Jan; 25(1):413-422
20- RANIA S.A.E. MANSOUR, M.D.; SAMAR F. EZZAT, M.D. and DOAA A. ABOU-BAKR, M.D.(2020) Ameliorative Effect of Propolis Against Thioacetamide Induced Hepatorenal Injury in Adult Male Rats. Kidney Injury Molecule-1 (KIM-1) a Biomarker of Renal Injury Med. J. Cairo Univ., Vol. 88, No. 1, March: 243-258, 2020
21- Benoît Marchand , Dominique Arsenault , Alexandre Raymond-Fleury , François-Michel Boisvert , Marie-Josée Boucher (2015) Glycogen Synthase Kinase-3 (GSK3) Inhibition Induces Prosurvival Autophagic Signals in Human Pancreatic Cancer Cells J Biol Chem 2015 Jan 5;290(9):5592–5605.
22- Yuan, X., Wang, J. and Zhang, Y. (2020) 'Tubeimoside-1 Protects Against Renal Ischemia Reperfusion Injury In Vivo and In Vitro', Natural Product Communications, 15(12), p. 1934578X20977647.
23- Patel, N. S. A. et al. (2005) 'Endogenous interleukin-6 enhances the renal injury, dysfunction, and inflammation caused by ischemia/reperfusion', Journal of Pharmacology and Experimental Therapeutics, 312(3), pp. 1170–1178.
24- Nur Fatin Zalikha Zailan , Niranjana Jaganathan , Thiban Sandramuti , Seri Narti Edayu Sarchio , Masriana Hassan Inhibition of GSK-3 by Tideglusib Suppresses Activated Macrophages and Inflammatory Responses in Lipopolysaccharide-stimulated RAW 264.7 Cell Line Mal J Med Health Sci 16(SUPP9): 2-8, Nov 2020
25- Vy Ngo , Martin L Duennwald (2022) Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease ;Antioxidants (Basel)2022 Nov 27;11(12):2345 .
26- Fei Tonga, Xinmei Zhoua (2017) :The Nrf2/HO-1 Pathway Mediates the Antagonist Effect of L-Arginine On Renal Ischemia/Reperfusion Injury in Rats; Kidney Blood Press Res 2017;42:519-529
27- Avenue Areej Turkistani ,Hayder M. Al kuraishy ,Ali I. Al Gareeb , Ali K. Albuhadily · Athanasios Alexiou,Marios Papadakis,Mohamed M. Elfky,Hebatallah M. Saad,Gaber El Saber Batiha(2024):Therapeutic Potential Efect of Glycogen Synthase Kinase 3 Beta (GSK 3β) Inhibitors in Parkinson Disease Molecular Neurobiology (2024) 61:7092–7108
28- Li, N., Hao, L., Li, S., Deng, J., Yu, F., Zhang, J., Nie, A., & Hu, X. (2024). The NRF-2/HO-1 Signaling Pathway: A Promising Therapeutic Target for Metabolic Dysfunction-Associated Steatotic Liver Disease. Journal of Inflammation Research, 17, 653–665.
29- Esraa H. Alsaaty , Ali M. Janabi (2024):Moexipril Improves Renal Ischemia/Reperfusion Injury in Adult Male Rats , JContemp Med Sci | Vol. 10, No. 1, January-February 2024: 25–30
30- Wenjun Zhang, Chao Guo, Yi Li, Hao Wang, Huabing Wang, Yingying Wanga, Tingting Wuf,Huinan Wang, Gang Cheng, Jiangwei Man, Siyu Chen, Shengjun Fue and Li Yang (2024) :Mitophagy mediated by HIF-1α/FUNDC1 signaling in tubular cells protectsagainst renal ischemia/reperfusion injury, Renal FailuR 2024, VOl. 46, nO. 1, 2332492

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31- Haitao Wang, Sammen Huang, Kuipo Yan, Xiaoyan Fang, Ahmed Abussaud, Ana Martinez, Hong-Shuo Sun, Zhong-Ping Feng, Tideglusib, a chem ical inhibitor of GSK3β, attenuates hypoxic-ischemic brain injury in neonatal mice, BBA- General Subjects (2016)
32- Zhang, H., & Sun, S. C. (2015). NF-κB in inflammation and renal diseases. Cell & Bioscience, 5(1), 63.
33- Hoffmeister, L., et al. "GSK3: A Kinase Balancing Promotion and Resolution of Inflammation." Trends in Pharmacological Sciences, vol. 41, no. 12, 2020, pp. 913–923.