RESEARCH ARTICLE

Effect of the Indomethacin Drug on Kidney Histology in Male Albino Rats

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ABSTRACT

The kidneys are major organs that clear the drugs. Urine is one of the primary elimination routes for drugs and metabolites to be excreted outside of the body. Most drugs are predominantly excreted via the kidneys as their metabolized products. The histopathological change of kidney in the rats that treated with indomethacin at a dose (20mg/kg)show the abnormal structure of glomerulus is more damage and bowman's space is very swelling, distortion glomerulus and the compound inside it is shrinkage with the presence of inflammation cell and bleeding fibrosis, when compared with control . While the change of kidney in the rats that treated with indomethacin at a dose (50mg/kg) Showed abnormal structure of glomerulus is shrinkage with tubular cellular swelling and necrosis and presence of interstitial inflammation and swelling tubular. When used hesperidin show a protective effect of the normal antioxidant structure of glomerulus and renal tubule also no necrosis or swelling, the Bowman's space and the capsule are normal.

Keywords: Indomethacin drug, Kidney histology; Male Albino Rats

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INTRODUCTION

The kidney is bean-shaped, with a concave hilum where the ureter and the renal artery and veins enter. Each kidney is supplied by a renal artery, a direct branch of the abdominal aorta.[1] The cortex and hilum are covered with a fibrous capsule.[2] Kidneys play important in deamination of amino acid that leads to producing urea removed from the blood. The kidneys are vital organs for the body that maintaining a stable internal environment or homeostasis. This function is performed by regulating the body's blood pressure, and acid-base balance, blood composition, pH and fluid volume.[3] The kidneys also produce urine, which is formed in these organs as a result of three main functions: filtration of blood in the glomeruli, reabsorption of nutrients and other valuable substances from the filtrate that enters the proximal and distal convoluted tubules, and also secretion or excretion of metabolic waste products or unwanted chemicals or substances into the filtrate.[3]

Indomethacin can cause a significant reduction in renal function, decreasing glomerular filtration rate, and urine output. It may precipitate acute renal failure, particularly in patients with a decreased extracellular volume or reduced renal perfusion, by inhibiting the production of vasodilating renal prostaglandins and allowing unimpeded vasoconstriction by circulating angiotensin and catecholamines. Sodium and water retention, interstitial nephritis and hyperkalaemic hyporeninaemic hypo-aldosteronism have also been documented as a result of the administration of indomethacin.[4,5]

The kidneys are major organs that clear the drugs. Urine is one of the primary elimination routes for drugs and metabolites to be excreted outside of the body. Excretion via the biliary and intestinal routes is also important for the elimination of metabolites, unchanged drugs, and unwanted substances. The elimination phase typically follows first-order kinetics. Most drugs are predominantly excreted via the kidneys as their metabolized products.[6,7] The indomethacin consider as oxidative stress is known to be associated with premature aging of cells and can lead to tissue inflammation damaged cell membranes, autoimmunity, and cell death. Recent evidence has shown abnormalities in membrane lipid metabolism and an imbalance in the immune system.[8]

Oxidative stress occurs when the generation of free radicals that can be produced by normal cellular metabolism and react with biomolecules like protein, lipid, and DNA to cause cellular damage and responsible for degenerative changes and active intermediates in a system exceeds the system's ability to neutralize and eliminate them.[9]

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Oxidative stress contributes to many pathological conditions and diseases, including cancer, neurological disorders, atherosclerosis, hypertension, ischemia, perfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and asthma.10 Also caused by an imbalance between production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products that result from drug metabolism.[11]

Indomethacin has adverse effects that similar to all other (nonsteroidal anti-inflammatory drug) NSAIDs that induced gastric ulcers.[12] The indomethacin inhibits both cyclooxygenase-1 and cyclooxygenase-2, which then inhibits the production of prostaglandins in the stomach and intestine responsible for maintaining the mucous lining of the gastrointestinal tract. Indometacin, therefore, like other non-selective COX inhibitors can cause peptic ulcers. These ulcers can result in serious bleeding and perforation requiring hospitalization of the patient.[13] Many NSAIDs, but especially indometacin, cause lithium retention by reducing its excretion by the kidney. Thus indometacin users have an elevated risk of lithium toxicity.[13] All NSAIDs, including indomethacin, also increase and aldosterone levels, and increase sodium and potassium retention, also vasopressin activity is enhanced.[14]

Hesperidin is a flavanone glycoside, abundantly found in lemon and oranges. The peel and membranous part of these fruits have the highest hesperidin concentration. Hesperidin exhibits various biological and pharmacological properties such as vitamin-like activity and can decrease capillary permeability (vitamin P), leakiness, and fragility. It also showed antioxidant, anti-inflammatory, anti-carcinogenic, anti-bacterial, anti-viral, anti-allergic, and anti-ulcer anticancer, lipid-lowering, antioxidant, vasoprotective, and antihypertensive and protect against ischemia-reperfusion tissue damage.15 As well as in food products and beverages derived from plants, such as tea and olive oil.[16]

A classical term 'Citrin' or 'Vitamin P' is used to refer to a mixture of Hesperidin and Eriodictoyl (another flavonoid), initially thought to have vitamin-like properties by having wound healing properties and treating scurvy; this was later attributed to Vitamin C.[17] Hesperidin is a plant flavanone (subclass of flavonoids) predominantly and abundantly found in citrus fruits . In nature, most flavonoids are bound to a sugar moiety and are called glycosides. Hesperidin is also a glycoside composed of the flavanone hesperetin (aglycone) and the disaccharide rutinose (rhamnose linked to glucose).[18] Hesperidin Works As an Antioxidant. Oxidants, such as hydrogen peroxide and other chemicals, cause oxidative stress. Oxidative damage causes disorders such as cancer and heart disease. Antioxidants help protect against oxidative stress.19 Both hesperidin and hesperetin function as antioxidants. They both have radical scavenging activity. This means that they stop free radicals from damaging cells and protect the kidney from damage.[19,20]

Hesperidin neutralizes reactive oxygen species that lead to protects DNA, proteins, and tissues from radiation, inflammation, and toxins. It also prevents oncogenes from causing cells to become cancerous. Oncogenes are genes that can cause cells to transform into tumor cells.[19,21,22] Hesperidin had significant radical scavenging activity in red blood cells. It stopped hydrogen peroxide from damaging the cellular membranes of blood cells. It also protected against DNA damage.[22,23]

MATERIALS AND METHODS

Animals

Adult male rats (150-250 g), these animals were obtained from the animal house of the Faculty of Science/University of Kufa, Iraq. All animals were kept under uniform and controlled conditions of temperature and light/dark (12/12 h) cycles, fed with standard rodent diet and water and libitum for two periods one and three months.

Chemicals

Hesperidin (HES) powder was purchased from (Sigma–Aldrich Chemical Co., USA) indomethacin was purchased from(Gmbh Hamburg, Germany) The doses of Indocin at dose 20 and 50 mg/kg, HES at a dose (40 mg/kg) used in the present study.

Experimental Design

The study was conducted in the animal house of the Faculty of the Science/University of Kufa. Used in these experiments 60 animals of male rats aged 3 months and the weight of 150-250 gm. Experimental rats were divided into six groups ten animals in each treated for 90 days as follows:

- Normal control gives distal water only orally.
- Second group gives (20 mg/kg of indomethacin) of body weight orally
- Third group gives (50 mg/kg indomethacin) of body weight orally
- Fourth group gives (indo20mg/kg + Hesperidin) of body weight orally
- Fifth group give (indo50mg/kg + (Hesperidin) of body weight orally
- Sixth group give antioxidant (Hesperidin40mg/kg) of body weight only orally

RESULTS

The histological sections of kidney tissue from intact male rat (Figure 1) shows the normal histological structure of kidney by presence glomerulus, proximal convoluted tubule (PCT), distal convoluted tubule (D.C.T) and Bowman's space. The

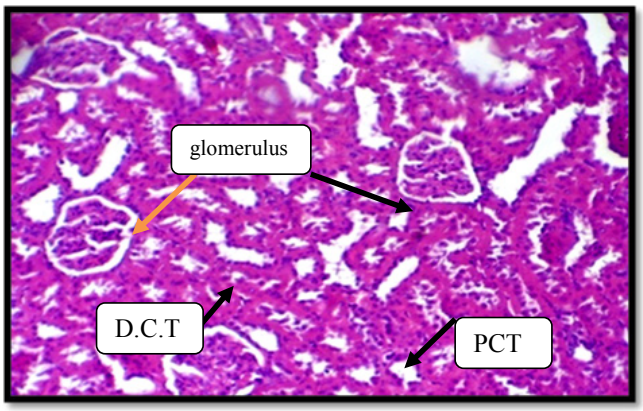

Figure 1: Histological section of male rat kidney (control) showed a normal structure of kidney with glomerulus, proximal convoluted tubule (PCT) and distal convoluted (D.C.T) (400 x)(H&E)

histopathological change of kidney in the rats that treated with indomethacin at dose (20mg/kg) (Figure-2)show abnormal structure of glomerulus is more damage and bowman's space (S.B.S) is very swelling ,distortion glomerulus and the compound inside it is shrinkage with presence of inflammation cell and bleeding fibrosis, when compared with control . While the change of kidney in the rats that treated with indomethacin at dose (50 mg/kg) (Figure 2) Showed abnormal structure of glomerulus is shrinkage with tubular cellular swelling and necrosis and presence of interstitial inflammation and swelling tubular , degenerative changes in the glomerulus enlargement in the interstitial connective tissue at three months (Figuress 3 and 4). But when used hesperidin shows a protective effect of the normal antioxidant structure of glomerulus and renal tubule also no necrosis or swelling, the Bowman's space and the capsule is a normal Figures 5 and 6.

DISCUSSION

Administration of indomethacin that caused chronic renal impairment were related with uric acid, urea, and creatinine elevation and consider as indicators of kidney disturbance, where the serum levels of creatinine does not until at least half of kidney nephrons are destroyed renal disturbance might contribute to the low serum levels of protein that may have resulted from remarkable excretion of the urine due to degeneration and necrosis of the glomeruli and kidney tubules. And anti-inflammatory effects of NSAIDs may be offset by an increased risk of (renal) side effects. We investigated the effect of indomethacin on urinary markers of glomerular and tubular damage and renal inflammation.[24]

The mechanism of this drug interaction appears to involve the inhibition of vascular and renal prostaglandin synthesis leading to vasoconstriction and sodium retention.[25] Such biochemical changes in the present work are the outcome of nephropathy which is manifested by markedly degenerated glomeruli and shrunken capillary tuft with increased cellularity and mild hydropic degeneration of tubules.[26]

Indomethacin causes renal effects and because kidney synthesizes several prostaglandins that important in the regulation of renal function. These prostaglandins (primarily

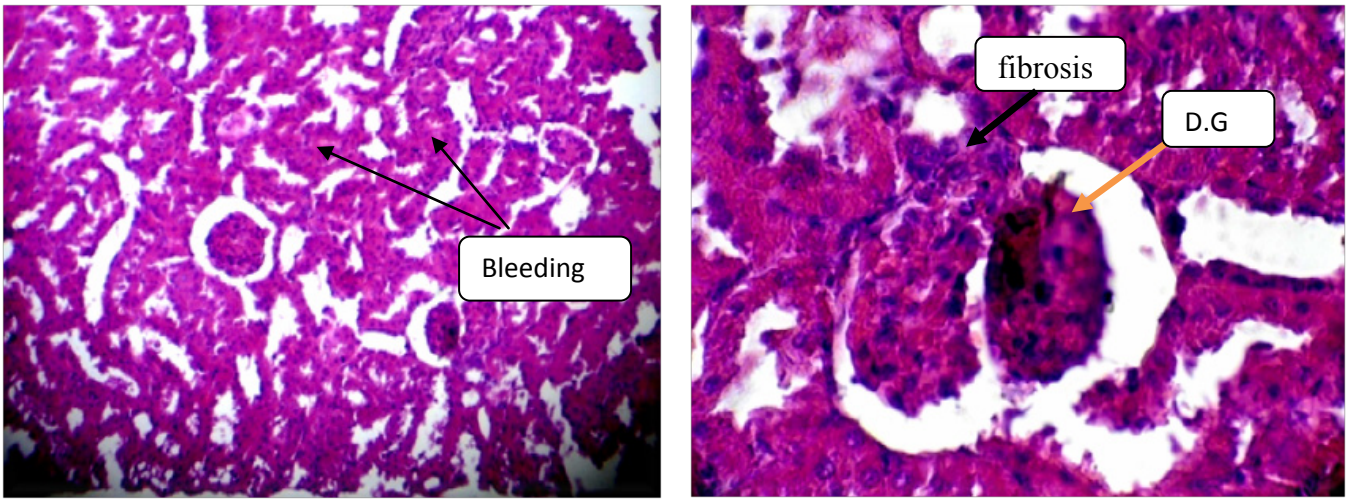

Figure 2: Histological section of male rat kidney (Indo20 mg/kg 3m) Showed abnormal structure, the glomerulus is damaged (D.G) with bleeding, the nucleus out the distal tubule(N.O.T) also presence the fibrosis (400 x)(H&E)

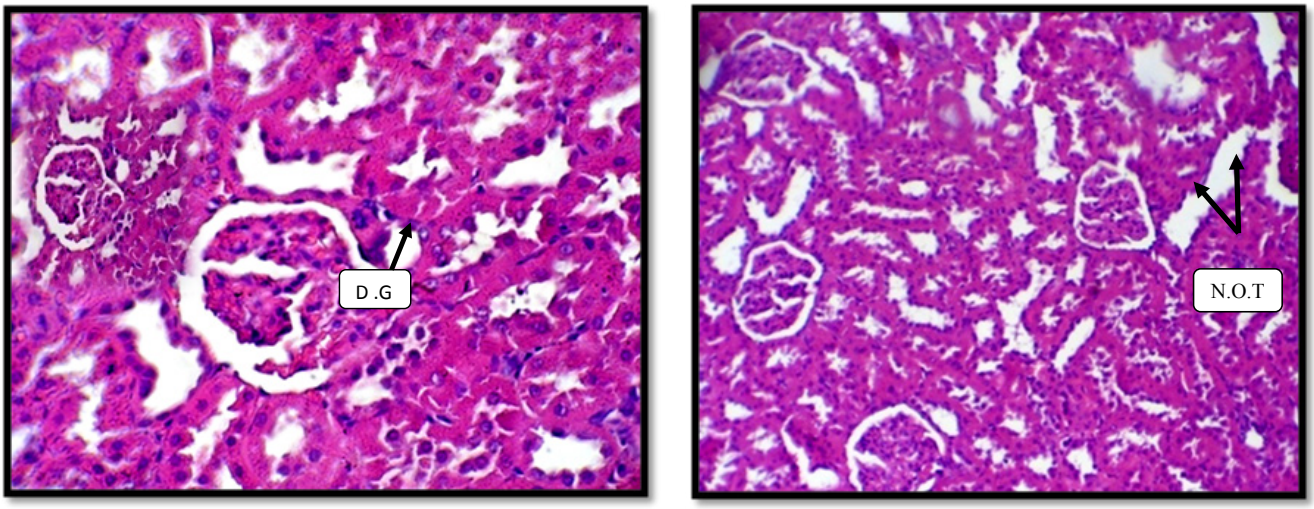

Figure 3: Histological section of male rat kidney (Indo 20 + Hesp mg/kg 3 m) showed a normal structure of the kidney (400 x) (H & E)

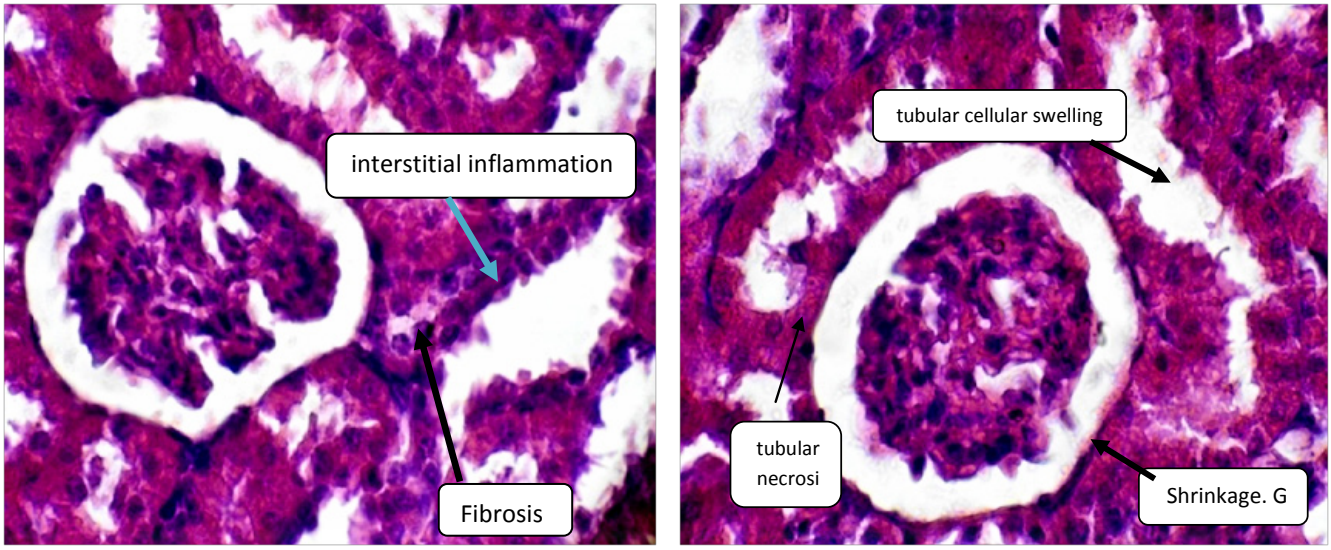

Figure 4: Histological section of male rat kidney (Indo50mg /kg 3m) Showed abnormal structure of glomerulus is shrinkage with tubular cellular swelling(T.C.S) and necrosis and presence of interstitial inflammation and swelling tubular S.T (400 x)(H&E).

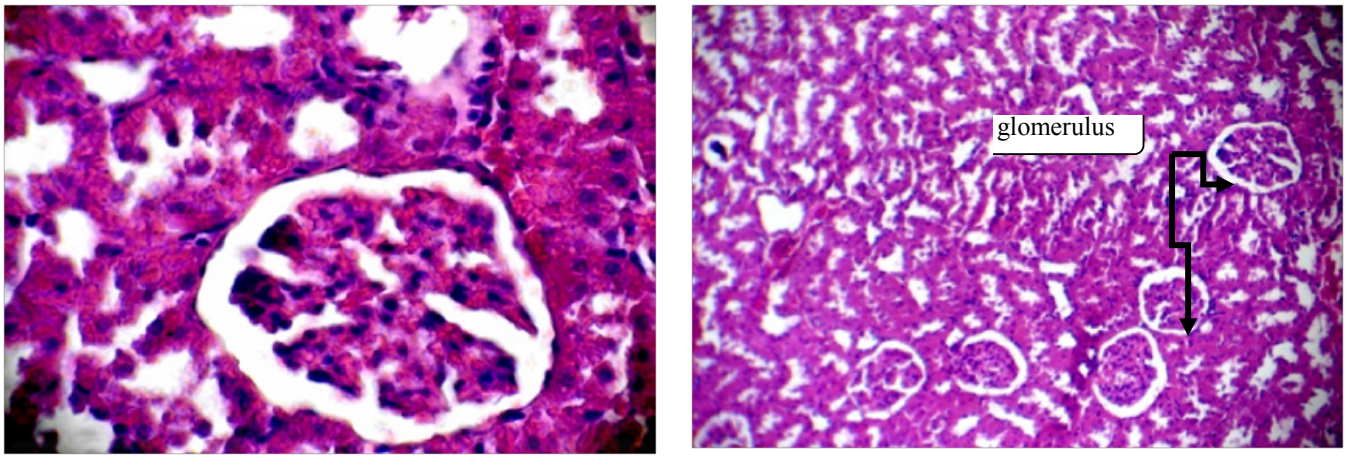

Figure 5: Histological section of male rat kidney (Indo50 +Hesp mg/kg 3m), showed the normal structure of kidney due to antioxidant and protective activity of hesperidin (400 x)(H&E)

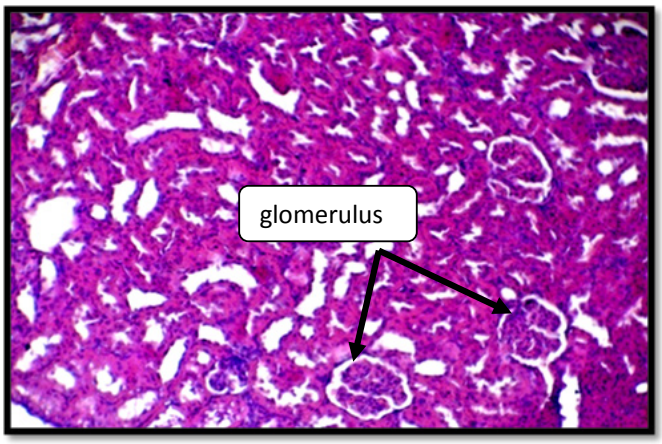

Figure 6: Histological section of male rat kidney (Hesperidin mg/kg 1m) showed a normal structure of the kidney (400 x) (H&E)

PGI2 and PGE2) affect the modulation of renal blood flow, glomerular filtration rate, renin release, the concentration mechanism and excretion of sodium and potassium. In animals, long term administration of indomethacin has resulted in structural as well as functional abnormalities. Structural renal changes, including enlargement of the Golgi bodies and an increase in inclusion bodies in the cytoplasm and rough endoplasmic reticulum of the podocytes, have been observed in the rat after administration of 4 mg/kg of intraperitoneal indomethacin.[27,28]

Excessive ROS production and oxidative stress have been demonstrated to play a role in drug-induced renal damage and tubular necrosis.[29-32] Non-steroidal anti-inflammatory drugs (NSAIDs) and indomethacin is known to be nephrotoxic in the adult animal and in humans. However, the injury has been seen on LM, and electron microscopy (EM) examination is a tubular one rather than glomerular.[33,34] NSAID usage is associated with kidney injury. The rise in serum creatinine often represents the irreversible process.[35]

The renoprotective effect of hesperidin on indomethacin-induced AKI was explained by, in addition to its free-radical scavenging activity and restoration of the antioxidant defense systems.36 HES has been reported to have antioxidant

properties, which may play an important role in the prevention of anticancer drug-induced toxicity in cells.[21,37]

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