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MECHANISM OF DRUG INDUCED RENAL FAILURE: A REVIEW

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ABSTRACT: Acute renal failure (ARF) is characterized by a rapid, potentially reversible decline in renal function, including a rapid fall in glomerular filtration rate (GFR) and retention of nitrogenous waste products over a period of hours or days. The mortality rate of patients with ARF has remained 25–70% despite the use of various pharmacologic agents. Due to the multiple causes of renal failure, many animal models have been developed to advance our understanding of human nephropathy. Among the experimental models, rodents have been extensively used to enable a mechanistic understanding of kidney disease induction and progression, as well as to identify potential targets for therapy. Numerous experimental models have confirmed the nephrotoxicity induced by gentamicin, cisplatin, acetaminophen, glycerol, CCl_4, adenine, potassium dichromate, and others. Nephrotoxicity induced in these experimental models showed pathophysiological, ultrastructural and functional renal impairments in the form of tubular desquamation and necrosis and elevated blood urea and serum creatinine. The aim of this study was to know the mechanism of actions of different nephrotoxic agents for inducing renal failure in an animal model. That will help in the prevention and treatment of drug-induced nephrotoxicity.

INTRODUCTION: The kidney is a highly complex organ consisting of well-defined components that function in a highly coordinated manner to allow the smooth regulation of a myriad of interdependent processes. Novel and imaginative approaches have led to the development of experimental techniques and models that now serve to direct the biochemical, cellular, and molecular approaches used to elucidate the mechanisms of disease at cellular and subcellular levels.

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Acute kidney injury (AKI) is responsible for approximately [2] million deaths annually worldwide [1, 2]. AKI ultimately leads to end-stage renal disease and kidney failure. AKI is increasingly common in critically ill patients, and those patients with the most severe form of AKI, requiring renal replacement therapy, have a mortality rate of 50–80% [3].

Over the past 10 years, there has been substantial progress in the field of AKI. Drug-induced renal failure also becomes very common nowadays. Different studies were done using a different type of drugs or agents for causing uremia and renal failure. The mechanisms of actions for causing renal failure by drugs are different according to the causative agents. Studies throughout the world are going to establish an effective alternative method

towards prevention and treatment of renal failure. For that purpose, researchers are establishing different experimental models for induce renal failure and treating them accordingly. Research involving animals is a critical step in understanding physiology, pathophysiology and the development of therapies in both humans and animals. Animal experiments have provided us with fundamental concepts of kidney biology, ranging from hyper-tension and diabetes to renal manifestations of systemic disease, primarily affecting the kidney, such as glomerulonephritis and tubular necrosis. Rodent models remain the most popular species to approximate human disease. There has been a progressive increase in research studies using mouse and rat models of renal disease.

Agents that cause acute renal failure are extensively used experimentally throughout the world. So this review work will facilitate the knowledge to the common people about the toxic effects of commonly used different drugs or agent and their mechanism of actions for causing renal damage. In a case of undiagnosed renal disease, there may be possibility of drug-induced renal failure. This study will help to know the toxic effects of many nephrotoxic agents and for the prompt removal of the drug and supportive management can reverse the renal dysfunction to a large extent.

1. Acetaminophen Induced Renal Failure: Among the various forms of AKI, drug-induced AKI is a common concern in clinic4. Kidneys are primarily involved in filtering and concentrating on various substances and chemical agents. Acetaminophen (APAP), an analgesic and anti-pyretic agent, is better known as paracetamol. APAP is used in adults and children worldwide with a safety profile in therapeutic doses [5]. However, excess dose of APAP can cause severe hepatotoxicity, nephrotoxicity and even death in experimental animals and humans [6, 7]. Recent studies suggested that both oxidative stress and inflammation contributed to APAP-induced renal injury [8].

1.1 Mitochondrial Dysfunction Related AKI: Mitochondria are the most complex intracellular organelles which are responsible for the important physiological functions.

Renal tubular cells are densely packed with mitochondria. Mitochondrial dysfunction is likely to be a key mechanism for the pathogenesis of AKI9. APAP-induced nephrotoxicity is frequently associated with an elevation in the blood urea nitrogen, serum creatinine, and acute tubular injury [10]. In addition to these traditional serums biochemical markers of renal injury, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) are considered as the more sensitive and reliable early biomarkers. The elevation of KIM-1 and NGAL is obvious; the proof of renal tubule damage and the increments in serum creatinine (SCr) and blood urea nitrogen (BUN) levels are found to be later. Mitochondrial damage leads to the excessive production of ROS, which could directly cause cellular injury.

1.2 Oxidative Stress-Related AKI: The primary toxicity of acetaminophen is the result of drug metabolism in both the liver and extrahepatic tissues. With therapeutic dosing in adults, approximately 63% of acetaminophen is metabolized *via* glucuronidation and 34% by sulfation. These reactions occur primarily in the liver and result in water-soluble metabolites that are excreted via the kidney. At therapeutic doses, 5% percent of APAP is oxidized by the microsomal P-450 enzyme system to a reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). In therapeutic dosing, this electrophilic metabolite is then reduced by glutathione and subsequently excreted as mercapturic acid, a relatively non-toxic compound. In the condition of excess APAP, stores of sulfate and glutathione are depleted. This shunts more of the acetaminophen to the CYP-450 mixed-function oxidase system, generating more NAPQI reactive intermediates. When large doses of a drug are ingested, there is more severe glutathione depletion, as well as a massive production of metabolites, leaving large amounts of reactive species unbound. These electrophilic intermediates then form adducts with sulfhydryl and glutathione moieties on cellular proteins [11]. This process disrupts homeostasis, with subsequent activation of caspases and lysosomal enzymes that initiate apoptosis, or programmed cell death. This has been demonstrated in both liver and kidney tissue in animal models. The resultant cell death leads to tissue necrosis and ultimately, organ dysfunction [12].

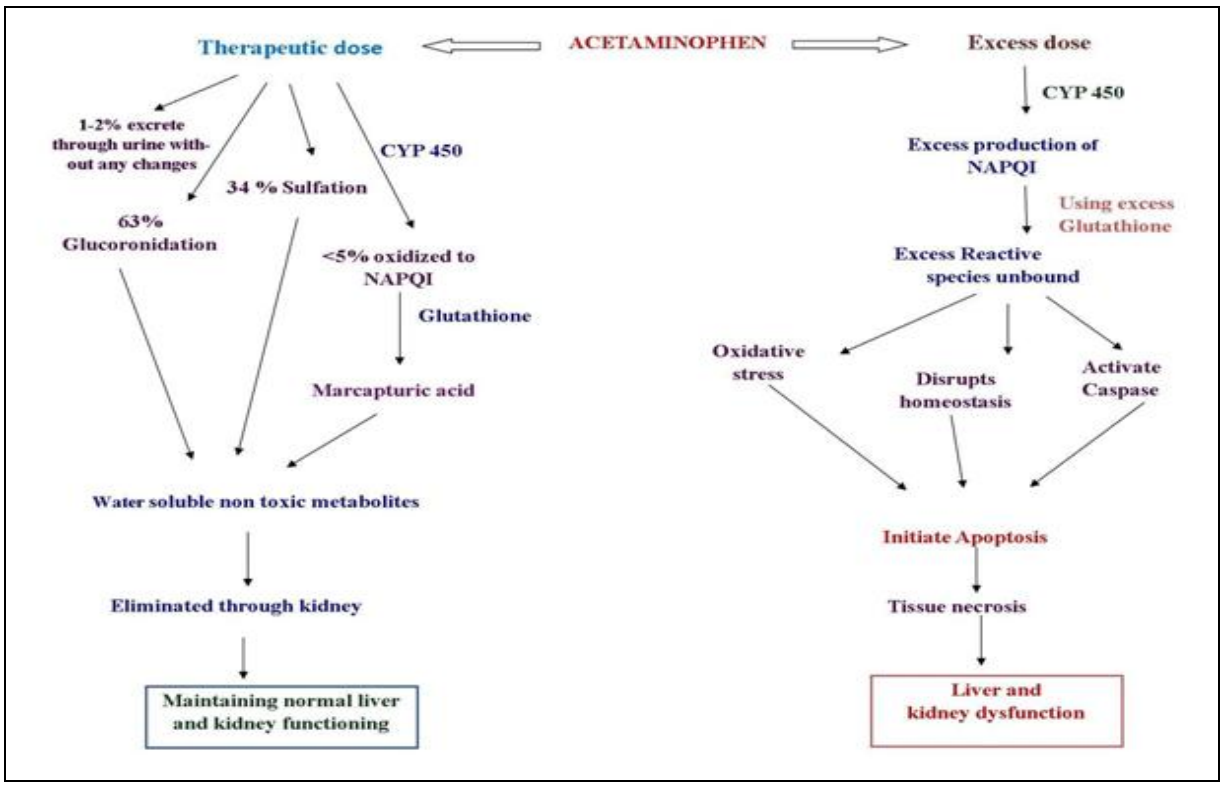

FIG. 1: ACETAMINOPHEN METABOLISM AND KIDNEY INJURY

2. Gentamicin Induced AKI: Consequences of drug toxicity include both glomerular and tubular injuries leading to acute or chronic functional abnormalities in kidneys. The frequency of drug-induced nephrotoxicity is approximately 14-26% in adult populations [13]. Gentamicin (GM) is a cheap important, and widely used antibiotic of the aminoglycoside group for the treatment of gram-negative bacterial infection. Gentamicin induced acute renal failure has proved to be an excellent useful animal model for exploring the pathogenesis of drug-induced acute renal failure [14].

2.1 ROS Production and Cell Injury: Normally, gentamicin is almost entirely eliminated by the kidney, but a small toxic portion is selectively reabsorbed and accumulates in lysosomes of proximal renal tubular cells and cause apoptosis at clinically relevant doses [15]. Gentamicin binds the cell wall phospholipids, blocking, thus the chain reaction of phosphatidylinositol, which impairs the cell integrity [16]. An excess amount of gentamicin can stimulate free radical formation. Therefore, it is claimed with great certainty that gentamicin induces oxidative stress. Kidney cells can produce free radicals in endothelial cells, glomerular mesangial cells, and in tubular epithelial cells [17]. Epithelial cells of proximal tubules are very sensitive to the effects of oxygen free radicals, as 50% of cells die after being exposed to the effect of H_2O_2 [18]. These free radicals impair the tubular function, destroy the glomerular basement membrane, degrade the collagen and other components of matrix [19]. ROS is also responsible for cellular damage and necrosis *via* several complex mechanisms, including peroxidation of membrane lipids, protein carbonylation, and DNA damage. Gentamicin has long been known to cause acute renal failure in patients, in addition to histological and functional signs of proximal tubule toxicity.

2.2 Role of Pro and Anti-apoptotic Protein: In cytoplasm, gentamycin acts on mitochondria both directly and indirectly, and activates intrinsic apoptosis pathway, breaks the respiratory chain, decrease ATP synthesis and leads to oxidative stress by creating superoxide anion and hydroxyl radical [20] resulting in cell death. The indirect mitochondrial effect is mediated by increased levels of Bcl-2 associated protein X (Bax) through inhibition of its degradation in proteasomes [15]. Lysosomal content is made of highly active proteases called cathepsins capable of inducing cell death. Large quantities of gentamycin inhibit protein synthesis, disrupts translation accuracy, and

post-translation modification of proteins. This results in endoplasmic reticulum stress and activation of apoptosis by caspase 12 and calpain. Apoptosis of mesangial cells induced by gentamycin is also characterized by an early increase in pro-apoptotic protein Bax and late increase in anti-apoptotic Bcl-2 protein [21].

3. CCl_4 Induced Renal Failure: Carbon tetrachloride (CCl4) is one of the xenobiotics that have been reported to induce acute and chronic tissue injuries and is a well-established hepatotoxin. It was used extensively to study hepatotoxicity in animal models by initiating lipid peroxidation and thereby causing injuries to kidney, heart, testis and brain by excessive production of free radicals. The liver is particularly susceptible to oxidative stress due to the direct release of CCl_4 metabolites and cytokines, which propagate the inflammatory response. CCl_4 shows a high affinity to the kidney cortex that contains cytochrome P-450 predominantly [22]. Due to CCl_4 hepatorenal injury, the transport function of hepatocytes and nephrotic cells gets disturbed, resulting in the leakage of the plasma membrane, thereby causing an increased enzyme level in the serum [23]. CCl_4 metabolism begins with the formation of $CCl_3^{\bullet}$ by cytochrome p-450 system. In the presence of oxygen, $CCl_3^{\bullet}$ reacts with oxygen to form $CCl_3OO^{\bullet}$, a highly reactive species. $CCl_3OO^{\bullet}$ attacks and destroys polyunsaturated fatty acids, thereby initiating the chain reaction of lipid peroxidation (LPO) [24]. It has been reported that LPO is one of the major causes of CCl_4-induced nephrotoxicity mediated by the production of free radical derivatives of CCl_4 [25]. In order to cope with the excess of free radicals produced upon oxidative stress, organisms have developed enzymatic and non-enzymatic antioxidant systems to scavenge or detoxify reactive oxygen species (ROS), block their production or sequester transition metals which are the source of free radicals [26] thereby causing a low level of the anti-oxidative defense system, and hepatorenal cellular necrosis occurs.

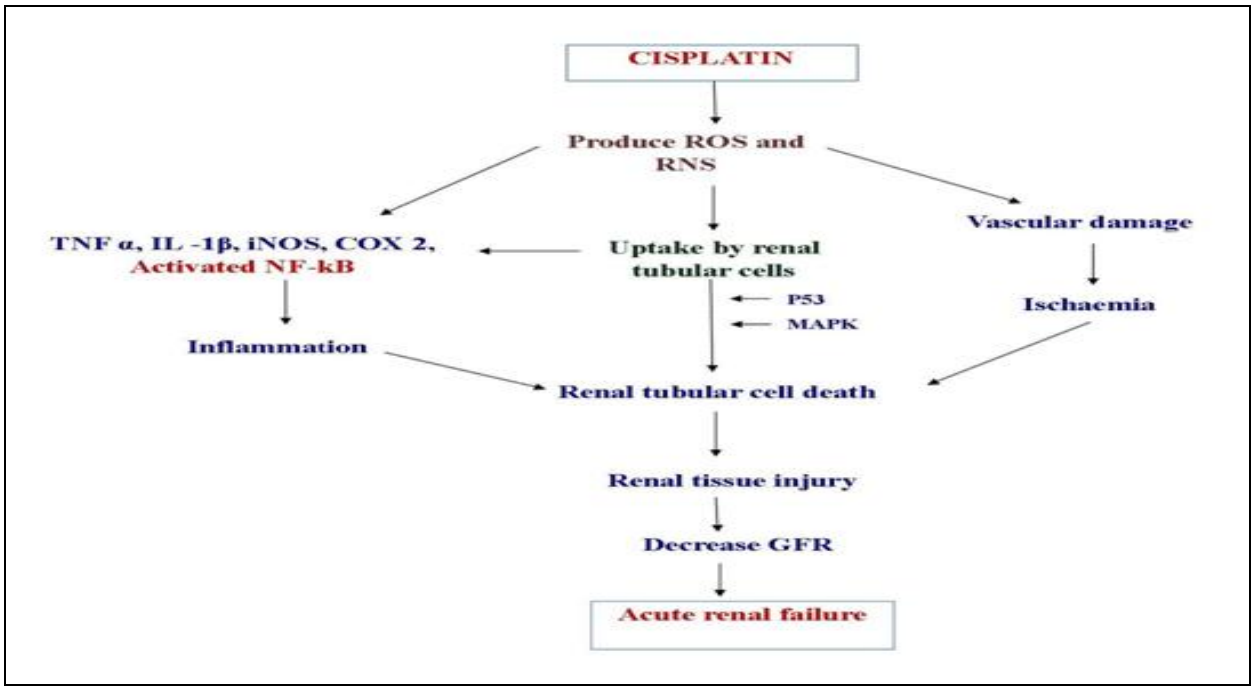

FIG. 2: CISPLATIN INDUCED RENAL FAILURE

4. Cisplatin Induced Nephrotoxicity:

4.1 Cisplatin Induced Cell Apoptosis and Necrosis: Cisplatin (cis-diaminedichloroplatinium) is one of the major standard antineoplastic drugs, which still has a central role in cancer chemotherapy. However, its significant antitumor activity is often limited due to the development of renal toxicity [27]. The accumulation of high concentrations of cisplatin in the kidneys caused nephrotoxicity. The development of renal tubule injury is caused by the oxidative stress induced by cisplatin. The reactive oxygen species (ROS) and reactive nitrogen species (RNS) production alter the structure and function of cellular membranes.

Cisplatin damages the DNA resulting in apoptosis induction. In response to cisplatin, several signaling pathways, which can be activated by lipid peroxidation and oxidative stress, modulate cell survival or apoptosis [28]. The mitogen-activated protein kinase (MAPK) pathways regulate differentiation, proliferation, apoptosis, and are activated by chemical and physical stresses [29]. The three major MAPK pathways terminate in ERK, p38 and JNK/SAPK enzymes. Cisplatin is known to activate these three pathways in various cell lines, including renal epithelial cells. p38 MAPK was involved in inflammation, cell cycle regulation, and differentiation [30]. Also, research suggests that p38 MAPK is able to control the p53-mediated response to cisplatin. Through this pathway, cisplatin-induced nephrotoxicity results in apoptosis and necrosis, vascular damages, and inflammation of the tubules [31].

4.2 Cisplatin Induced Lipid Peroxidation: Cisplatin-induced nephrotoxicity occurs by increasing MDA levels and reducing activities of enzymatic antioxidants, including SOD and catalase [32]. NADPH oxidase is a membrane-bound enzyme complex which donates an electron from NADPH to molecular oxygen (O_2) to produce O_2•. Thereafter, O_2•-is converted into H_2O_2 by SOD. H_2O_2 is also converted to •OH by the Fenton reaction. Cisplatinplay a key role in ROS production by enhancement of NADPH oxidase gene expression, causing increased lipid per-oxidation, ultimately may cause membrane damage and cell death.

5. Glycerol Induced Acute Kidney Injury: The most commonly used model for studying ARF is obtained in the rat by intramuscular injection of glycerol, which produces a myoglobinuric state similar to clinical Rhabdomyolysis (RM) and is characterized by rapid increases in BUN and serum creatinine which are associated with a marked reduction in glomerular filtration rate within 3 h after glycerol administration [33]. Creatine kinase level is the most sensitive damage index for muscle cell damage and marks the occurrence of RM. Rhabdomyolysis is defined as a massive break-down of skeletal muscle in which a potentially large amount of damaging intracellular content enters into blood [34]. RM is measured by estimation of creatine kinase the development of RM is associated with causes such as crush syndrome, exhaustive exercise, medications, infections, and toxins [35]. AKI is one of the most severe complications of RM, with approximately 15% of patients with RM developing AKI6, and 5–15% of AKI cases are attributed to RM. Myoglobin-induced renal toxicity plays a key role in RM-associated AKI by increasing oxidative stress, inflammation, endothelial dysfunction, vasocon-striction, and apoptosis [36].

In glycerol-induced AKI, myoglobin heme induces oxidative stress and lipid peroxidation of the proximal tubular cells, triggering the release of a series of mediators, including cytokines and chemokines, leading to leukocyte activation and subsequent tubular necrosis in the renal cortical area [37].

6. Adenine Induced Chronic Kidney Disease: Orally administered adenine metabolizes to 2, 8-dihydroxyadenine, which forms crystal in the proximal tubular epithelia leading to inflammation and subsequent tubulointerstitial fibrosis [38], as well as anemia. Fifty mg/kg oral administration of adenine for 28 days caused a significant reduction in hematocrit and plasma EPO levels. It has been reported that long–term consumption of adenine suppresses the excretion of nitrogenous compounds through occlusion of renal tubules, and produces metabolic abnormalities resembling CRF in humans.

In mammalian metabolism, when adenine is present in excess, it becomes a significant substrate for xanthine dehydrogenase. This enzyme can oxidize adenine to 2, 8-dihydroxyadenine (DHA) [39]. Because adenine and DHA have low solubility, they precipitate in renal tubules [40]. It is not known whether mice transform adenine to a renal damaging metabolite more efficiently than rats, or whether there are other genetic, biochemical, or histological explanations for this species difference. Biochemical indicators of cell death include caspase-3, which is a crucial mediator of programmed cell death (apoptosis). Caspase-3 activation by cleavage has been considered as an apoptotic index, and this is essential for the formation of apoptotic bodies and commitment to loss of cell viability. Adenine - treated mice and rats showed detectable caspase-3 cleavage, which

may be considered a possible mechanism involved in the adenine-induced kidney damage [41].

7. Potassium Dichromate Induced Nephro-toxicity: Potassium dichromate is a hexavalent form of Cr and it has been used in the induction of renal oxidative stress. $K_2Cr_2O_7$ is a potent oxidizing agent displaying a marked affinity, once reduced to trivalent chromium (Cr^{+3}) by numerous cell metabolites, to form several complexes with diverse biological ligands, nucleic including acids.

7.1 $K_2Cr_2O_7$ Induces Oxidative Stress: It was reported that acute exposure induces anatomical lesions at the proximal tubular cells and lipid peroxidation in the human kidney. Chromium reduced intermediates were thought to reacted with hydrogen peroxide to form hydroxyl radicals [42], with subsequent alterations in proteins, DNA, and phospholipids leading to disturbing cellular functions and its integrity [43]. So that, rats were intoxicated with $K_2Cr_2O_7$ with subsequent increase in the serum creatinine, urea, uric acid, proteins and sodium levels and severe alteration in the histo-pathological examination in comparison with normal control group, through the elevation of reactive oxygen species (ROS) that induces tissues damage such as liver, pancreas, cerebellum and kidney [44]. ROS generated by this process can bring on injury to cellular proteins, lipids, and DNA leading to oxidative stress also ROS generation enhances activation of key signaling molecules that regulate cell death, survival, differentiation, and proliferation [45]. The incredible increase in MDA and NO and decrease of GSH, SOD and CAT are excellent indicators for oxidative stress through the activation of inducible nitric oxide synthase (iNOS), leading in over production of NO and generation of toxic peroxynitrite that reflected on reducing body weight and kidney enlargement [46].

7.2 $K_2Cr_2O_7$ Induces Inflammation: Another elucidation of nephrotoxicity induced by $K_2Cr_2O_7$ is by the activation of the inflammatory process as shown by elevated pro-inflammatory cytokine renal TNF-α level. This was proved before that hexavalent chromium could upshot ROS generation, induce the Akt, NF-kB, and MAPK pathways beside elevation of cytokines, including TNF-α and IL-1α levels [47].

CONCLUSION: Large numbers of drugs are available today. Judicious use of such drugs is required to prevent untoward side effects, especially on such a vital organ like the kidney. Identifying high-risk patients and quick recognition of drug-induced injury-related syndrome with the prompt cessation of the offending drug are the keys to managing such a case before the injury causes permanent damage to the renal tissue. Physicians should be up to date with the wide range of medications harmful to the kidney and be aware of the lesions they bring about. The incidence of drug-induced nephrotoxicity is rising in the worldwide population. It is the time to focus on the therapeutic uses on the drugs with proper doses that will prevent the harmful effect on the overdoses of medicines.

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