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Research Article

Renal Damage a Worldwide Trouble with Its Risk Factors and Amelioration

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ABSTRACT

Acute kidney injury (AKI), formerly called acute renal failure (ARF), is commonly defined as decline and damage of renal function, with a reversible acute increase in nitrogen waste products—measured by blood urea nitrogen (BUN) and serum creatinine levels over hours to weeks. It's generally characterized by the risk, injury, failure, loss, and end-stage kidney disease (RIFLE). In last decay, reducing or protecting against its nephrotoxicity has become the most concerning one. This article reviews some of the literature published during the last decade on the effects of agents that ameliorate or augment GM nephrotoxicity. Notable among the ameliorating agents are antioxidant agents. During the last decade, ameliorating nephrotoxicity has gained much effort and attention throughout the world. Most of the ameliorating agents are antioxidant agents, hormones (melatonin), β-blockers (metoprolol), vitamins (Vit. C and E), Superoxide dismutase, Iron chelators (fereptossin), and some medicinal plants (garlic). Other ameliorating agents include antibiotics (e.g. ceftriaxone), antiplatelet drugs (e.g. trapidil), and Ca^{++}. Some agents that may augment nephrotoxicity include cyclosporin and the Ca^{++}-channel blocker (verapamil), antibiotics (Gentamicin), chemotherapeutics (Doxorubicin), PPIs, and NSAIDs. Although these augmenting agents are vital agents for life threatening conditions, so we have to find out the ameliorating agents which may reduce and protect against nephrotoxicity. Various drugs (i.e., cobicistat, trimethoprim, and cimetidine) are potent inhibitors of these transporters, affecting the tubular secretion component of Cr clearance and can increase SCr levels by 0.2–0.4 mg/dL and decrease Cr clearance by 15–34 mL/min. Some antibiotics (piperacillin, tazobactam, and vancomycin) could significantly diminish the number and activity of organic anion transporters (OAT) on the basolateral membranes of proximal tubular cells and cause impaired Cr secretion and increased SCr, with apparent AKI. The risk factors that are included in AKI are prolonged duration of therapy, concomitant nephron-toxin exposure, and a variety of comorbidities.

Abbreviations: AKI (Acute kidney injury), OAT (Organic anion transporter), SCr (Serum Creatinine)

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1. INTRODUCTION

After liver toxicity kidney toxicity is the second highest cause of new drug failure, resulting in many adverse pharmaceutical drug performance issues in clinical trials. The lack of reliable drug identification and toxicity screening methods results in costly consequences when drugs fail late in the development process. [1]

Nephrotoxicity is another term for "renal disease or dysfunction" due to contact with medications, chemical compounds, and industrial or noxious agents of environments. According to Collins Dictionary "Nephrotoxic" are agents that are deadly or poisonous for the kidney, which is the most essential organ to keep homeostasis with extracellular environments, (for example detoxification, and excretion of toxic metabolites, medications) [2]. Nephron which is the elementary unit of kidney with numerous cell types and failure of kidney indicated by loss in intra-renal blood vessels, tubules and glomeruli. The proximal tubule is the primary target for the vast majority of nephrotoxicity. Therefore, the kidney can be considered as a major target organ for exogenous toxicants. Nephrotoxicity is a kidney-specific feature in which excretion does not go smoothly owing to toxic chemicals or drugs. Approximately 20% of nephrotoxicity is induced by drugs, but medication in the elderly increases the incidence of nephrotoxicity up to 66% as the average life span increases. Chemotherapy or anticancer medicine has been of limited use due to nephrotoxicity. [3] Drug-induced AKI accounts for 19–26% of all hospitalized cases. Drugs can cause damage to different nephron fragments, with the tubules being the most exposed to injury. The injuries follow diverse mechanisms. [4]

Renal tubular cells particularly proximal tubule cells, are vulnerable to the toxic effects of drugs due to the concentration and reabsorbing at exposure to high levels of circulating toxins. Drugs that cause tubular cell toxicity, do so by impairing mitochondrial function, interfering with tubular transport, increasing oxidative stress, or forming free radicals. Drugs associated with this pathogenic mechanism of injury include aminoglycosides, amphotericin B (Fungizone; brand not available in the United States), antiretrovirals (adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread), cisplatin (Platinol), contrast dye, foscarnet (Foscavir), and zoledronate (Zometa). [5] Changing your diet is crucial to avoid kidney damage a high-protein diet isn't recommended for nephrotic syndrome. Too much protein is dangerous because it can damage nephrons (the functioning units of kidneys) and cause renal insufficiency. [6] Overall, due to the metabolic role of the kidneys in drug biotransformation, renal clearance is the dominant component of total clearance for most drugs. The kidney itself is a privileged target of their noxious action and numerous drugs may produce renal-adverse reactions. The general rationale for the thesis is an assumption that numerous kidney diseases significantly influence the pharmacokinetic profile of drugs, especially the stages of excretion and, in part, the metabolism. On the other hand, however, drugs and their metabolites excreted by the kidneys may themselves cause functional and/or structural renal dysfunction due to their nephrotoxic potential. The proximal tubules are the most sensitive to the nephrotoxic effects of xenobiotics and drugs, as they are characterized by the highest metabolic activity, are high on the osmotic gradient, as mentioned above, and due to the presence of tubular transport systems involved in the excretion and resorption of compounds from primary urine ultrafiltrate. [7]

Usually, there are three stages to kidney disease and these are: your blood pressure, the blood's eGFR (estimated glomerular filtration rate), and your urine's ACR (albumin: creatinine ratio). Depending on your stages of kidney disease, your test result will vary. Kidney infection is silent and classified according to its structure, function, cause, duration, and outcomes. Classification of this disease is independent of age, sex, race, location and co-morbid conditions. We can divide renal failure into two broad categories- one is intrinsic and another is extrinsic renal failure. Table- I show general classification of kidney disease [8,9,10,11]. Chronic kidney disease (CKD) is far more prevalent worldwide than was previously assumed. It affects 10 - 15% of the adult population in Western countries, many of whom require costly treatments or renal replacement therapy. According to the Third National Health and Nutrition Examination Survey and the National Kidney Foundation, Kidney Disease report nearly 26 million persons in the USA fall into this category and another 20 million are at an increased risk for CKD [12].

1. Diseases that augment nephrotoxicity

Cardiovascular disease:

Coronary artery disease (CAD) is quite common in patients with chronic kidney disease (CKD), and the risk of cardiovascular death increases linearly with decreasing eGFR. [13]. Cardio-renal syndrome is a group of illnesses affecting both the heart and the kidneys in which acute or chronic malfunction in one organ can cause acute or chronic dysfunction in the other. It represents the convergence of heart-kidney interactions at numerous interfaces. These include the hemodynamic cross-talk between the failing heart and the response of the kidneys and vice versa, as well as alterations in neuro-hormonal markers and inflammatory molecular signatures characteristic of its clinical phenotypes. [14] We are mostly wondered with cardiac and kidney diseases that often happen together. The heart's job is to send an uninterrupted supply of oxygenated blood around the body while the kidney filters the blood and extracts waste in the form of urine while maintaining body water and salt levels which help in controlling blood pressure. Recently it has been known that heart failure is a significant risk factor for kidney disease and atherosclerosis which are responsible for narrowing the main renal arteries. Cardiac failure also causes decreased renal perfusion, and diuretics are used to manage fluid retention while lowering GFR. The potential of cardiac and renal failure is known as Cardio-renal syndrome [15]. The pathogenesis of combined cardiovascular and renal illness spans multiple interfaces. To begin, traditional risk factors for atherosclerosis include coronary artery disease, renal artery stenosis, endothelial dysfunction, and small vessel disease. The second category is hemodynamic interactions, which include resistant hypertension, fluid overload, and significant blood pressure changes associated with an aberrant regulatory response. Next is the activation of the renin-angiotensin–

aldosterone system, which is recognized in both CKD and heart failure, and plays an important role in the maintenance of cardiovascular homeostasis. Anemia and chronic inflammation can contribute to the overlap of morbidities, along with uremic toxins. Finally, the mineral-bone condition worsening CKD generates hyperphosphatemia and a positive calcium balance, which promotes vascular calcification, accelerated atherosclerosis, and structural abnormalities in the heart. The term "cardio-renal syndrome" refers to the mutual influence of acute or chronic heart or kidney failure on the other organ [14].

Liver Failure:

Hepatotoxicity is defined as an increase of bilirubin greater than 1.5 mg/dl or AST and ALT greater than three times the normal range. Nephrotoxicity is defined as a serum creatinine increase of 0.5 mg/dl or a 50% increase over baseline. Acute kidney injury (AKI) is characterized by impaired renal function in tubular necrosis and a high creatinine level [16]. Furthermore, this one develops 1gA nephropathy, glomerulonephritis, or nephron sclerosis [17,18,19]. Extreme vasoconstriction of the renal vascular bed during HRS (Hepatic Renal Syndrome) may predispose the kidneys and impair renal perfusion. (fig- 1) In addition to hepatotoxicity, the clinical significance of nephrotoxicity in paracetamol overdose, and the importance of monitoring renal function while caring for such patients, must be acknowledged. Its severity and course may not be closely related to those of hepatotoxicity, and it may occur in a low-risk patient. N-acetylcysteine (NAC) is an effective antidote to prevent the occurrence of liver injury. Paracetamol poisoning may also cause acute kidney injury (AKI) as a secondary effect of liver damage (hepato-renal syndrome) [20]. The evidence suggests that aminoglycoside antibiotics are associated with a greater incidence of renal dysfunction in patients with liver disease and that this interac- tion is clinically important. Moreover, a knowledge of the interaction could contribute to our understanding of the pathophysiology of both aminoglycoside nephrotoxicity and the hepatorenal syndrome. [21]

Lung Failure:

Kidney and lung both are physiologically and pathologically interact. Both organs are targeted for the same systemic disease. When lung fails tissue of the body do not receive enough oxygen and kidneys do not get enough blood for working (fig- 1). COPD (Chronic Obstructive Pulmonary Disease) can cause systemic swelling, hypoxemia, endothelial abnormalities, sympathetic activation and aortic stiffness, microvascular damage, albumin-urea, and a decline in renal function [22]. CKD has a profound impact on pulmonary physiology because it alters fluid homeostasis, acid-base balance, and vascular tone. In the lung, hemodynamic disturbances cause changes in ventilatory control, pulmonary congestion, capillary stress failure, and pulmonary vascular disease. Haemodynamic changes in the kidney cause salt and water retention, as well as impairment in renal function [23].

Beyond the common CKD-associated complications, lung diseases can have profound negative effects on kidney function, especially in the presence of other comorbidities, and correlate independently with increased mortality in patients with CKD. Lung diseases are a major cause of mortality and morbidity worldwide, with chronic obstructive pulmonary disease (COPD) alone causing more than 2.7 million deaths [24].

Obesity:

Obesity is directly links, with several diseases as well as kidney injury. In the case of direct mechanism, kidney injury there is a deranging of adipose tissue synthesis with various cytokines and nephrotoxic potential. Diabetes and hypertension are the indirect causes of kidney injury (fig-1). Extra weight forces, kidney to work harder and filter wastes above the normal level and this extra work increase the risk for kidney disease and development of CKD [25,26,27]. Obesity has become a worldwide epidemic, and its prevalence has been projected to grow by 40% in the next decade. This increasing prevalence has implications for the risk of diabetes, cardiovascular disease, and also for chronic kidney disease (CKD). A high body mass index is one of the strongest risk factors for new-onset CKD [28]. Obesity is one of the epidemics of our era. Its prevalence is higher than 30% in the U.S. and it is estimated to increase by 50% in 2030. Obesity is associated with a higher risk of all-cause mortality and it is known to be a cause of chronic kidney disease (CKD). Typically, obesity-related glomerulopathy (ORG) is ascribed to renal hemodynamic changes that lead to hyperfiltration, albuminuria and, finally, impairment in glomerular filtration rate due to glomerulosclerosis [29].

Diabetes:

Diabetic nephropathy is a significant consequence of both type 1 and 2 diabetes. It's also known as diabetic kidney disease. Diabetic nephropathy affects almost one-third of all diabetics in the United States [30]. Diabetics' nephrons gradually thicken and scar over time. The nephrons begin to leak, allowing protein (albumin) into the urine. Diabetic nephropathy is a frequent phrase for kidney damage that occurs promptly. Protein in urine is a common occurrence after diabetic kidney injury (fig. 1). During diabetes, sugar levels in the blood lead kidney arteries to narrow and clog [31]. Diabetic kidney disease (DKD) is usually a clinical diagnosis in a patient with long-standing diabetes (>10 years) with albuminuria and/or reduced estimated glomerular filtration rate (eGFR) in the absence of signs or symptoms of other primary causes of kidney damage. Proteinuria is the characteristic laboratory finding. Deterioration in renal function may develop as the disease advances. However, the pattern of albuminuria and reduced glomerular filtration rate (GFR) is changing, and reduced GFR without albuminuria is becoming more common [32].

Glomerular Nephritis:
The "nephron" is a functional unit of the kidney that works to filter blood and produce urine. Glomerulonephritis is an inflammation of the kidneys' glomeruli or small blood vessels [33]. Because of the high incidence of infection during glomerulonephritis and interstitial nephritis (fig-1), these are the most common causes of CKD and the second leading cause of death after diabetic nephropathy [34]. A million glomeruli are small filters that remove waste and fluid from your blood. If glomeruli are damaged, which is known as glomerulonephritis , will be unable to perform their functions. If not treated, glomerulonephritis can cause serious kidney damage, including kidney failure. Acute glomerulonephritis (GN) can be caused by either a primary renal etiology or a secondary illness with renal signs. Acute post-streptococcal glomerulonephritis (PSGN) is a common type of acute glomerulonephritis caused by a streptococcal infection; similarly, Staphylococcus aureus infection can cause glomerulonephritis. [35]

Kidney Stone:
Kidney stone moves around within the kidney or pass into one of the ureters, it shows symptoms of kidney disease. Calcium stones and uric acid stones are several types of kidney stones and their formation relates to high levels of minerals or too little liquid [36]. Some hereditary disorders like- primary hyperoxaluria, 2-8-hydroxy adenine crystal urea, cystinuria, nephrocalcinosis, or renal crystal deposition can lead to progressive loss of GFR and ESRD with kidney stone formation and ultimate result of renal failure, cardiovascular disease, diabetes. The stone matrix is mostly composed of proteins, non-amino carbohydrates, glucosamine, water, and inorganic ash [37, 38]. Primary hyperoxaluria type 3 (PH3) is characterized by reoccurring calcium oxalate stones that appear in childhood or adolescence, as well as nephrocalcinosis or impaired kidney function. PH3 is most commonly diagnosed in childhood (median age 2 to 3 years) with stone-related signs or symptoms such as hematuria, frequent urination, dysuria, blood in the urine, or stone-associated discomfort. [39] Kidney stones are a known risk factor for CKD; consequently, patients with stones should have regular renal function monitoring and receive appropriate treatment to avoid CKD. [40]

Polycystic Kidney disease:
Polycystic kidney disease (commonly known as PKD) causes many cysts to form in the kidneys. The cysts are filled with fluid. If there are too many cysts or they get too large, the kidneys can be harmed. PKD cysts can gradually replace much of the kidneys, lowering kidney function and ultimately leading to renal failure. It accounts for around 5% of all renal failure. [41] Autosomal dominant PKD (ADPKD) is the most frequent of the hereditary renal cystic illnesses, which are characterized by the formation of renal cysts as well as a variety of extra-renal complications. [42]

During inherited kidney disease with PKD1, PKD2 genes cluster of cysts (non-functioning tubules filled with fluid) forms within the kidney, and kidney size enlarges (fig-1). Autosomal dominant polycystic kidney disease (ADPKD) causes mutation of Glucosidase (alpha) and ultimate mutation of PKD1 and PKD2 [43,44].

Renal Fibrosis:
Renal fibrosis is a condition in which the kidney loses its ability to recover from damage and requires regular dialysis. This is one of the most common causes of CKD, which is a degenerative kidney disease that affects the elderly [45,46]. Fibrosis is a condition defined by an excess accumulation of the extracellular matrix in response to various forms of tissue damage, resulting in organ failure. The process can be triggered by a variety of triggers and pathogenic factors, which begin a cascade of reparation that culminates in molecular signals that initiate and drive fibrosis.[47] In the kidney, this results mainly in glomerulosclerosis, tubular atrophy and dilation, tubulointerstitial fibrosis, and capillary rarefaction. Fibrosis development usually takes a similar course independent of the underlying organ disease and is therefore particularly suitable as a therapeutic target. [48]

2. Signs and Symptoms:
Patients with Nephrotoxicity may face several signs and symptoms usually decreased urination, increased serum β2-microglobulin, swelling from fluid retention, elevated creatinine levels, anemia, and increased blood pressure. Including these patients may also face blood in urine, muscle cramps, weakness, or numbness. Damaged kidneys can't produce erythropoietin hormone, and as a result hampered in red blood cell formation, and may feel itchy due to having too much phosphorus.

Anemia:
People with CKD experience a decrease in erythropoietin production, a reduction in red cell life span, and problems with iron metabolism. During CKD, iron shortage is the primary cause of erythropoiesis, which leads to anemia. Patients undergoing hemodialysis experience iron loss, resulting in an anemic condition [49, 50]. The kidneys produce an important hormone called erythropoietin (EPO). Hormones are chemical messengers that travel to tissues and organs to maintain your health. EPO tells your body to produce red blood cells. Kidneys are unable to produce enough EPO in renal illness. Low EPO levels induce a decline in red blood cell count, which leads to anemia. [51]

Malnutrition:
CKD has become an important public health problem which has a high prevalence, poor prognosis, and expensive medical expenses. CKD is a complex disease including many important factors which affect the status and progression of CKD patients. Old ages and low glomerular filtration rates are more probably to develop geriatric syndromes and malnutrition. [52]

Malnutrition is a common term during CKD and during malnutrition protein-energy wasting, and micronutrient deficiency are very common [53]. Increased protein catabolism, metabolic acidosis, systemic inflammation, and intestinal dysbiosis are common in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [54]. Deficiency of 25-hydroxyvitamin D (25OHD) is highly prevalent in case of CKD, patients in the state of dialysis or non-dialysis decrease in the intake of several vitamins, minerals, and iron [55, 56]. Hormonal imbalance and anorexia lead to nutritional deficiency during CKD.

Feeling itchy:

Itching of the skin is also called uremic and it's a serious problem for many people in their quality of life during CKD. The normal phosphorous level in the blood is 2.5 to 4.5 mg/dL, however during CKD, excess phosphorous cannot be excreted correctly, resulting in skin itching [57]. End-stage renal disease and uremia are frequently characterized by skin pruritus, which is common among patients with uremia and skin problems [58]. Itching (uraemic pruritus) is a common symptom in persons with end-stage kidney disease (ESKD), affecting 42% to 57% of those on dialysis. Itch has a major negative impact on quality of life (QoL) due to discomfort, sleep disturbances, anxiety, and depression. Despite its widespread prevalence, the processes behind uraemic itch are poorly known; two common theories include hyperactive and dysfunctional immune or opioid systems. However, roles have been hypothesized for hyperparathyroidism, aberrant serum chemistry, mast cell hyperactivity, and dialysis method. [59]

Mineral and bone disorder:

Mineral metabolism dysregulation is a common cause of CKD, and it can also improve bone health. CKD patients frequently exhibit hypocalcemia, hyperparathyroidism, hyperphosphatemia, decreased vitamin D metabolite levels, and elevated fibroblast growth factor 23 levels. [60]. The formation of healthy bone is dependent on hormone and mineral metabolism. In the stage of CKD, the kidneys are unable to filter blood and there is an imbalance of hormones and minerals such as calcium and phosphorus. These anomalies cause bone regeneration disorders [61].

High blood pressure:

Hypertension is a leading cause of kidney disease and kidney failure (end-stage renal disease). Kidney disease can also cause a type of high blood pressure called renal hypertension. Hypertension can cause damage to the blood vessels and filters in the kidney, making removal of waste from the body difficult. Whenever a person is diagnosed with end-stage renal illness, they must undergo dialysis (a blood-cleansing procedure) or a kidney transplant [62]. Damaged kidneys are unable to function and regulate blood pressure. In this case, physical activity, stress management, and smoking cessation are all critical steps toward blood pressure control [63].

3. Agents that augment Nephrotoxicity:

Chemotherapeutics:

Chemotherapeutics and the combination of multiple medications with chemotherapeutics enhance the risk of nephrotoxicity. Doxorubicin (DOX) is a widely used medicine for antineoplastic and carcinomas with progressive glomerulosclerosis and tubulointerstitial disruption, as well as when paired with hypoalbuminemia, hypercoagulability, dyslipidemia, proteinuria, edema, and ascites development [64]. Cisplatin is a chemotherapy used to treat head, neck, testicular, cervical, ovarian, lung, and bladder tumors. It causes extensive renal proximal tubular (RPT) cell death, necrosis, and apoptosis [65]. Cyclophosphamide is one of the most effective chemotherapeutic drugs used to treat lymphomas and other solid malignancies, but its metabolites cause kidney damage such as apoptosis and fibrosis [66]. Vancomycin is an excellent choice for treating granulocytopenic patients, which are responsible for nephrotoxicity via the indirect creation of reactive oxygen species and oxidative stress [67]. Methotrexate, a folic acid antagonist, is commonly used to treat a variety of cancers, although it induces kidney damage via oxidative stress and inflammation [68].

Antibiotics:

Aminoglycosides a broad-spectrum antibiotic (including gentamicin, tobramycin, amikacin, neomycin, plazomicin, paromomycin, and streptomycin) cause renal tubular toxicity with decreased blood flow to the kidneys and reduced GFR [69,70]. β-lactam are wide-spectrum antibiotics (penicillin, cephalosporin, carbapenems) used for various infections and these drugs may lead to proximal tubular necrosis [71]. Colistin and imipenem also cause nephrotoxicity through oxidative stress, proximal tubule cell death and loss of the brush border membrane and polarity [72].

PPIs:

According to one study, Chronic Interstitial Nephritis (CIT) is caused by overuse of PPIs, which is associated with AIT (acute Interstitial Nephritis) and progressive end-stage renal disease (ESRD) [73,74]. PPI can deposit in the kidney's tubule-interstitial tissue and act as a hapten, or it can directly stimulate T-cells, impairing lysosomal acidification and proteostasis, causing hypomagnesemia, increased oxidative stress, dysfunction, and accelerated wear and tear damage in human renal endothelial cells [75,76]. PPIs are intended to reduce acid output in the stomach while increasing the pH of the gastric juice. They inhibit the action of the enzyme H+/K+-ATPase, preventing the exchange of K+ for H+, and distinguish themselves from other medications used to treat gastric disorders by additionally inhibiting the final stage in the synthesis of hydrochloric acid. This process increases the strength of the inhibitor, making PPIs the current medicine of choice. PPIs inhibit the enzyme by combining with its receptor and covalently attaching to cysteine residues, resulting in irreversible inhibitors. Following the process, the proton pump cannot renew, and acid generation begins only until new enzymes are synthesized. Irreversible inhibition guarantees that the medicine remains active for 24 to 48 hours. [77]

Non-steroidal anti-inflammatory drugs:
Nonsteroidal anti-inflammatory drugs (NSAIDs) are common nephrotoxic treatments, particularly when used long-term. The risk of NSAID nephrotoxicity rises with increasing age and co-morbidities [78]. NSAIDs primarily suppress the formation of specific prostaglandins (PGs) by inhibiting the cyclooxygenase enzymes COX-1 and COX-2. COX-1 controls renal hemodynamics and glomerular filtration rate (GFR), whereas COX-2 regulates salt and water excretion and the production of PGs, which govern pain, fever, and inflammation [79]. Inhibition of COX-1 and COX-2 results in undesirable side effects such as GI and renal toxicities with AKI [80].

4. Drugs used to prevent or treat Nephrotoxicity:
Antioxidants:
Food derived AO:
Studies on naturally derived bioactive compounds have shown that natural compounds reduce the side effects of nephrotoxicity. Curcumin, garlic, fenugreek, parsley, peppermint, pomegranate, propolis, olive leaves, rosemary, sesame, and plant sources contain bioactive compounds that show remarkable kidney protection against nephrotoxic agents [81]. Curcumin ameliorates cadmium and doxorubicin-induced nephrotoxicity either by reducing urinary excretion of AKI biomarkers or by modulating inflammatory cytokines, apoptosis, oxidative stress, and oxidative DNA damage [82,83]. Garlic is another natural derivative that ameliorates gentamicin and cisplatin induces nephrotoxicity either by preventing or ameliorating oxidative stress. Garlic extract and honey are helpful for cadmium-induced nephrotoxicity by restoring antioxidant activities, biochemical modifications and oxidative stress markers [84].

Other antioxidants:
Some genetic factors also play an important role as an antioxidant. Nuclear erythroid-related factor 2 (Nrf2) is a significant regulator of redox balance that can improve kidney disease by eliminating ROS. Ferulic acid acts as an anti-oxidant for methotrexate nephrotoxicity via suppression of NF-κB/NLRP3 [85]. Hesperidin protects gentamicin-induced nephrotoxicity via Nrf2/HO-1 signaling and inhibits inflammation by NF-κB mediation [86]. Monotropein is another drug that can attenuate cisplatin-induced acute kidney injury (AKI) through regulating Nrf2/ HO-1 signaling and inhibiting NF-κB signaling pathway [87].

Beta-blockers:
Cisplatin-induced nephrotoxicity ameliorates through β-adrenoceptor blockers (carvedilol, metoprolol, and propranolol) that may desensitize receptor/G protein coupling within nephron and offer potential therapeutic benefits [88]. Since the pathogenesis of gentamicin-induced nephrotoxicity involves oxygen free radicals, the antioxidant carvedilol (B-blocker) may protect against gentamicin-induced renal toxicity. [89]

Hormones:
Melatonin is one of the hormones that have antioxidant activity on gentamicin-induced nephrotoxicity [90]. Serum thymic factor (Thymic peptide hormone) may suppress ERK activation initiated by cisplatin-induced nephrotoxicity [91]. Melatonin (N-acetyl-5-methoxytryptamine) which is released from the pineal gland as an endocrine hormone used as a potentially useful agent in the treatment of several diseases and conditions is also released from is also synthesized at numerous extra pineal sites. Melatonin protective against mitochondrial damage and tissue injury by scavenging RNS (reactive nitrogen species) or ROS (reactive oxygen species) in vitro and in vivo and has been considered as a potential endogenous free radical scavenger. Melatonin protects cells and tissues from radical damage as a strong antioxidant by reducing NF-κB and inhibiting pro-inflammatory cytokines (interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α). In one study, it also shows that administration of melatonin prevents structural and functional injuries in the kidney [92].

Iron-Chelators:
Cisplatin-induced apoptosis and necroptosis were inhibited by treatment with Fer-1 (Feroptossin), an inhibitor of ferroptosis. Moreover, deferoxamine, an iron chelator, inhabits CIN (Cisplatin-induced nephrotoxicity) by decreasing the expression of COX-2 and 4-HNE [93]. A study on Cisplatin reveals that it increases the protein expressions of transferrin receptor-1 ferritin, and iron content in the kidney. In addition, treatment with cisplatin may augment renal ferrous iron and hydroxyl radical levels with co-localization. Cisplatin demonstrates kidney injury, with renal dysfunction and increased inflammatory cytokine expression; these changes by Ferrostatin-1 (Fer-1), an inhibitor of ferroptosis. The expression of the ferroptosis markers, COX2 and 4-hydroxynonenal (4-HNE), increases with cisplatin administration, and decreases with the administration of Fer-1. However, cisplatin-induced apoptosis and necroptosis inhibition are possible by treatment with Fer-1 and deferoxamine (iron chelator) inhibits by CIN and decrease expression of COX-2 and 4-HNE. [94]

Vitamins:
Vitamin C, E, and riboflavin are natural antioxidants that decrease serum urea levels. These also helpful as an antioxidant enzyme after treatment with cisplatin induction in cancer patient because these vitamins are the potent antioxidant and anti-inflammatory medicine [95]. Among the different antioxidants tested, vitamin C exhibited a powerful scavenging property against free radicals and activated oxygen species. At the same time, vitamin C is an electron donor that protects by neutralizing reactive oxygen species (ROS) and decreasing oxidative damage. Vitamin C also exhibits anti-inflammatory effects, prevents endothelial dysfunction and apoptosis, and reduces the risk of cardiovascular diseases. If we study the treatment profile of vitamin C which improves

kidney function in renal allograft recipients, decreases renal inflammation, and improves impaired renal function [96].

Medicinal Plants:
Plants containing flavonoids, steroids, and alkaloids have significant nephron-protective and diuretic activities. Serum and urine biochemical analysis and kidney histopathology show that patients pretreated with plant extract dose-dependently prevent kidney injury [97].
Some plant extract also shows antioxidant and nephron-protective effect on nephrotoxicity induced with cisplatin with improving the biochemical parameters and kidney function as well as restoring antioxidant activity in CP-induced nephrotoxicity [98].

Antibiotics:
Ceftriaxone (CTX) shows antioxidant and nephron-protective efficacy alone or in combination with vitamin E (Vit. E) against Cisplatin (CDDP: cis-diamminedichloroplatinum II)-induced acute renal injury. CDDP administration with vitamin E may also activate endogenous antioxidant enzymes (glutathione peroxidase, superoxide dismutase, and catalase) and total antioxidant capacity [99]. Diosmin is another potent antibiotic that can ameliorate gentamicin-related kidney injury due to its antioxidant and anti-inflammatory activities [100].

Antiplatelet drug:
Renal and hepatic toxicity induced by CsA exposure may be diminished by trapidil one of the anti-platelet-derived growth factors and vasodilators. Trapidil works by showing its multiple effects on lipid peroxidation and inflammatory mediator- MCP-1 and cytokines- TNF-alfa. This may inhibit the accumulation of macrophages during injury in the arterial wall, and probably elevate nitric oxide (NO) levels that may neutralize free superoxide anion radicals. NO is considered to be an important regulator of renal vascular tone and a modulator of glomerular function under both basal and physio-pathological conditions [101].

5. CONCLUSION:

Renal failure and nephrotoxicity are the damage of one of the major executive organs. Therefore, during renal failure discontinuation of drug and dose and in some conditions, supplementary drugs and antioxidants are helpful for treatment. Continuous observation and diagnosis, and dialysis all are helpful for recovery from nephrotoxicity, and the patient must maintain another physical exercise with health-related consciousness in this situation. If we look at the safety and efficacy profiles, antioxidant drugs were found to produce the best nephron-protection and especially the natural antioxidants, seem to possess the highest potential for use in the clinic. Drugs that can impair renal function (for example verapamil, cyclosporine, and some diuretics, such as mannitol) and these drugs must not be given with aminoglycoside drugs that may potentiate nephrotoxicity. Therapeutic doses of several important drugs have become suboptimal due to the emergence of drug resistance and become necessity of taking toxic higher doses. These higher doses are associated with severe toxicities that need therapeutic adjuncts to compensate for the toxicities. The favorable safe nature and nephron-protective properties of melatonin have suggested it to be a pharmacological adjunct and become essential in clinical trials. Mitigation of drug-induced nephrotoxicity by melatonin involves the complex series of biochemical improvements at cellular levels. Melatonin attenuates the nephrotoxicity of most drugs through its potent antioxidant action as it is believed to reinforce the antioxidant enzymes and direct free radical scavenging at subcellular levels.

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Annexure

Table 1: Types of Kidney Failure

Intrinsic Kidney Failure	Glomerular Nephritis
	Kidney Stone
	Polycystic kidney disease
	Renal fibrosis
Extrinsic Kidney Failure	Cardiovascular Disease
	Liver Failure
	Lung Failure
	Obesity
	Diabetes

Table 2: Signs and Symptoms of Kidney Failure

Disease name	Disease condition	Criteria
AKI	SCr increases by 0.3 mg/dl (26.5 µmol/l) or more in 48 h or rises to at least 1.5-fold from baseline within 7 days	Usually, no criteria or anuria for ≥ 12 Hrs
AKD	Serum creatinine ≥ 4.0 mg/dL (≥ 353.6 µmol/L) in patients < 18 years and decrease in eGFR< 35 mL/min per 1.73 m^2	Kidney damage less than 3 months with GFR<0.3 mL/kg/h for ≥ 24 hours and anuria for ≥ 12 hours
CKD	50% reduction in eGFR or a fall below 15 ml/min per 1.73 m^2	Albuminuria with kidney damage for more than 3 months
NKD	(eGFR) ≥60 ml/min per 1.73 m^2	No kidney damage

AKI-Acute Kidney Injury or Impairment, AKD- Acute Kidney Disease, CKD- Chronic Kidney Disease, NKD- Unknown Kidney disease, SCr- Serum Creatinine, GFR- Glomerular Filtration Rate.

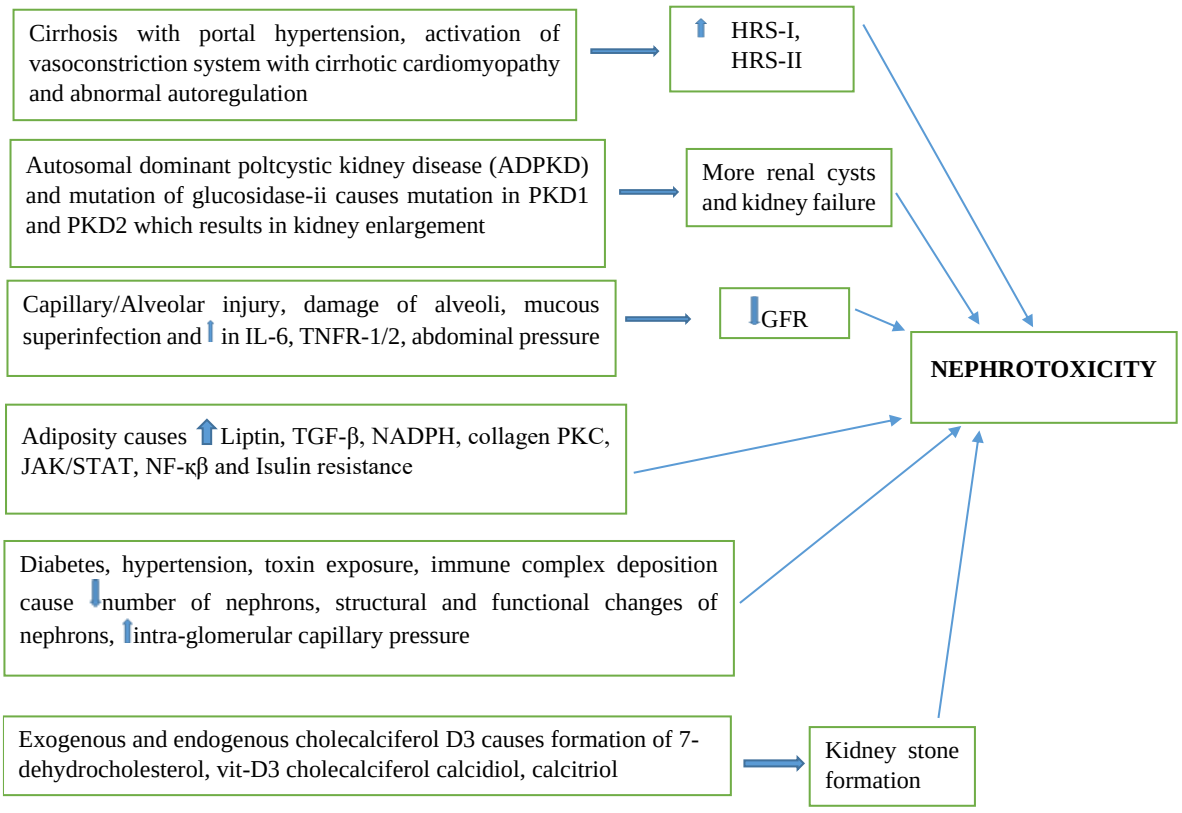

Fig (1): Diseases related to kidney damage