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AN OVERVIEW ON NEPHROTOXICITY AND THE PHARMACOLOGICAL USES OF BOMBAX CEIBA

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ABSTRACT There is a rising incidence of kidney disease across the globe. In India, it has been recently estimated that >100,000 new patients enter renal replacement programs annually. Bombax ceiba , commonly called as silk tree is having wide range of pharmacological activities based on the presence of chemical constitutents like flavonoids, alkaloids, tannins etc. Natural compounds like Bombax ceiba, having antioxidant flavanoids could be used as an alternative herbal treatments for paracetamol induced or free radicals induced renal toxicity. This plant was widely used for various infections and ailments by the tribals. In this present review, we want to focus on nephrotoxicity, especially drug induced nephrotoxicity and the uses of Bombax ceiba extract.

KEYWORDS : Flavonoids, Free radicals, Nephrotoxicity, Constitutents, Biomarkers, Toxicants

Nephrotoxicity can be defined as the adverse effect of substances on renal function. It occurs when kidney specific detoxification and excretion do not work properly due to the damage or destruction of kidney function by exogenous or endogenous toxicants. General nephrotoxic substances include molds, fungi, or drugs like cisplatin, aminoglycosides, metals such as mercury, arsenic and lead. Medications are relatively a common cause of kidney injury. Drug induced nephrotoxicity in adults ranges between 14 % –26 % in prospective cohort studies of AKI.

1.1 DIAGNOSIS

Nephrotoxicity can be diagnosed through a simple blood tests that includes the measurements of blood urea nitrogen (BUN), serum creatinine, and renal parmeters like glomerular filtration rate and creatinine clearance. However, these assessments of nephrotoxicity are only possible when a majority of kidney function is damaged1.

1.2 BIOMARKERS

Biomarkers designate the biomolecules showing the relationship between exogenous toxic substances and diseases. Generally, biomarkers enable us to determine early damage to health caused by exposure to exogenous toxic substances, and provide an insight into the mechanism of the onset of these toxicants2. Some of the nephrotoxic biomarkers include Proteinuria, Albumin, Immunoglobulin G, Cytokines, Interferons, Interleukins, TNF, and Type IV collagen.

1.3 FACTORS ASSOCIATED WITH DRUG INDUCED TOXICITY

The factors that contribute to the development of drug-induced nephrotoxicity3

- Drug related factor
- Patient related factor

1.3.1 DRUG RELATED FACTORS

1.3.1.1 Drug dose and duration of therapy
1.3.1.2 Drug characteristics
1.3.1.3 Drug combinations
1.3.1.4 Innate drug nephrotoxicity
1.3.1.5 Drug-induced inflammation
1.3.1.6 Drug-induced cast nephropathy

Drugs may cause renal injury moderate to severely on the basis of their structure, dose, metabolic handling, and excretory pathway. Some medicinal plants may even interact with conventional drugs and may produce potential nephrotoxicity.

1.3.1.1 Drug dose and duration of therapy

Innate kidney toxicity is one of the important nephrotoxicity. A number of drug characteristics and their varied mechanisms play a major role. Frequent doses or higher doses of drugs like aminoglycosides, platinums, amphotericin B, and colistin will enhance the risk for kidney injury[4].

1.3.1.2 Drug Characteristics

Drugs and their metabolites that are insoluble in the urine may cause acute crystalline nephropathy by precipitating in distal tubular lumen4. Drugs like methotrexate, acyclovir, indinavir/atazanavir, sulfadiazine, vitamin C, foscarnet, oral sodium-phosphate, and triamterene are associated with development of crystalline nephropathy whereas dextran, hydroxyethyl starch causes osmotic nephropathy by accumulate within phagolysosomes of proximal tubular cells[5].

1.3.1.3 Drug Combinations

Combination of potential nephrotoxic drugs can increase risk for kidney injury. Medications compete with transport proteins, influx/efflux transporters may modifies the cellular events, thus increases intracellular drug concentration and risk for kidney injury[6].

1.3.1.4 Innate drug nephrotoxicity

A number of medications have higher potential to cause kidney injury on the basis of their more significant chemical structure. Polycationic aminoglycosides deposited within intracellular lysosomes causes phospholipid membrane injury, oxidative stress, and mitochondrial dysfunction that inturn cause apoptosis. Amphotericin B, and the other lipid/liposomal formulations to a lesser degree, cause kidney injury by disrupting tubular cell membranes and increasing permeability to cations, which result in tubular dysfunction due to cell swelling/dysfunction. In general, the antimicrobial agents, colistin and polymyxin B, are highly nephrotoxic with a very narrow therapeutic window. Nephrotoxicity is related to their D-amino content and fatty acid component, which increases cellular membrane permeability and allows cation influx which may leads to tubular cell swelling and lysis with AKI development.

1.3.1.5 Drug-Induced Inflammation

Drug-induced nephrotoxicity is through induction of an inflammatory response by the host, which can target the kidney. Sometimes hapten or other molecules can cause nephrotic inflammation.

1.3.1.6 Drug-Induced Cast Nephropathy

Vancomycin produce noncrystal nanospheric vancomycin

aggregates entangled with uromodulin in patients with AKI. Patients under vancomycin treatment may show high drug concentration in the plasma. Vancomycin casts were reproduced experimentally in mice using in vivo imaging techniques.

1.3.2 PATIENT RELATED FACTOR

Some of the patient related factors include
1.3.2.1 Genetic makeup
1.3.2.2 Comorbid diseases
1.3.2.3 Metabolic disturbances.

Nonmodifiable, risk factors include old age and female sex, which are associated with decreased lean body mass and reduced total body water that can lead to excess drug dosing5. A "normal serum creatinine" in these patients may actually due to their lower GFR. Elderly women with hypoalbuminemia, show more nephrotoxicity due to free drug concentrations. The elderly have an increased propensity to vasoconstriction from excessive circulating angiotensin II, endothelin levels and have higher levels of oxidatively modified biomarkers.

1.3.2.1 Genetic Makeup

Host genetic makeup can increase vulnerability of the kidney to potential nephrotoxins Metabolic pathways, transport proteins, and drug transporters vary between the individuals due to their genetic composition. Polymorphism of genes encoding proteins involved in the metabolism and subsequent elimination of drugs by the kidney as well as the repair pathways after drug injury are correlated with drug sensitivity. Polymorphism in genes encoding ERCC1, a key enzyme in the DNA repair pathway, may be associated with increased nephrotoxicity7. Polymorphism in detoxifing the drugs by phase II metabolising enzymes can lead to kidney damage.

Loss-of-functional mutations in apical secretory transporters that reduce drug efflux from the cell into the urine, and mutations in kinases that regulate drug carrier proteins, can impair drug elimination and promote nephrotoxicity by elevating intracellular drug concentrations.

1.3.2.2 Comorbid Diseases

Underlying AKI and CKD are also important risk factors for increasing vulnerability to nephrotoxicity8. The decline in GFR, increase in tubular secretion of endogenous substances and medications increase risk for adverse drug-related kidney effects. GFR reduction can also result in excessive drug dosing for medications excreted by the kidneys, increased drug exposure in a reduced number of functioning nephrons, ischemia preconditioned tubular cells, and more robust oxidative injury response to various medications by the kidney.

1.3.2.3 Metabolic Disturbances

A number of metabolic abnormalities can also increase risk for adverse kidney effects with certain drugs. Electrolyte disorders such as hypokalemia, hypomagnesemia, and hypocalcemia increase the nephrotoxicity associated with the aminoglycosides3. Severe hypercalcemia leads to afferent arteriolar vasoconstriction, tubular sodium and water wasting, which induces prerenal physiology, which enhances nephrotoxic drug injury.

Alkaline urine (pH>6.0) increases crystal precipitation within tubular lumens from drugs such as indinavir, atazanavir, oral sodium phosphate solution, and ciprofloxacin. Nephrotoxicity is toxicity in the kidneys, an unintended effect of substances, chemicals or medications on renal function. Drugs may affect kidney function in more than one way. Some medications like heparin, aminoglycosides are predominantly excreted by the kidneys and may require dose adjustment in case of decreased renal function.

Drug-induced nephrotoxicity is a common condition and the cause of around 8% to 60% of all acute kidney injury cases in the intensive care unit. Acute kidney injury (AKI) is a sudden loss of kidney function resulting in the accumulation of waste materials such as creatinine and urea in the body. Water and sodium retention, decrease in glomerular filtration rate, hyperkalemia, and metabolic acidosis are the other features of AKI.

There is a rising incidence of kidney disease across the globe. In India, it has been recently estimated that >100,000 new patients enter renal replacement programs annually. Nephrotoxicity was commonly seen in the geriatric population secondary to polypharmacy, drug interactions, bone marrow transplantation, high-dose chemotherapy, total-body irradiation, and other comorbid conditions.

Cytotoxic chemotherapy may also produce nephrotoxic effects like tumor lysis syndrome, paraneoplastic glomerulonephritis, obstructive uropathy, nephrotoxicity with renal failure and electrolyte disturbances. Apart from that, NSAIDs are the most widely used medication in several countries, for treatment of pain and inflammation, especially paracetamol on long term use increases toxic metabolites, leads to acute tubular necrosis and renal failure. Serum urea and creatinine levels indicate acute tubular necrosis. Apart from that, free radicals produced due to drug toxicity, and oxidative damage leads to hepatorenal injuries. Flavonoids, a highly diverse class of secondary metabolites with potential human benefits.

Medicinal plants posses protective activity against nephrotoxicity through their various pharmacological actions. Several studies have shown that the co-administration of different medicinal plants along with various ne\phrotoxic drugs may reduce the incidence of kidney injury.

Therefore, plants like Bombax ceiba having antioxidant activity may be used in the treatment of paracetamol-induced toxicity by free radical scavenging activity8. Based on the above basis, this present study was planned and aimed to evaluate the nephroprotective effect of herbal extract of Bombax ceiba on paracetamol-induced nephrotoxic rats.

1.4 Reported Activities of Bombax ceiba

Bombax ceiba (Bombacaceae), was popularly known in different parts of the world. The plant is known to be useful in different GI Disorders, inflammatory conditions and it is also used in liver disorders, cardiovascular disorders. The Bombax ceiba consists of naphthol, naphthoquinones, polysaccharides, anthocyanins, shamimin, and lupeol in this plant. The plan had shown inhibitory action on bloodvessel growth, hence used as antiangiogenic agent[9].

Antidiabetic, hypoglycemic effect of bark of BC was conducted using diferent even concentrations of solutions and found to show the decrease in blood glucose and lipid levels in a twenty one day study. Hence it can be used in the treatment of diabetes and hyperlipidemia[10].

On extraction of BC with methanol, a novel compound shamimicin was isolated and found to act as hypotensive agent. It had also shown unwanted effect on the cardiovascular, hemopoetic, and hepatic system of the mice [11].

An antimicrobial study of Bombax ceiba was conducted on different microorganisms. Methanolic extract of BC was found to be effective against Bacillus subtilis, Pseudomonas aeruginosa. The tests were performed using disc diffusion

method. BCME was found to decrease the bacterial growth and the ethanolic extract also had shown the same results. The exhibited antimicrobial activity may be because of presence of alkaloids, tannins, glycosides and terpenoids. The aqueous extract was found to have relatively less antimicrobial activity[12].

Cultivation of plants was followed from the ancient history. Bombax ceiba known as silk tree bbelons to the family of Bombacaceae. It has been used in the traditional systems of medicine. All the parts of the plant are having medicinal benefits. This plant has been used by different tribal peoples. The plant literature survey shows that the plant possesses cell shrinking property, increases urination, improves sexual desire and decreases bowel motility. It consists many phytochemical constituents[13].

Bombax ceiba bark was found to possses inhibitory effect on bacteria, have free radical scavenging property. Methanolic extract of BC was found to be effective towards gram negative and gram positive organisms. So, the extract can be known as antibacterial effective against broad spectrum microbes14.

Dried stemen of plant can be used as food in some countries. In this study the leaves and the flowers are selected. Apart from that crude extract was also used in the study. Water, ethanol of different concentrations was used. The study on conducting, showed free redical scavenging activity. The presence of phytochemicals like alkaloids, flavonoids may be the cause. 95% ethanol had shown good results when compared with others[15].

CONCLUSION:

Nephrotoxicity, either acute or chronic can lead to kidney damage. Some times free radicals produces kidney damage. Hence, the plant like Bombax ceiba having various biological activities may be evaluated in furture for its nephroprotectivity.

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