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REVIEW ARTICLE

A Brief Study of Nephrotoxicity and Nephroprotective Agents

Shamna[1], Jasteena Jose[2], Shijikumar[3], Riyaz Ahmed[4]*

ABSTRACT

A kidney is particularly prone to the action of nephrotoxins because it receives 25% of the cardiac output. The presence of the metabolic processes in the renal tubular cells, nephrotoxins can release toxic components and induce damage. Nephrotoxicity can be diagnosed through a simple blood test. Evaluation of nephrotoxicity through blood tests includes the measurements of blood urea nitrogen (BUN), the concentration of serum creatinine, glomerular filtration rate and creatinine clearance. The majority of cases of renal disease remain unnoticed unless they progress to advance stages when conventional therapeutic interventions are usually not sufficient to cure them completely. In this review, the study attempted to identify biomarkers that are more sensitive than the established markers and that are more indicative of pre-renal damage. Research is also focused on identifying biomarkers that can indicate the nature of the mechanisms involved. Nephrotoxicity assays such as measurement of the concentration of serum creatinine or blood urea nitrogen (BUN) do not have the sensitivity and selectivity required to determine nephrotoxicity in an early stage. Recently identified biomarkers described in this review may provide useful information to diagnose nephrotoxicity earlier and more selectively.

Keywords: Blood urea nitrogen, Biomarkers, Creatinin clearance, Nephrotoxicity.

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INTRODUCTION

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin. A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome because there is an increasing number of potent therapeutic drugs like aminoglycoside antibiotics, NSAID's, chemotherapeutic agents have been added to the therapeutic arsenal in recent years. Exposure to chemical reagents like ethylene glycol, carbon tetrachloride, sodium oxalate, and heavy metals such as lead, mercury, cadmium, and arsenic also induces nephrotoxicity.[1]

Several chemicals (both therapeutic and non-therapeutic) have toxic effects on one or more anatomical elements of the kidney. Toxic effects may be acute or chronic, and they may be direct or mediate indirectly through immunological mechanisms. The health impact of nephrotoxic chemicals is related to risk factors, which include the intergrade of the renal functional reserve and factors such as pre-existing renal damage, disease, age, sex, and diet. Irrespective of the mechanism however, the toxicant set into motion a number of physicochemical processes that initiate a series of degenerative changes and alter the morphology and the functions of the kidney. Prompt recognition of the disease and cessation of responsible drugs are usually the only necessary therapy.[2]

[1]Bachelor of Pharmacy, Jamia Salafia Pharmacy College, Pulikkal, Kerala, India.

[2]Department of pharmacy practice, Jamia Salafiya Pharmacy College, Pulikkal, Kerala, India.

[3]Department of pharmaceutical analysis, Jamia Salafiya Pharmacy College, Pulikkal Kerala, India.

[4]Department of pharmacy, Salamath multispecialty hospital, Hail, Saudi Arabia.

Corresponding Author: Riyaz Ahmed, Department of pharmacy, Salamath multispecialty hospital, Hail. Saudi Arabia. E-Mail: riyaz99.a@gmail.com

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In modern medicine angiotensin converting enzyme (ACE) inhibitors and ARBs are mainly used to induce renoprotection; however, these agents are neither the drugs of choice for this purpose nor can be used exclusively to produce renoprotective effects, rather they are mainly effective in nephropathies associated with blood pressure and diabetes etc.[3] Thus, by treating a patient with the above-mentioned drugs, is obligatory to induce a pharmacological

effect that may not be necessarily needed by him. The associated toxicities of these agents also limit their use to a great extent. Although ARBs are comparatively safer than ACE inhibitors, some of the side effects are common to both such as neutropenia, proteinuria, angioneurotic edema, hyperkalemia, especially in patients with a renal impairment which undermine the therapeutic utility of these agents.[4] A drug categorized to be effective specifically as a nephroprotective agent without having liability to produce some serious side effects will be the obvious choice for the patients suffering from renal dysfunction or failure.[5]

The study aimed to provide knowledge and guide to encourage future toxicity studies on the kidney. This article presents information about the toxicity of drugs on kidney functions. Here reviewed some of the researches done on nephrotoxicity and nephro protection in recent years.

REVIEW OF LITERATURE

Azade sari 2019 has done a study on Nephrotoxic effects of drug. The study concluded that Drugs can cause mild to moderate nephrotoxic problems leading to acute or chronic kidney injury. Many drugs, both prescribed or over-the-counter, have the potential to cause kidney damage. Therefore, some basic items such as past medical history, age and weight of the patient, drug-related risk factors, and nephrotoxic drug combinations should be taken into consideration before starting the treatment. If nephrotoxic drug use is mandatory, patients should be followed up closely and frequently with appropriate biomarkers. Basic renal functions should be evaluated before treatment. The early detection of drug-induced nephropathies and the application of appropriate treatment methods are critical because many patients recover when the drug is discontinued.[6]

Cynthia AN, 2008. Conducted review on drug-induced nephrotoxicity and suggested that Drugs are a common source of acute kidney injury. Drug-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of pathogenic mechanisms of renal injury, patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention. Some patient-relatedd risk factors for drug-induced nephrotoxicity are age older than 60 years, underlying renal insufficiency, volume depletion, diabetes, heart failure, and sepsis.[7]

QaziZaid A, *et al*. 2014. Investigated on Appraisal of Nephroprotection and the Scope of Natural Products in Combating Renal Disorders. Although the concept of nephroprotection is relatively new pieces of evidence are accumulating to demonstrate that the drugs described to be useful in various renal disorders because of their nephroprotective and nephrotonic effect as described in Unani or other traditional medicines, have diverse therapeutic uses and can be used to manage many renal diseases and their complications or at least to arrest their progression. The traditional systems of medicines would offer some novel drugs, which may be effective in different pathological conditions of the kidney.The drugs of traditional systems of medicines are frequently used to protect the renal function and to delay the progression of renal diseases to chronic kidney disease (CKD) and end-stage renal disease (ESRD).[8]

Neife AG, *et al*. 2012. Conducted a review study on Cisplatin-induced nephrotoxicity and targets of nephroprotection. Cisplatin is a highly effective antitumor agent whose clinical application is limited by the inherent nephrotoxicity. The current measures of nephroprotection used in patients receiving cisplatin are not satisfactory, and studies have focused on the investigation of new possible protective strategies. Many pathways involved in cisplatin nephrotoxicity have been delineated and proposed as targets for nephroprotection, and many new potentially protective agents have been reported. Finally, the design and development of improved molecules based on the structure of the reported protective compounds will also contribute to obtain cytoprotection with increased safety as well as selectiveness toward specific targets.[9]

Lillie MA, *et al*. 2018. Explained a contemporary review on Nephrotoxicity and Renal Pathophysiology. This review summarizes the current state of the field of nephrotoxicity. It emphasizes integrating our understanding of nephrotoxicity with pathological-induced renal failure. Such approaches are needed to address major questions in the field, which include the diagnosis, prognosis and treatment of both acute and chronic renal failure, and the progression of acute kidney injury to chronic kidney disease.[10]

Joanne YC, *et al*. 2018. Conducted a review on Advances in predictive in vitro models of drug-induced nephrotoxicity. In vitro screens for nephrotoxicity are currently poorly predictive of toxicity in humans. Although the functional proteins that are expressed by nephron tubules and mediate drug susceptibility are well known, current in vitro cellular models poorly replicate both the morphology and the function of kidney tubules and therefore fail to demonstrate injury responses to drugs that would be nephrotoxic in vivo. Advances in our understanding of kidney development, regeneration of human kidney cell types from pluripotent stem cells, and

increasingly complex 3-D platforms for tissue culture have sparked the development of new approaches to address this challenge. The main goal will be to generate cellular models that demonstrate improved functional maturity and consequently improved injury responses and predictivity for known and new nephrotoxicants.[11]

Sun Young K, *et al*. (2012) studied drug-induced Nephrotoxicity and its Biomarkers. Biomarkers have been identified for the assessment of nephrotoxicity. The discovery and development of novel biomarkers that can diagnose kidney damage earlier and more accurately are needed for effective prevention of drug-induced nephrotoxicity. Although some of them fail to confer specificity and sensitivity, several promising candidates of biomarkers were recently proved for the assessment of nephrotoxicity. Early diagnosis of drug-induced nephrotoxicity would be advantageous to reduce the economic costs losses during a safety inspection of new drugs. Therefore, the need for the discovery and development of sensitive and selective biomarkers for nephrotoxicity has been increased. The present review presents recently identified biomarkers for kidney damage, providing useful information on the assessment of nephrotoxicity induced by drugs.[12]

Awdishu L, *et al*. 2017. Reviewed on The 6R's of drug induced nephrotoxicity. Our current knowledge of drug-induced kidney disease is limited due to varying definitions of kidney injury, incomplete assessment of concurrent risk factors, and lack of long term outcome reporting. This review presents a 6R framework to identify and manage drug-induced kidney injury – risk, recognition, response, renal support rehabilitation and research.[13]

Mark AP, *et al*. 2018. Presented a review on Pharmacology behind Common Drug Nephrotoxicities. Medications are widely prescribed and ingested by patients and remain a relatively common cause of kidney injury. Drug nephrotoxicity is a complicated process that involves a combination of factors including the innate nephrotoxicity of drugs, underlying patient characteristics that enhance their risk for kidney injury, and the metabolism and excretion of the potential offending agent by the kidney.[14]

Krishna M, *et al*. 2017. Evaluated Nephroprotective Activity Of Ethanolic Extract Of Allium Cepa Linn. In Gentamicin-Induced Nephrotoxicity In Rats. Kidney diseases are a major problem of worldwide proportions, and renal damage is very common since the kidney has the capacity to excrete toxic substances. This study aimed to evaluate the protective effect of the ethanolic extract of Allium cepa Linn. (EEAC) plant leaves against gentamicin-induced nephrotoxicity in rats. The nephroprotective activity of EEAC treatment was found compared with the standard group (Vitamin E–250 mg/kg) and control group against the toxic control group animals in parameters including serum creatinine, total protein, kidney weights, and body weights. The histopathological studies were also evinced the protective effect of EEAC.[15]

DISCUSSION

Nephrotoxicity can be defined as the adverse effect of substances on renal function. These substances can include molds and fungi, cancer therapeutics such as cisplatin, antibiotics such as aminoglycosides, metals such as mercury, arsenic and lead, and drugs of abuse such as cocaine. One indication of nephrotoxicity is a change in renal function as assessed by the glomerular filtration rate (GFR), BUN, serum creatinine (sCr), or urine output.[16]

Nephrotoxicants can induce kidney damage without changing any established clinical marker of renal function. For example, studies have shown that proximal tubule necrosis in male Sprague Dawley rats exposed to gentamicin can be as high as 75% prior to any increases in BUN or sCr. Time is a key consideration between acute kidney injury (AKI) and CKD, both in terms of the rate of functional decline and the length of time that renal function is decreased. The terms AKI and CKD represent a relatively newer way to refer to the historical terms of acute renal failure (ARF) and chronic renal failure (CRF).[17]

Although the concept of nephroprotection is relatively new but evidences are accumulating to demonstrate that the drugs described to be useful in various renal disorders because of their nephroprotective and nephrotonic effect as described in Unani or other traditional medicines, have diverse therapeutic uses and can be used to manage many renal diseases and their complications or at least to arrest their progression. The traditional systems of medicines would offer some novel drugs, which may be effective in different pathological conditions of the kidney. The drugs of traditional systems of medicines are frequently used to protect the renal function and to delay the progression of renal diseases to CKD and ESRD.[18]

The nephroprotective effect of Ginger was studied and found to be significantly protected the renal cells and reduced the severity of tubular damage caused by gentamicin. It showed tubular regeneration potential in animal models.[19] Another study in which pomegranate seed oil is evaluated for its nephroprotective activity the findings clearly showed improving kidney function by reducing urinary glucose, reducing serum urea and creatinine, decreasing MDA concentration.[20] The co-administration or post administration of garlic juice found to be effective in gentamicin-induced acute kidney failure.[21]

A polyherbal formulation was studied for its protective effect on mice administered with 3 mg/kg of Cisplatin. Among the ingredients of the formulation, Angelica radix was more effective, and it showed strongest protective effect against the toxicity. The effectiveness of Angelica radix was found to be due to its constituent L- malate, which was isolated and tested for nephroprotective activity.[22] The results are reported on the clinical, experimental, and immunological studies on Biskhapra (Boerhaviadiffusa). The observations reveal equivalent diuretic effect of frusemide, Biskhapra(Boerhaviadiffusa) increases serum protein level and decreases urinary protein excretion in patients of nephritic syndrome. Clinically Biskhapra was proved to be useful and safe drug in patients of nephritic syndrome.[23] Simultaneous administration of Gokhroo(Tribulusterresteris) 200 mg/kg/day/orally and gentamicin to female rats decreased the gentamicin induced nephrotoxicity in both structural and functional terms. The effects were comparable to that of Verapamil. Methanolic extract of Icacina tricantha tuber was found to be effective in carbon tetra chloride-induced nephrotoxicity.[24]

An Unani formulation, "BanadequlBuzoor" was tested for nephroprotective activity. The formulation was found to decrease the serum urea and serum creatinine levels significantly.[25] The Effects of Geranin tannin extracted from the herb Geranium humbergii on Puromycin Amino nucleoside nephrosis were studied in rats. The urine protein excretion reduced approximately 35% in animals treated intramuscularly with geranin. increase in serum cholesterol and lipid peroxide produced by puromycin amino nucleoside were also suppressed by geranin, observation by electron microscopy revealed that the degree of abnormality in glomerular epithelial cells was lower in rats treated with geranin after the puromycin amino nucleoside injection than in the rats treated with the puromycin amino nucleoside alone. An Unani formulation, "Jawarish Zarooni Sada" has been reported to possess nephroprotective activity. An Unani drug Kababchini (Pipercubeba) was investigated for the nephroprotective activity in chemically induced nephrotoxicity showed significant nephroprotective effect against gentamicin and cisplatin nephrotoxicity. Another study demonstrated that Khurfa (Portulacaoleracea Linn) possesses significant nephroprotective effect against gentamicin and doxorubicin-induced nephrotoxicity Milk thistle (Silybummarianum) seeds containing several potent antioxidant flavonolignans collectively called silymarin have both hepatic and renal protective effects in rodent models. The main constituents composing silymarin are silibinin, silicristin, isosilibinin, and silidianin. Silibinin and silicristin, aside from their antioxidant effects against damaging free radicals, also stimulate RNA and protein synthesis which is important for renal and hepatic repair mechanisms.[26]

In addition, some flavonolignans protect kidney cells in culture from the renal toxic effects of the drugs paracetamol, cisplatin, and vincristine. Another study in rats demonstrated that silibinin protected renal tubular cells from the oxidative damage from cisplatin. Silibinin also protects against experimental cyclosporine nephrotoxicity. Extracts from the roots and rhizomes of picroliv (Picrorhizakurrooa) offer protection against various hepatic and renal toxins. Picroliv protects the kidney in a renal ischemia-reperfusion induced injury (IRI) model in rats.[27]

CONCLUSION

These reports mentioned above are although of preliminary nature and most of them have been carried out on animals models but showing great potential of Traditional Medicine viz Unani, Ayurveda to deliver some promising agents that can be used to treat the kidney diseases or at least, preserve its function and slow its progression. Therefore, the comprehensive clinical trial of Unani diuretics, tonics and nephroprotective drugs gain importance as one of the means of characterizing and identifying a better group of drugs that can be used as actual nephroprotective agent after scientific validation.

Drug-induced nephrotoxicity is closely associated with acute renal damage as well as with chronic kidney diseases. However, traditional nephrotoxicity assays such as measurement of the concentration of serum creatinine or BUN do not have the sensitivity and selectivity required to determine nephrotoxicity prior to the severe progression of renal damage.Recently identified biomarkers described in this review may provide useful information to diagnose nephrotoxicity earlier and more selectively.

Many drugs both prescribed or over the counter, have the potential to cause kidney damage. Therefore, some basic items such as past medical history, age, and weight of the patient, drug-related risk factors, and nephrotoxic drug combinations should be taken into consideration before starting the treatment. If a nephrotoxic drug use is mandatory, patients should be followed up closely and frequently with appropriate biomarkers. Basic renal functions should be evaluated before treatment. The early detection of drug-induced nephropathies and application of the appropriate treatment methods are critical because many patients recover when the drug is discontinued.

CONFLICT OF INTEREST

We declare that we have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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