



Review Article

ROLE OF AYURVEDA IN THE PREVENTION AND MANAGEMENT OF NEPHROTOXICITY

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ABSTRACT

Nephrotoxicity, the prevalence and incidence of which is increasing day by day, is affecting very badly the quality of life of the sufferers in addition to the impalement of physical, mental, social and economical damages. The fact that the mortality rate of hospitalized patients with acute kidney injury over the last 40–50 years is almost constant and is not improving itself iterates its graveness. Treatment/management of acute kidney injury is primarily supportive, with the goals of preventing further damage and promoting recovery of renal function. It may include discontinuation, dose adjustment or monitoring of the medications prescribed. There are only few drugs like melatonin and lithium which are supposed to be having the potential of mitigation of drug-induced nephrotoxicity. If metabolic derangements from acute kidney injury do not respond to conservative treatment, either dialysis or renal replacement therapy is the only option to ensure the maintenance of homeostasis. But neither hemodialysis nor renal transplantation, which themselves bring about a lot of personal and familial difficulties, is free from side/adverse effects. Ayurveda, the ancient healing science, describes a lot of measures for the prevention and management of diseases in a great detail. Although nephrotoxicity seems to be a new entity, it can be very well prevented and managed with the adoption of Ayurveda in a cost effective and safe way. This article presents the nephroprotective effect of Ayurvedic advocacy and that of Ayurvedic plants evident by experiments in animal model.

INTRODUCTION

Nephrotoxicity may be referred to as the adverse effect of substances on renal function. These substances can include moulds, fungi, cancer therapeutics, antibiotics, metals, drugs of abuse etc. The vulnerability of the kidneys to the development of drug toxicity is attributable to their role in the metabolism and excretion of toxic agents.

Owing to the individual drug mechanisms, wide spectrum of nephrotoxicity results and it is reflected by damage to different nephron segments. Acute or chronic functional changes may occur, since the targets for drug toxicity are both glomerular and tubular injuries.

A change in renal function is capable of being assessed by the Glomerular Filtration Rate (GFR), Blood Urea Nitrogen (BUN), Serum Creatinine (sCr), or urine output. However, kidney damage can be induced by nephrotoxics without changing any established clinical marker of renal function. Studies by Zhou et al.(2008) have shown that proximal tubule necrosis in male Sprague Dawley rats exposed to gentamicin can be as high as 75% prior to any increase in BUN or sCr.

The clear-cut prevalence of nephrotoxicity is lacking because of the same being evaluated in the light of limited knowledge of the epidemiology of nephrotoxicity mainly associated with drug induced acute kidney injury (AKI). The frequency of drug-induced nephrotoxicity has been documented to be approximately 14-26% in adult populations as per the Prospective cohort studies of AKI.^[1-3] 16% of hospitalized AKI events being attributable primarily to a drug in paediatrics is itself ample to delineate its graveness.^[4]

The graveness of nephrotoxicity enhances with the fact that the mortality rate of hospitalized patients suffering from AKI is almost static with little

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improvement during the last 40–50 years. As per the report of a retrospective study assessing the occurrence of AKI from the 1970s to 2002, 50% of patients with AKI (called ARF in the study) died prior to discharge (Mehta *et al.*, 2002). In a review, incorporating summary of several recent studies, Makris and Spanou (2016) has reported the prevalence of AKI in “community” patients to be around 4.3% and it was enhanced to near about 15% in admitted patients and to 60% in patients with critical illness. In this way, nephrotoxicity is a significant public health problem and its prompt addressal is the need of hour.

Risk Factors for Nephrotoxicity

The risk factors for nephrotoxicity can be patient-related or drug-related. Older patients, underlying renal insufficiency (CKD prior to treatment), Diabetes mellitus, volume depletion (decreased hydration), heart failure, sepsis etc. are the major patient-related risk factors.^[5,6]

Certain drugs including aminoglycosides, amphotericin B, cisplatin, contrast dye, and cyclosporine are prime drug-related risk factors, since they are inherently nephrotoxic.^[7,8] On the other hand, drugs related to crystal deposition and chronic interstitial nephritis bring about dose dependant nephrotoxicity or that linked with prolonged duration of treatment.^[9] Frequent drug administration, short infusion, certain drug combinations (e.g. cephalosporins with aminoglycosides, vancomycin with aminoglycosides, and cephalosporins with acyclovir) also contribute to the drug-related risk factors.

Prevention of Kidney Injury

Certain patients and specific clinical situations are more frequently associated with nephrotoxicity. Therefore, patient-related risk factors, drug-related risk factors and defensive measures coupled with vigilance and early intervention must be taken into account for an effective prevention of nephrotoxicity.^[7] Correction of risk factors should be ensured up to the maximum possible level.

Use of alternative non-nephrotoxic drugs up to the maximum possible level, Correction of risk factors in superlative degree, assessment of baseline renal function before initiation of therapy, judicious adjustment of dosage, monitoring of renal function as well as vital signs during therapy and avoidance of nephrotoxic drug combinations are the general preventive measures against nephrotoxicity.

Due attention should be paid to the Minimum Inhibitory Concentration (MIC) while administering antibiotics and it is usually far lower than the levels recommended in medication regimens. Only the patients with severe infections should be introduced with higher concentrations.

Nephrotoxic drugs should be used under strict monitoring of risk benefit ratio and dose should be calculated accordingly. Additionally, appropriate hydration must be ensured.

A systematic approach reflecting via the adoption of an electronic medical record may lead to an automated monitoring of all patients in general and patients at risk of nephrotoxicity in particular.

Management of Nephrotoxicity

Management of acute kidney injury is primarily supportive, with the goals of preventing further damage and promoting recovery of renal function.^[10] It may include discontinuation, dose adjustment or monitoring of the medications (e.g. Cisplatin, Aminoglycosides, Amphotericin, NSAIDs, Antifungals, Antimicrobials, Antivirals, etc.).^[11]

There are only few drugs like melatonin and lithium which are supposed to be having the potential of mitigation of drug-induced nephrotoxicity. Suggestion of melatonin to be used as a pharmacological adjunct along with important nephrotoxic drugs has been made owing to its safe nature and nephroprotective property in clinical trials.^[12] On the other hand, the success of lithium therapy is dependent on individual’s mental health and is not free from the risk of impending end stage renal disease.^[13]

If metabolic derangements from acute kidney injury do not respond to conservative treatment, either dialysis or kidney transplantation under expert hands, is the only option to ensure the betterment of the condition. Anuria, hyperkalemia, poisoning or intoxication, pronounced azotemia, Severe metabolic acidosis, Severe oliguria, uremic complications, Volume overload etc. are the major indications for the initiation of renal replacement therapy.^[10,14-16] But neither hemodialysis nor renal transplantation is free from side/adverse effects. Low blood pressure, access site infection, muscle cramps, itchy skin, and blood clots are some common side effects of hemodialysis, whereas those of Kidney transplantation include infection, bleeding, and damage to the surrounding organs. Additionally, both these procedures themselves bring about a lot of personal and familial difficulties.

Role of Ayurveda

Preservation of the health of healthy persons and emancipation of miseries of the patients is the hallmark of Ayurveda. Although, the prevention of the disease before the appearance of its complexity is the primary focus of Ayurveda, the management of the disease in its progression has also been dealt with in a great detail in the Ayurvedic texts. Taking a lead from this, the prevention and management of nephrotoxicity, which seems to be a new entity, is very much possible.

In Ayurveda, side effects of medicines may be assumed as the poisonous effects of *Gara Viṣha*, which refers to an artificial poison capable of producing symptoms such as generalized oedema, anaemia, enlargement of abdomen etc. if retained in the body for a long time or it may even kill the person by virtue of its potency.^[17]

It is apparent that nephrotoxicity mostly arises due to medications for disorders like diabetes, heart failure, cancer, depression etc. and these are life style disorders as per the general consensus. Most of the sufferers are the usual violators of codes and conducts essential for leading a disease-free/ healthy life in one or another way. In Ayurveda a lot of Do's and Don'ts like *Acharya Rasayana* (sublime behaviour), *Dinacharya* (daily regimen), *Ritucharya* (seasonal regimen), *Pathyaapathya Ahara* (what to eat and what not to eat) have been mentioned in a very lucid way and its adoption is inherently associated with a positive health. Thus, adoption of Ayurveda may lead to a drastic decrease in the burden of health budget against the conditions like nephrotoxicity.

Besides the preventive aspect, Ayurveda has also a potential to contribute in the field of management/ treatment of nephrotoxicity. Owing to the availability of a number of plants with a capacity to ameliorate the nephrotoxicity, Ayurvedic physicians have been successfully using it.^[18]

The elicited nephroprotective potential of Ayurvedic medicinal plants and formulations in animal models at different laboratories/platforms may be exemplified as follows:

1. Water decoction of *Varun (Crataeva nurvala)*, *Bidarikand (Pueraria tuberosa)*, *Lalchandana (Pterocarpus santalinus)*, *Shirish (Albizia lebbek)*, *Punarnava (Boerhaavia diffusa)* and *Chhota Gokshuru (Tribulus terrestris)* had shown significant protection against cisplatin induced Acute Kidney Injury in rats.^[19]
2. Following Ayurvedic medicinal plants have been proved as nephroprotective against cisplatin induced nephrotoxicity in animal models: ^[20]
 - *Amalaki (Embllica Officinalis)*
 - *Manjishtha (Rubia cordifolia)*
 - *Lashuna (Allium sativum)*
 - *Guduchi (Tinospora cordifolia)*
 - *Allium sativum (Azadiracta indica)*
 - *Yashtimadhu (Glycyrrhiza glabra)*
 - *Kutaki (Picrorhiza kurroa)*
 - *Karanj (Pongamia pinnata)*
 - *Gokshur (Tribulus terrestris)*
 - *Plaksha (Ficus religiosa)*
 - *Kakodumbar (Ficus hispida)*
 - *Kanchnar (Bauhinia variegata)*

- *Krushnajeerak (Nigella sativa)*
 - *Kakmachi (Solanum nigrum)*
 - *Aamlavetas (Garcinia pedunculata)*
 - *Sahadevi (Vernonia cinerea)*
 - *Jambu (Syzygium cumini)*
 - *Bala (Sida cordifolia)*
 - *Nilini (Indigofera tinctoria)*
 - *Kapitan (Thespepsia populnea)*
3. Ayurvedic formulations mentioned below have also been proved as nephroprotective against cisplatin induced nephrotoxicity in animal models: ^[20]
 - i. Cystone
 - ii. *Aarogyavardhini vati*
 - iii. *Nisha- Amalaki*
 - iv. *Ashmarihar Kashaya*
 4. *Bilvādi Agada* has shown nephroprotective activity based on biochemical changes viz. serum creatinine, urine creatinine and potassium levels in gentamicin induced nephrotoxicity in male Wistar rats.^[21]
 5. Following plants have also been found to be associated with nephroprotective activity: ^[22]
 - Whistling pine tree (*Casuarina equisetifolia*)
 - Water spinach (*Ipomea aquatica*)
 - Mountain knotgrass (*Aerva lanata*)
 - Red Sorrel (*Hibiscus sabdariffa*)
 - *Varuna (Craaeva nurvala)*
 - *Nirmali (Strychnos potatorum Linn)*
 - Desert Cotton (*Aerva javanica*)
 - *Pipal (Ficus religiosa (L.))*
 - *Sahadevi (Vernonia cinere)*
 6. Fruits/herbs mentioned below have also been found to be enriched with nephroprotective capability:^[22]
 - *Kushmanda (Benincasa hispida)*
 - *Karkotaki (Momordica dioica)*
 - Date palm (*Phoenix dactylifera*)
 - *Kantakari (Solanum xanthocarpum)*
 - *Dugdika (Euphorbia hirta L.)*
 - *Vantulsi (Orthosiphon stamineus Benth.)*
 - *Kondakothimera (Pimpinella tirupatiensis)*
 - *Syamaparni/ green tea (Camellia sinensis).*
 7. The alcoholic (ethanolic) extract of *Bacopa monniera* has shown its nephroprotective potential by significantly regulating renal lipid levels, renal markers, oxidative stress, mRNA expression of nitric oxide synthase (NOS), and morphology of renal tissue, probably due to its hypocholesterolemic and antioxidant properties.^[23]

8. Aqueous extract of *Pimpinella anisum* is capable of mitigating the severity of gentamicin-induced renal damage as per the experiment carried out in Wistar rats.^[24]
9. Elevations in the level of markers viz. serum level of uric acid, urea, blood urea nitrogen and creatinine were significantly ($p < 0.001$) attenuated by aqueous methanolic extract of *Cuscuta reflexa* (AMECR) pre-treatments, indicating drastic reduction in gentamicin-induced nephrotoxicity.^[25]
10. The nephroprotective potential of *Euphorbia paralias* ethyl acetate fraction (*Ep EtOAc*) was established in male rats with thioacetamide-induced kidney injury, where it reversed the nephrotoxicity and restored elevated levels of kidney biomarkers toward normality.^[26]
11. The dose-dependent nephroprotective activity of the *Eurycoma longifolia* extract was witnessed in a rat model of PCM-induced nephrotoxicity, where pre-treatment with the extract dose-dependently prevented kidney injury as evidenced by kidney histopathology and serum and urine biochemical analysis.^[27]
12. NEERI-KFT (a polyherbal formulation) has also shown its effective nephroprotective role against gentamicin induced nephrotoxicity in experimental rat model.^[28]

In this way, the role of Ayurveda in the prevention and management of Nephrotoxicity is obvious and it is the need of time. Hence, Ayurveda must be involved in the Kidney care on a larger scale.

DISCUSSION

The enhancing incidence and prevalence of nephrotoxicity even after the availability of newer and newer drugs with the help of advanced technology iterates its graveness and demands its prompt addressing. Ayurveda, the Ancient Indian healing science describes a lot of affordable and cost effective ways for not only the prevention, but also for its management. But, its potential has not been exploited yet.

Now-a-days, sufficient numbers of trials/experiments in animal models at different platforms by various scientists have been carried out to investigate the nephroprotective action of various Ayurvedic medicinal plants and formulations. It is noteworthy that most of the trials have confirmed the efficacy of these plants in ameliorating the nephrotoxicity.

The nephroprotective action of the Ayurvedic medicinal plants and formulations gets reflected by the changes in renal markers, oxidative stress levels, mRNA expression of NOS (nitric oxide synthase) and morphology of renal tissue. These changes might be attributed to their anti-oxidant activity mainly by

direct radical scavenging action or by inhibition of reactive oxygen species (ROS) producing enzymes (e.g. xanthine oxidase, lipoxygenase etc.). The presence of a high content of phenolics and flavonoids in the plants might have played a pivotal role in bringing out these results.

CONCLUSION

Nephrotoxicity is affecting very badly the quality of life of the sufferers in addition to the physical, mental, social and economical damages. Ayurveda has a great potential of preventing and managing nephrotoxicity, as clarified above. Leaders of every walk of life should disseminate awareness lectures along with distribution of IEC (information, education and communication) material on the line of Do's and Don'ts described in Ayurveda to diminish the burden of this disorder. Taking lead from enough successful animal trials carried out on the nephroprotective activity of Ayurvedic medicinal plants, scientists/authorities must undertake multi-centric black box, cross-sectional and subsequent RCT on human participants for emancipation of miseries imposed by nephrotoxicity.

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