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Special Article - Nephroprotection

Nephroprotection Regimen to Combat the Global Challenge of ESRD (End Stage Renal Disease) and RRT (Renal Replacement Therapy)

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Editorial

Kidney disorders are increasing with fast pace and emerged as major health challenge in recent decades. It has been emphasised in various studies published in reputed journals to take serious preventive measures about alarming situation of prevalence of kidney diseases leading to acute or chronic renal failure, (ESRD) end stage renal disease thereby resulting in kidney transplantation. The epidemiological evidence at present indicates that nephrotoxicity leading to acute and chronic renal failure has a substantial financial burden on the society [1].

Why the Kidney is More Vulnerable for Toxicity?

Being the main organ of excretion for many endogenous metabolites and waste products, and also various exogenous substances like chemicals and drugs that are used to treat different ailments of the body, kidney always remains in contact with substances of aversive nature. This makes the kidney vulnerable to toxicity and injury. Secondly, the effect of occupational or therapeutic exposure to metals on kidney is well established; furthermore, a number of drugs which are frequently used in the management of various diseases cause significant degree of nephrotoxicity even at normal therapeutic dose levels. There are several chemicals which cause such nephropathies, which remain unrecognized for quite some time. These include toxicities caused by cadmium and other heavy metals, anti cancer drugs, cyclosporins, analgesics, antibiotics etc. [2,3] and recently reported nephropathies caused by plant drugs containing aristolochic acid [4]. The specific physiologic characteristics of kidney are localized to specific cell types, which further makes it susceptible to and targets for chemicals. Furthermore, kidney remains under tremendous pressure to maintain the homeostasis of the body in several pathophysiological conditions like edema, obesity, CHF and other diseases that adversely affect the kidney function and produce oxidative changes leading to cellular injury. The nephron, that performs a variety of physiological functions; also bioconverts chemicals and metabolically activates a variety of compounds. Not with standing there is a substantial capacity within the kidney for repair, but there are also several circumstances where damage may be irreversible [5].

An impairment in kidney function leads to decreased glomerular filtration rate (GFR) and subsequently to renal failure, where retention of metabolic by-products occurs as a consequence of deteriorating renal functions, which requires medical intervention. But the major problem with kidney diseases is their progression to chronic stage (CKD) and end stage renal disease (ESRD), which sooner or later warrants renal replacement therapy (RRT). The recent advances in areas of medical science have revolutionized the treatment of renal failure by introducing haemodialysis and renal transplantation. These procedures are inarguably very costly and out of reach of common man. Majority of patients of kidney diseases in poor countries where such facilities are scarcely available die because of uremia [6].

National and International Burden

In India the projected number of deaths due to chronic kidney diseases is on a rise. In 1990 it was 3.78 million and is expected to become 7.63 million in 2020 [7]. The alarming increase in the prevalence of CKD that progresses to end stage renal disease requiring renal replacement therapy, demands huge fund allocation [6,8].

CKD constitutes a major cost burden to healthcare systems worldwide. The high prevalence and the extensive existing evidence that intervention is effective in reducing CVD events demonstrates a need for national initiatives that will slow the progression to end stage renal disease and reduce CVD (Cardio vascular disease) related events in CKD patients. 10% of the population worldwide is affected by chronic kidney disease (CKD), and millions die each year because they do not have access to affordable treatment. Systematically reviewed data from more than 120 countries in order to calculate the world's "RRT gap" or the difference between the number of people receiving RRT (Renal replacement therapy) and the number needing it. These investigators demonstrated that, RRT gap might result in 2.3 to 7.1 million premature deaths [9,10].

This scenario almost ensured that RRT cannot be provided to every patient who is in need of it. This forced the physicians to think of some alternative measures to preserve the renal function as far as possible and slow the renal disease progression with an aim to protect the kidney function and delay the need of RRT to the maximum extent. After the experimental demonstration of ACE inhibitors slowing the progression of loss of renal function in a number of renal diseases, it was thought that a treatment strategy could be devised to preserve the renal function by providing a passive and comprehensive therapy to the kidney disease patients [11,12]. Thus the concept of Nephroprotection was perceived which encouraged the physicians to practice it aiming at early detection and subsequent prevention of progression of kidney disease, mainly through lifestyle adjustment and with the use of new pharmacological agents [13].

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The concept of Nephroprotection thus involves:

1. Preservation of renal function as long as possible.

2. Treating the kidney disease at the onset/primary stage.

3. Slowing the progression of kidney disease.

4. Delaying the need of RRT to maximum possible extent.

A number of mechanisms have been reported to be involved in the causation and progression of renal diseases; the mechanisms depend upon the nature of toxicants, causative factors, course of a specific disease and its associated effect on the other part or function of the body. However, irrespective of the mechanism, the toxicants or causative factors cause numerous bio-chemical changes that initiate a series of degenerative changes leading to the alterations in morphology and the function of the kidney. A nephroprotective agent can be a drug, which improves the kidney function or delays the degenerative changes occurring in the kidney through any of the mechanisms. Some of the related pharmacological actions of a drug like diuretic, ant-inflammatory etc. have also been shown to complement the nephroprotective effect 16. A few drugs have been found in the recent past which possesses significant nephroprotective effect; though their mechanism of action is not fully understood still they qualify the criteria of Nephroprotection due to their overall renal function improving effect [14].

Presently ACE (Angiotensin converting enzyme) inhibitors and ARBs (Angiotensin II receptor blockers) are used for Nephroprotection, as they slow the progression of renal disease [15,16], but these agents are not the drug of choice and cannot be used exclusively for Renoprotection as they are mainly used in nephropathies associated with hypertension and diabetes etc [17]. Therefore, by using these drugs as nephroprotective agents, a pharmacological effect would be induced, which may not be desired by the individual who is being treated. Furthermore, the associated toxicities of these drugs limit their use to a great extent. Though ARBs are comparatively safer than ACE inhibitors, but some of the side effects are common to both such as neutropenia, proteinuria, angioneurotic edema, hyperkalemia, especially in patients with renal impairment. So the discovery and development of low cost and effective nephroprotective agent from the natural source and different traditional system may provide a lead or solution for this problem. In this direction with other traditional system, Unani System of Medicine is also not lagging behind and is offering drugs for numerous kidney diseases. It claims to possess a number of drugs that can be used in treating renal diseases successfully [18]. Some of the drugs mentioned in Unani literature and being practiced by Unani physicians since hundreds of years have been demonstrated to produce some important actions such as diuretic, anti-inflammatory, antioxidant and nephroprotective in various experimental and clinical models [19,20]. These reports are suggestive of great potential of Unani medicines to offer promising nephroprotective drugs.

Nephroprotective Potential of Traditional Medicine

It is being appreciated that CAM (complementary and alternative systems of medicine) can offer some effective drugs from their treatise to be useful in diverse pathological conditions of kidney and thus can be used to protect the renal function and prevent/slow the progression of renal diseases to CKD or ESRD. A number of drugs from herbal sources have been shown to possess promising nephroprotective and related effects in some recent studies and researchers are making it a point to concentrate seriously on the development of nephroprotective agents from traditional sources [19]. Recently, attentions are mostly on protection or prevention as well as accelerating the regeneration of tubular cells against injurious insults to the kidney [20,21]. Medicinal plants which mostly possess a lot of phytochemicals with antioxidant properties have been recently in the focus of researchers and scientists for treatment and prevention of various oxidative stress-related complications. These plants have antioxidant activities due to phytochemicals including phenolic and carotenoid compounds and can reduce the risk of several chronic and degenerative complications [22,23].

Traditional System of Indian Medicine including Ayureveda, Unani etc. are also not wanting in offering drugs for numerous kidney diseases. It claims to possess a number of drugs that can be used successfully in the treatment of renal diseases [19]. Some of the drugs mentioned in Ayurveda and Unani literature and being practiced by physicians, have been demonstrated to produce some important effects such as diuretic, anti-inflammatory, antioxidant & nephroprotective effect against known toxicants. Some important drugs such as Kabab chini *(Piper cubeba)* demonstrated significant protective effect against gentamicin and cisplatin induced nephrotoxicity in experimental model [25,26].

Results are reported on the clinical, experimental and immunological studies on Biskhapra *(**B**oerhavvia diffusa)* the observations reveal equivalent diuretic effect as of frusemide, Biskhapra 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 [27,28]. Simultaneous administration of Gokhroo (*Tribulus terresteris)* 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 [29]. Methanolic extract of *Icacina trichantha* tuber was found to be effective in carbon tetrachloride induced nephrotoxicity. Histopathological examination of the kidney revealed complete protection against carbon tetrachloride induced nephrotoxicity [30]. The hydroalcohol standardized extract of *Echinacea pallida* given to mice in association with the intraperitoneal administration of cisplatin exhibited protective effect [31]. The protective effect of Ashwagandha (*Withania somnifera*) on Cadmium induced toxicity in mice kidney has been reported [32]. A Unani formulation *"Banadequl Buzoor"* was tested for nephroprotective activity, and was found to decrease the serum urea and serum creatinine levels significantly [33]. The increase in serum cholesterol and lipid peroxide produced by puromycin amino nucleoside were 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 [34]. A Unani formulation Jawarish Zarooni sada has been reported to possess nephroprotective activity [35].

These reports mentioned above are although of preliminary

nature but showing great phramcotheraputic potential of CAM or Traditional Medicine viz Unani, Ayurveda to deliver some promising agents that can be used to protective as well as curative in the kidney disorder or at least, preserve its function and slow its progression. Therefore, the study of natural 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.

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