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J. Sci. Trans. Environ. Technov. 2015, 9(2) : 101-106

Scientific Transactions in Environment and Technovation

Formulation and evaluation of *Abutilon indicum* and *Boerhaavia diffusa* forthe determination of nephroprotective activities

https://doi.org/10.56343/STET.116.009.002.007
http://stetjournals.com

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Abstract

In vivo anti nephrotoxic activities of the whole plants of *Abutilon indicum* and *Boerhaavia diffusa,* their formulation and individual extracts were determined in *in vivo* models against nephrotoxicity in rats, induced with gentamicin. A control group (water, group I, n = 6) was compared with rats administrated 40 mg/kg gentamicin, once daily for 21 days (Groups II, III, IV, V and VI). The effect of ethanolic extract of *Abutilon indicum* and *Boerhaavia diffusa* formulation and individual extract (Groups IV,V and IV) at a dose level of 200 mg/kg was compared in gentamicin-induced nephrotoxicity. The activities of urea, uric acid, creatinine, sodium and potassium were significantly increased in rats exposed to gentamicin. Administration of ethanolic extract of formulation prevented severe alterations of biochemical parameters. In conclusion, this study obviously demonstrated that pretreatment with ethanolic extract of formulation significantly attenuated the physiological alterations induced by gentamicin. Also, the present study identifies new areas of research for development of better therapeutic agents for kidney diseases.

Keywords: Formulation of *Abutilon indicum* and *Boerhaavia diffusa*, Gentamicin, Nephrotoxicity

INTRODUCTION

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin (Porter and Bennet, 1981). 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, etc., have been added to the therapeutic arsenal in the recent years (Hoitsma, *et al*., 1991). Exposure to chemical reagents like ethylene, glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic also induces nephrotoxicity. Prompt recognition of the disease and cessation of responsible drugs are usually the only necessary therapy (Paller, 1990). The term renal failure primarily denotes failure of the excretory function of kidney, leading to retention of nitrogenous waste products of metabolism in the blood (Herfindal and Gourley 2000). In addition to this, there is a failure of regulation of fluid and electrolyte balance along with endocrine dysfunction. The renal failure is fundamentally categorized into acute and chronic renal failure (Barry *et al*., 2000).Acute renal failure (ARF) refers to the sudden and usually reversible loss of renal function which develops over a period of days or weeks. There are many causes for acute renal failure which mainly includes acute tubular necrosis that commonly accounts for 85% of incidence. Mostly acute tubular necrosis occurs either due to ischemia or toxins. The toxins may be exogenous or endogenous. The exogenous agents are radio contrast agents, cyclosporine, antibiotics, chemotherapeutic agents, organic solvents, acetaminophen and illegal abortifacients (Herfindal and Gourley 2000; Barry *et al*., 2000).

Chronic renal failure (CRF) is an irreversible deterioration in the renal function which classically develops over a period of years, leading to loss of excretory metabolic and endocrine functions. Various causes of renal failure have been recognized like hypertension, diabetes mellitus, antineoplastic agents like cyclophosphamide, vincristin and cisplatin etc (Herfindal and Gourley 2000).

A number of environmental contaminants, chemicals and drugs including antibiotics dramatically alter the structure and function of various tissues and produce multiple adverse effects in the liver, kidney, heart and intestine (Kohn *et al*., 2005). Aminoglycoside antibiotics are frequently used in the treatment of severe infections of the abdomen and urinary tract (Nagai and Takano, 2004). Gentamicin (GM) is still considered to be an important aminoglycoside antibiotic against life threatening bacterial infections. However, nephrotoxicity and ototoxicity remain major problems due to its long term clinical use (Khan *et al*., 2009). GM is known to cause a number of morphologic, metabolic and functional alterations in the kidney and the specificity of GM nephrotoxicity is apparently related to its accumulation in the renal proximal convoluted tubules leading to tubular necrosis (Pedraza-Chaverri, 2000).Aminoglycoside antibiotics have been widely used for gram-negative bacterial infections. However, their nephrotoxicity and ototoxicity are the major limitations in clinical use. Among several aminoglycoside antibiotics, the grade of nephrotoxicity has been reported to be in the following order as, neomycin > gentamicin >

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tobramycin (Hu *et al*., 1996). Gentamicin nephrotoxicity occurs in about 15-30% of treated subjects, is manifested clinically as non-oliguric renal failure, with a slow rise in serum creatinine and hypoosmolar urinary output developing after several days of treatment (Abdel-zaher *et al*., 2008). The drug enters into the cells by adsorptive/ receptor mediated endocytosis after binding to acidic phospholipids and megalin and is found essentially in lysosomes. Animals treated with low, therapeutically relevant doses of aminoglycosides show both lysosomal phospholipidosis and apoptosis in proximal tubular cells (Suzuki *et al*., 1995).

Though there are many allopathic drugs have been prescribed to treat nephrotoxicity and related kidney problems, their negative side effects cannot be ignored. Awareness in this regard is growing, and the need of searching for alternative user friendly drugs is often emphasized in various forums and the traditional knowledge and the plants as viable alternative source for finding solution for such ailments have been globally accepted and research is gaining momentum for scientific validation of the traditional knowledge and herbals as the alternative source of therapeutics.(reference).The present article deals witht two herbal formulations of *Abutilon indicum* and *Boerhaavia diffusa* with reference to the nephrotoprotective activities in the gentamicin induced nephrotoxicity in male rats.

Figure 1: *Abutilon indicum*

Figure 2: *Boerhaavia diffusa*

MATERIALS AND METHODS

Plant Collection and Identification

Abutilon indicum (Fig 1*)* and *Boerhaavia diffusa* (Fig 2) were collected in and around Mannargudi, Thiruvarur (Dt), Tamil Nadu.

Preparation of plant powder

The plants were air dried under shade for 10-15 days. Then the dried materials were grinded to fine powder using an electric grinder and stored in air tight bottles. The powders were used for further determination of nephroprotective activities.

Extraction of plant material

Ethanolic extracts were prepared according to the methodology of Indian pharmacopoeia (Anonymous, 1996). The coarse powder material was subjected to soxhlet extraction separately and successively with ethanol and distilled water. These extracts were concentrated to dryness in flash evaporator under reduced pressure and controlled temperature (40°C-50°C). The ethanolic and aqueous extracts were put in air tight container and stored in refrigerator.

Anti nephrotoxic activity in animal model

Male albino rats of Wistar strain approximately weighing 150-180g were used in this study. They were healthy animals purchased from the Indian Institute of Science, Bangalore. The animals were housed in spacious polypropylene cages bedded with rice husk. The animal room was well ventilated and maintained under standard experimental conditions (Temperature 27 ± 2° C and 12 hour light/dark cycle) throughout the experimental period. All the animals were fed with standard pellet diet and water was provided *ad libitum*. They were acclimatized to the environment for one week prior to experimental use. The animal feed composition included crude protein (22.3%), crude oil (4.01%), crude fibre (4.02%), Ash (8.02%), calcium (1-2%), phosphorous (0-6%) and sand silical (1.02%).

Experimental design

In this experiment, a total of 24 rats were used. The rats were randomly divided into four groups of six rats in each group.

Group I : Normal animal received standard feed and water

Group II: Animals received oral administration of gentamicin (40 mg/kg body weight) for 21 days (Annie *et al*., 2005)

Group III: Treatment group received gentamicin as group II treated with extract of *Abutilon indicum* at a dose of 200 mg/kg body weight for 21 days.

Group IV: Treatment group received gentamicin as group II treated with furosemide at a dose of 13 mg/kg bodyweight for 21 days (Viviane Gomes Portella *et al*., 2012).

Group V: Treatment group received gentamicin as group II treated with extract of *Abutilon indicum* at a dose of 200 mg/kg body weight for 21 days.

Group VI: Treatment group received gentamicin as group II treated with formulation (equal concentrations of *Abutilon indicum* and *Boerhavia diffusa*) at a dose of 200mg/kg body weight for two weeks.

During the experimental period, food and water consumption were measured every day and the body weight was measured at the initial (day 1) and final day (day 21) of the experiment.

Collection of blood and preparation of serum sample

At the end of the experimental period, the animals were anaesthetized using chloroform vapour prior to dissection. Blood was collected by cardiac puncture into serum separator tubes. The blood was allowed to clot by standing at room temperature for 30 minutes and then refrigerated for another 30 minute. The resultant clear part was centrifuged at 3000 rpm for 10 minutes, and then the serum (supernatant) was isolated and stored in refrigerator until further analysis.

RESULTS AND DISCUSSION

In the recent years, although technology and medicine have developed extensively, some countries have made it obligatory to use natural products for treatment diseases and many different purposes. Many other countries have taken initiative for the exploitation of the traditional knowledge and the plants known to people with health benefits and the idea is extensively used for the treatment of various diseases. Indian system of medicinal practices has traditionally used the locally available herbals for the treatment of various ailmenents. *A. indicum* and *B. diffusa* are the two important herbals with proven medicinal properties. *A. indicum* is reported to haveanalgesic (Kalyani, 1985; Ahmed *et al*., 2000), hepatoprotective (Roshan *et al*., 2004), hypoglycemic activity (Seetharam *et al*., 2000), wound healing activity (Roshan *et al*., 2008), antidiabetic (Adisakwattana *et al*., 2009), and anti diarrheal (Chandrashekhar *et al*., 2004). Different parts of the *B. diffusa* have been widely used for the treatment of dyspepsia,jaundice, enlargement of spleen, abdominal pain, abdominal tumors, and urinary disorders used in the traditional medicine (Kersten *et al*., 1998). Pharmacological studies have demonstrated that *B.diffusa* known to possess diuretic (Kirtikar and Basu, 1956); nephrotic syndrome (Gaitonde and Kulkarn, 1974); anti-inflammatory and anti-nociceptive (Singh and Udupa, 1972); anticonvulsant (Hiruma-Lima *et al*., 2000); immunomodulatory (Kaur and Goel, 2009); hepatoprotective (Mungantiwar *et al*., 2001); antiurolithiatic (Rawat and Mehrotra, 1997); antioxidant and antidiabetic activity (Pareta and Patra, 2011), The whole plant analysis of *B. diffusa* is known to contain numerous phytochemical constituents that include flavonoids, alkaloids, triterpenoids, steroids, lipids, lignins, tannins,phlobaphenes and ursolic acid (Satheesh and Pari, 2004; Jain and Singh, 1994). The present investigation reveals the following findings *In vivo* anti nephrotoxic activity

Nephroprotective activities of *Abutilon indicum* and *Boerhaavia diffusa* formulation and individual extract were as follows

Changes in renal functional markers

The effects of the plants on the selected kidney functions are presented in Table 1. It represents the levels of uric acid, potassium, sodium, urea and creatinine in serum of experimental rats. Group II gentamicin intoxicated rats showed a significant increase in the level of uric acid, potassium, sodium, urea and creatinine when compared to Group I rats. Group III gentamicin intoxicated rats treated with *Abutilon indicum* extract and Group IV gentamicin intoxicated rats treated with furosemide showed significant decrease in the level of uric acid, potassium, sodium, urea and creatinine when compared to group II.

Table 1: Effect of extract of *Abutilon indicum* and *Boerhaavia diffusa* formulation and individual extract on gentamicin induced nephrotoxicity in experimental rats

Parameters	Group I	Group II	Group III	Group IV	Group V	Group VI
Creatinine (mg/dl)	0.95±0.232#	2.65±0.328*	0.955±0.152#	1.38±0.177 #	0.95±0.15#	1.21±0.215 #
Urea (mg/dl)	46.66±13.23#	140.94±17.58*	49.52±12.34#	81.9±9.33 #	40.9±3.98#	65.71±10.69#
UricAcid (mg/dl)	2.23±0.891 #	7.62±1.251 *	2.88±0.71 #	4.226±0.91 #	4.23±1.07#	4.035±0.721#
Potassium (Meq/L)	4.03±0.248 #	9.28±0.12 *	5.09±0.02 #	6.89±0.18 #	5.43±0.15#	5.89±0.17#
Sodium (Meq/L)	151.69±3.48#	175.76±4.32 *	148.60±1.73#	155.54±2.41#	143.3±2.25#	152.46±1.99#

*Significantly different from Group I, III and IV ($p<0.05$); # Significantly different from Group II ($p<0.05$)

Urea is an end product of protein catabolism. It is freely filtered by the glomerulus, passively reabsorbed in both the proximal and distal nephron and excreted in high concentration in urine. The excretion of urea was recognized as an estimate of kidney function. The serum urea level is used as an index of kidney function (Lesley and Lvey, 2005). Drugs that can increase urea levels include allopurinol, some diuretics, gentamicin and indometacin (Mason, 2004). In the present study also observed that the increased level of urea in gentamicin intoxicated rats. Supplementation of formulation restored the increased level of urea in gentamicin-induced rats. This result is in line with the findings of Ali Noorani *et al*. (2011) and Kotnis *et al.* (2004).

Creatinine is an end product of muscle catabolism, which is removed at a constant rate by the kidneys. The concentration of creatinine in serum is the most widely used and commonly accepted measure of renal function in clinical medicine. The clinical utility of the serum creatinine concentration centers on its relation to the glomerular filtration rate (GFR) (Perrone et al., 1992). The serum creatinine concentration is the most commonly used index of the kidney function. The level of creatinine in the blood rises if the kidney does not function properly (Lesley and Levey, 2005). Gentamicins have been reported to increase creatinine measurements (Mason, 2004). In the present study also it was found that the creatinin level was increased in response to gentamycin. Administration of formulation restored the level of creatinine in gentamicine treated rats. This study is consisted with Sara et al. (2009) and Kotnis et al (2004) studies

Uric acid is the end product of purine degradation. It is produced by xanthine oxidase from xanthine which in turn is produced from purine. It is sparingly soluble in water. Degradation of uric acid mainly takes place in liver. Elevated serum uric acid is correlated inversely with renal blood flow/m^2body surface area and directly with renal vascular and total resistance and metabolic syndrome with or without a low globular filteration rate (Suchetha Kumari *et al*., 2011).

Sodium is the most abundant cation in the extracellular fuid and is the major regulating factor for bodily water balance. Extracellular (i.e., intravascular and interstitial) and intracellular sodium contents are closely affected by the body fluid status. The kidneys are the primary organ responsible for the retention and excretion of body sodium and water. Potassium is the primary cation in the intracellular space, with an average intracellular fluid concentration of about 140 mEq/L (140 mmol/L) (Rose, 2001). The major physiological role of potassium is in the regulation of muscle and nerve excitability. It may also play important roles in the control of intracellular volume (similar to the ability of sodium in controlling extracellular volume), protein synthesis, enzymatic reactions and carbohydrate metabolism (Zull, 1989). Acid, bases and salts are collectively called electrolytes. Electrolyte imbalance can lead to serious consequences as it affects the homeostasis of the body. Homeostasis is the process by which the body cells maintain their internal balance in spite of changes in the external environment, commonly measured electrolytes are sodium, potassium, calcium, chloride, bicarbonate, etc., which are good indicators of kidneys function (Cohen and Lemann, 1991). In the present study, gentamicin treated rats showed significantly increased sodium and potassium levels when compared to normal control rats. Administration of formulation restored the normal level of sodium and potassium in gentamicin treated rats. This result coinsides with Ali Noorani *et al*. (2011).

The ethanolic extract at equal concentrations of formulation showed maximum nephroprotective activity compared to furosemide. On the basis of the results obtained in the present study, it is concluded that the formulation has potent nephroprotective activity.

ACKNOWLEDGEMENTS

The authors are grateful to the Management of Sengamala Thayaar Educational Trust Women s College, Sundarakkottai, Mannargudi for the facilities and encouragement and support.

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