SCIENTIA

Peer Reviewed National Science Journal

Volume 14. No.1 ◆ Jan-Dec.2018 ◆ ISSN: 0976-8289

Published by:

MERCY COLLEGE

PALAKKAD 678006, KERALA, INDIA

Scientia ISSN: 0976-8289
Vol. 14, No.1, Jan.-Dec., 2018, pp.11-15

Nephroprotective Potential of *Boerhaavia diffusa* L. in Drug Induced Nephrotoxicity Scenario

Keerthana C.K.
Department of Zoology, University of Madras, Chennai, Tamil Nadu-600025, India.

Abstract

Kidney is considered as a major target organ for exogenous toxicants. Drug induced nephrotoxicity is more common in patients receiving certain medication and undergoing certain specific clinical treatments resulting in deterioration of kidney functions. Some of the common nephrotoxic drugs include aminoglycosides, sulphonamides, NSAIDs, anti-cancer drugs which further leads to acute kidney injury. *Boerhaavia diffusa* L. is used in herbal medicines as well as functional food in many countries such as Vietnam, Philippines, Brazil and India. This medicinal plant contains phytochemical constituents such as flavonoids, alkaloids, steroids, triterpenoids, lipids, lignins, carbohydrates, proteins and glycoproteins. The plant has been used in the treatment of nephrotic syndrome and urinary disorders. Ayurvedic literature indicates that *B. diffusa* improves the function of impaired kidneys and also helps the normal kidneys expel the excess fluid out of the body thereby illustrating its diuretic and possible nephroprotective effects against drug induced nephrotoxicity. Administration of compounds with antioxidant activity used for ameliorating drug induced nephrotoxicity have shown positive results in several experimental models but have either failed to show constant amelioration or proved ineffective when used for a long term. Given these limitations of modern medicine, plant based therapeutics can be considered a better alternative.

Keywords: *Boerhaavia diffusa*, *Punarnava*, Nephroprotective, Nephrotoxic drugs, Acute kidney injury.

Introduction

Kidney performs several important functions such as the maintenance of homeostasis, detoxification, and excretion of toxic metabolites and drugs and thus inescapably exposed to high concentrations of both endogenous and exogenous toxins.[1] One of the underlying causes of nephrotoxocity is the usage of nephrotoxic drugs. Gentamicin, cisplatin, non-steroidal anti-inflammatory drugs, ifosfamide-induced acute renal failure resembles the renal failure resulting from administration of drugs in the clinical set-up leading to complications. Some other nephrotoxic drugs include aminoglycosides, sulphonamides, amphotericin-B, neomycin, polymyxin, chloro-tetracyclines, ibuprofen, acetaminophen, heavy metals (lead, mercury, uranium and arsenic), anti-cancer drugs (cyclosporine, cisplatin and cyclophosphamide), which may lead to acute kidney failure.[2,3] Intrinsic renal damage due to cytotoxins is a common cause of acute kidney injury (AKI). AKI is characterized by the sudden impairment of kidney function resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys. Nephrotoxicity can be diagnosed through blood test and the levels of blood urea nitrogen (BUN), concentration of serum creatinine, glomerular filtration rate and creatinine clearance are used as parameters for evaluating nephrotoxicity.

Drug induced nephrotoxicity mechanism

Drugs can exert direct toxic effects on renal tubules, inducing cellular injury and death in acute tubular necrosis, or induce inflammation in the renal interstitium

* *Corresponding author, E-mail: keerthanack8@gmail.com*

in acute interstitial nephritis (AIN).General mechanisms leading to nephrotoxicity include changes in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Nephrotoxe icity is enhanced by the positive charge of polycationic aminoglycosides, which are attracted to the negatively charged proximal tubular membrane phospholipids. This facilitates drug binding to the megalin/cubilin receptor complex. Medications and endogenously produced substances compete with each other for transport proteins and influx/efflux transporters, which may increase intracellular drug concentration and risk for kidney injury.[4,5,6] These drug-drug interactions increase kidney injury and overall drug toxicity. Accumulation of high concentrations of the polycationic aminoglycosides within intracellular lysosomes causes lysosomal injury, which is associated with phospholipid membrane injury, oxidative stress, and mitochondrial dysfunction. This promotes proximal tubular cell apoptosis and necrosis with clinical manifestations such as an isolated proximal tubulopathy.[7,8] The 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. The polymixin antimicrobial agent induced nephrotoxicity is related to their D-amino content and fatty acid component, which increases cellular membrane permeability and allows cation influx.[9] This effect causes tubular cell swelling and lysis followed by AKI development. The acyclic nucleotide phosphonates (adefovir, cidofovir) enter the cell *via* basolateral human organic anion transporter–1(hOAT1-) and promote cellular injury primarily through disturbing mitochondrial function. Mitochondrial injury is manifested by mitochondrial enlargement, clumped cristae, and convoluted contours that impair cellular energetics. Tenofovir, which is employed widely to treat hepatitis B virus and HIV infection, is associated with proximal tubulopathy and AKI.[10,11] Reduction in VEGF levels or signaling pathways by antiangiogenic drugs promotes loss of the healthy fenestrated endothelial phenotype and promotes microvascular injury and thrombotic microangiopathy, causing proteinuria and AKI. By interfering with local alternative complement pathway regulators, these drugs may also activate complement and increase risk for thrombotic microangiopathy.

Researchers have tested different approaches like atrial natriuretic peptide, low dose dopamine, endothelin antagonists, loop diuretics, prostaglandin analogues, sodium bicarbonate, and α-lipoic acid to manage AKI. However, the current treatment of AKI is still pragmatic.[12,13,14] Though these agents have shown favorable results in several experimental models of ischemic or nephrotoxic AKI, they have either failed to show consistent benefit or proved ineffective when used therapeutically for a long term.[15,16,17] Owing to the limitations of these agents of modern medicine, researchers are exploring the traditional system of medicine for compounds that are already being used by ayurvedic physicians for treating patients having impaired renal function.[18]

B. diffusa in Ayurveda

The science of Ayurveda does not describe the kidney disorders in terms of acute or chronic renal failure. However, it mentions disorders of renal function in terms of various symptoms and signs like dysurea (*Mutrakrucchra*), suppression of urine (*Mutraghata*) and retention of urine (*Mutravrodha*). *B. diffusa* alone or in combination with other herbs has also been used to relieve edema (*shotha*) of several causes. *B. diffusa* is a part of several polyherbal preparations such as *Vidarighrita* and *Bhadravahaghrita* which are used to relieve symptoms presumably occurring due to renal dysfunction.[19] As per the Ayurvedic literature, it is believed to rejuvenate the urinary system. Ayurvedic texts also mention that *B. diffusa* improves the function of impaired kidneys and in edematous conditions, it helps the normal kidneys expel the excess fluid out of the body very effectively.[20] Various experimental

studies have also illustrated its diuretic and possible nephroprotective effects against acetaminophen-induced renal damage. However, the exact mechanism of diuresis and nephroprotective potential has not been understood.

B. *diffusa* : An Overview

Boerhaavia is a highly polymorphic genus of Nyctaginaceae also known as four-o'clock family because most of the species open their flowers four hours after noon i.e. in early evening or morning. It is commonly known as *Punarnava* in Sanskrit, which means 'renews the body'. Nyctaginaceae constitutes 391 species across 32 genera. Most *Boerhavia* species possess worldwide medicinal uses and hence occupied positions in different systems of medicine including Indian Ayurveda, Siddha and Unani, African medicine, traditional Chinese medicines as well as Brazilian traditional medicine. Six important species i.e; *B. diffusa*, *B. repens*, *B. chinensis*, *B. erecta*, *B. elegans* and *B. reniformis* are found in India. *B. diffusa* shared about 131 compounds out of 180 compounds isolated from this genus and for most of these compounds, it is currently an exclusive source. [21] The compounds from *Boerhavia* genus include characteristic chromoalkaloids, quinonolizidine alkaloids, flavonoids, phenolic glycosides, phenolic acids, sterols, organic acids, triterpenoids, lignins and glycoproteins. Besides nephroprotective and diuretic activity, *B.diffusa* also possesses antioxidant, immunomodulatory, anti-cancer, anti-diabetic, hepatoprotective, anti inflammatory, anti- fibrinolytic, antimicrobial, spasmolytic, anti-asthmatic and anticonvulsant activities.

Taxonomic description

Punarnava is a herbaceous perennial with a large root and highly branched stems that are prostrate or ascending to a height of up to a metre. The leaves are simple, ovate-oblong, acute or obtuse at the tip and rounded or subcordate at the base, glabrous above, white with minute scales below. The small rose or white coloured flowers are borne in small umbels arranged in corymbose, axillary and terminal panicles, giving way to a detachable indehiscent seed with a thin pericarp.[20]

Systematic Position

Kingdom:	Plantae
Subkingdom:	Tracheobionta
Division:	Magnoliophyta
Class:	Magnoliopsida
Subclass:	Caryophyllidae
Order:	Caryophyllales
Family:	Nyctaginaceae
Genus:	*Boerhaavia*
Species:	*diffusa*

Fig.1. *Boerhaavia diffusa*
Source: Plant Description bioinfo.bis.res.in

Geographical distribution

Boerhaavia species are widespread and their dispersal is aided by birds and human activity. The distribution of *Boerhaavia* species is in the warmer parts up to an altitude of 2000 m. Besides this, they are found in disturbed areas, waste places, roadsides, dry pinelands, among scrub on tropical reefs. Although native to India and Brazil, *B. diffusa* is found in the tropical, subtropical and temperate regions of the world.[21] This suggests that the worldwide distribution of *B. diffusa* may have helped in establishment of its broader ethnomedicinal

spectrum. In India, *Rakt punarnava* (*B. diffusa*) is known to possess more medicinal importance than *Shweta punarnava* (*B. erecta*). [22]

Nephroprotective Activity

The effect of aqueous ethanolic extract on *E. coli*-induced acute pyelonephritis in rats at a dose 50mg/Kg p.o. administered twice orally showed 42.85% decrease in number of animals showing signs of renal changes. Administration of the extract (50mg/Kg p.o.) twice orally showed 99.09% decrease in bacterial count per mL of urine.[21] The study on antioxidant potential of BD extract in urinary stones by means of inhibition of oxidative trauma and kidney cell damage and showed decrease in calcium oxalate deposition.[18] Studies approving diuretic and kidney stone dissolving properties of BD extracts along with the isolation of a diuretic alkaloid, punarnavine, describe the use of BD in urinary disorders. The studies in mercury chloride toxicity rats demonstrated that 200 mg/kg b.w. aqueous leaf extract of *B. diffusa* was given orally for 5 days effectively protect kidneys from damage.[23] In eupalitin-3-O-β-D-galactopyranoside treated Koi carp (*Cyprinus carpio*) fish, the levels of urea, creatinine and marker enzymes were normal and no pathological changes in renal tissue were observed .[24] Although these studies lack of positive controls, their results suggested the traditional significane of *Boerhavia diffusa* in urinary disorders. A recent study in gentamicin-induced nephrotoxicity rats was carried out in two parts for different parameters. Among five different groups of rats in each part, a positive control group received α-lipoic acid in 0.5% CMC while test groups received 200 mg/kg and 400 mg/kg of aqueous extract of *B. diffusa* orally for 10 days. Assessment of parameters such as blood urea nitrogen (BUN), serum creatinine level, kidney malondialdehyde (MDA), and glutathione (GSH) levels, kidney injury on histopathology. However, their results demonstrated that *B. diffusa* did not show significant improvement in PAH clearance, which was reduced due to gentamicin damage. The results of the study showed that, aqueous extract of *B. diffusa* showed comparable results with positive control. *Boerhaavia diffusa*, at a dose of 100 μg/ml, protected oxidative damage against quinolinic acid (QA), 3-nitropropionic acid (NPA), sodium nitroprusside (SNP), and Fe (II)/EDTA complex induced oxidative stress in rat brain homogenates.[25] *B.diffusa* has shown nephroprotective potential with special relevance to its antioxidant mechanism of recovery from renal damage.[26]

Discussion

Previous experiments have evaluated the nephroprotective effects of *B.diffusa* crude extract against various drug induced nephrotoxicity models and have suggested *B.diffusa* to be an effective plant based therapeutic for amelioration of renal damage. However, the specific mechanisms governing these therapeutic effects and similarities and or differences in their mode of action under both *in vivo* and *in vitro* conditions are yet to be studied in detail. Additionally, isolation and purification of new bioactive compounds with therapeutic properties have to be further explored in order to utilize the medicinal properties of *B.diffusa* to the fullest.

References

1. Ferguson, M. A., V. S. Vaidya & J. V. Bonventre. 2008. Biomarkers of nephrotoxic acute kidney injury. *Toxicology,* 245: 182-193.
2. Shivalinge, G. K. P. 2014. Study of protective effects of stem bark extracts of *Ficus racemosa* in drug induced nephrogenic diabetes insipidus and nephrotoxicity in animal models. Shodhganga (http://hdl.handle.net/10603/14584).s
3. Cuzzocrea, S., E. Mazzon, L. I. DugoSerraino, R. Diaola, D. Britti, A. De Sarro, S.Pierpaoli, A. Caputi, E. Masini& D. Salvemini. 2002. A role for superoxide in gentamicin mediated nephropathy in rats. Eur. J. Pharmacol., 450: 67-76.
4. Perazella MA: Drug use and nephrotoxicity

in the intensive care unit. 2012. Kidney Int 81: 1172–1178.

5. Markowitz GS., Perazela MA: Drug-induced renal failure: A focus on tubulointerstitial disease. 2005. Clin Chim Acta351: 31–47.
6. Perazella MA: Drug-induced renal failure: Update on new medications and unique mechanisms of nephrotoxicity.2003. Am J Med Sci 325: 349–362.
7. Alexander BD., Wingard JR: Study of renal safety in amphotericin B lipid complex-treated patients.2005. Clin Infect Dis 40[Suppl 6]: S414–S421.
8. Markowitz GS., *et* al: Toxic acute tubular necrosis following treatment with zoledronate (Zometa).2003. Kidney Int 64: 281–289.
9. Keir LS., *et* al: VEGF regulates local inhibitory complement proteins in the eye and kidney. 2017.J Clin Invest 127:199–214.
10. Izzedine H: Antiviral drug-induced nephrotoxicity. 2005.Am J Kidney Dis 45: 804–817.
11. Waikar S. S. & J. V. Bonventre, Acute kidney injury. 2011.Harrison's Principles of Internal Medicine. In: Longo DL, Kasper D, Jameson JL, Fauci AS, Hauser SL, Loscalzo J, editors. 18th ed. Vol. 2. New York: McGraw Hill; pp. 2293–308.
12. Karahan, I., A. Atessahin, S. Yilmaz, A. O. Ceribassi& F. Sakin. 2005. Protective effect of lycopene on gentamicin-induced oxidative stress and nephrotoxicity in rats. Toxicology, 215, 192–204.
13. Gogte, V. M. 2000. Ayurvedic Pharmacology and Therapeutic Uses of Medicinal Plants Dravyagunavignyan In: Ramakrishnan S, editor. 1st ed. Mumbai: Bharatiya Vidya Bhavan; 427-9.
14. MacDougall C, Chambers HF. Brunton LL, Chabner BA, Knollmann BC. Goodman and Gilman's The Pharmacological Basis of Therapeutics.2011. 12th ed. China: McGraw Hill. Aminoglycosides; pp. 1505–20.
15. Rajpoot, K., & R. N. Mishra. 2011.*Boerhaaviadiffusa* roots (Punarnavamool) –Review as Rasayan Rejuvenator/ Antiaging. Int. J. Res. Pharm. Biomed. Sci., 60-1451 :2.
16. Gaitonde, B. B., H. Kulkarni & S. D. Nabar. 1974. Diuretic activity of punarnava *Boerhaaviadiffusa.* Bull Haffkine., 5-24 :2
17. Pareta, S. K. 2011. Protective effects of *Boerhaaviadiffusa* against acetaminophen induced nephrotoxicity in rats. Pharmacol., 706-698 :2.
18. Pereira, D. M., J. Faria, L. Gaspar, P. Valentão, P. G. Pinho& P. B. Andrade. 2009. *Boerhaaviadiffusa*: metabolite profiling of a medicinal plant from nyctaginaceae. Food.Chem. Toxicol., 47(8): 2142-9.
19. Shastri A, editor. 2001.14th ed. Vol. 3. Varanasi: Chaukhamba Prakashan; Ayurvedtatvasandipika, Susruta Uttartanga; pp. 428–35.
20. Balakumar P, Rohilla A, Thangathirupathi A. Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it?. 2010. Pharmacol Res;62:179–86.
21. Kapil S. Patil and Sanjivani R. Bhalsing, Ethnomedicinal uses, phytochemistry and pharmacological properties of the genus *Boerhavia Journal of Ethnopharmacology,* http://dx.doi.org/10.1016/j.jep.2016.01.042
22. Spellenberg R.W., 2004. *Boerhavia diffusa*: in: Flora of North America, Editorial Committee. Oxford University Press, pp. 18.
23. Indumathi, T., *et* al., 2011. Journal of Pharmacy Research 4(6), 1848-1850.
24. Fathima, K.A., 2012. Nephroprotective effect of Eupalitin-3-O-β-D-galactopyranoside in Koi carp
25. (*Cyprinus carpio*) Journal of Pharmacy Research 5(5): 2590-2592.
26. Sawardekar, S. B., Patel, T. C., 2015. Evaluation of the effect of *Boerhavia diffusa* on gentamicin
27. induced nephrotoxicity in rats. Journal of Ayurveda and Integrative Medicine. 6(2), 95-103.
28. Swapna Bal Sawardekar., Tejal Chetan Patel., 2015. Evaluation of the effect of *Boerhavia diffusa* on gentamicin-induced nephrotoxicity in rats. J Ayurveda Integr Med. 2015 Apr-Jun; 6(2): 95-103.

Scientia (Annual)

Volume 14. No.1 ◆ Jan-Dec.2018 ◆ ISSN: 0976-8289

ISSN 0976-8289
9 770976 828007