Original Article

CHEMOPROTECTIVE EFFECT OF NONI (*MORINDA CITRIFOLIA* L.) FRUIT JUICE AGAINST CISPLATIN-INDUCED NEPHROTOXICITY

MOHAMMAD ALI[a], MRUTHUNJAYA K.[b], NANDINI C.[a], NABEEL K.[a], MANJULA S. N. [a*]

[a]Department of Pharmacology, [b]Department of Pharmacognosy, JSS College of Pharmacy, JSS University, SS Nagar 570015, Dist Mysuru, State Karnataka, India
Email: snm.manjula@gmail.com

ABSTRACT

Objective: Cisplatin **(**CIS) consumption has become a common problem that affects the health of patients around the globe. Kidney has been suspected to be particularly susceptible to the destructive effects of CIS and nephrotoxic effects are still contentious which in turn affects the Quality of Life (QoL) of patients and increase the mortality rate. This study was conducted to investigate the nephroprotective effect of Noni Juice (NJ) and Divine Noni Gold (DNG) as herbal medicine with established antioxidant properties against the controversial nephrotoxic effect of CIS in mice.

Methods: Mice were divided into four groups, each group contained six mice. Group I was kept as normal, Group II received CIS (5.0 mg/kg b. wt. i. p.) on day one for 14 d. **G**roup III and IV received NJ (0.35 ml/mouse p. o.) and DNG (0.35 ml/mouse p. o.) respectively once daily for 14 d, Group V received CIS (5.0 mg/kg b. wt. i. p.) on day one and NJ (0.35 ml/mouse p. o.) once daily for 14 d. Similarly, Group VI received CIS (5.0 mg/kg b. wt. i. p.) on day one and DNG (0.35 ml/mouse p. o.) once daily for 14 d. On day 15 blood from all the mice was collected from the carotid vein and cardiac puncture routes, and the biochemical markers viz. lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), and urea were assessed. Kidney from all the animals was isolated, and catalase (CAT), glutathione (GSH), superoxide dismutase (SOD), thiols and lipid peroxidase (LPO) were estimated.

Results: CIS-induced marked kidney injury; congestion of tubules, glomerular distortion foci, thickened and blocked blood vessels. Also showed significant elevation of LDH, CPK, and urea with significant inhibition of CAT, GSH, SOD, thiols activities and simultaneously elevation of LPO level. Co-administration of NJ and DNG respectively with CIS protected kidney tissues via oxidative stress inhibition.

Conclusion: NJ and DNG possess protective effect against CIS-induced cellular damage in the kidney by decreasing the level of serum biochemical markers, enhancing the level of enzymatic and non-enzymatic antioxidants and maintaining the LPO level. Results suggest that NJ and DNG have strong nephroprotective effect against CIS-induced nephrotoxicity.

Keywords: Noni**,** *Morinda citrifolia*, Antioxidant, Cisplatin, Toxicity

INTRODUCTION

CIS is an antineoplastic agent, widely used in various human malignancies which include head, neck, lung, ovary, bladder, testis, and cervical areas [1]. Nephrotoxicity, GI-toxicity, myelotoxicity, testicular toxicity, cardiotoxicity, hepatotoxicity, immunotoxicity, peripheral nerve toxicity and genotoxicity are some of the observed adverse effects [2, 3]. A total of 20% patients are receiving a high dose of CIS has severe renal dysfunction where it intercalates double-strand DNA cross-links causing cytotoxic lesions in malignant as well as normal cells [4]. Generally, DNA damaging agents have less toxicity on non-proliferating cells, yet the proximal tubule cells are selectively damaged by CIS because of its accumulation in the kidney to a greater extent compared to other organs [5]. Suggests that this injury is due to inflammation, oxidative stress and apoptosis [6].

Several studies have shown that revelation to CIS interrupts the redox balance of tissues, directly act on cell components, including lipids, proteins, and DNA, suggesting that biochemical and physiological disturbances result from oxidative stress [7, 8]. Various studies have reported that signaling pathways are involved in modulating cell survival or apoptosis in response to DNA damage induced by CIS [9] and these signaling pathways can also be activated by oxidative stress and lipid peroxidation [10, 11]. CIS engenders superoxide anion radical (SAR) and hydroxyl radical (OH⁻) which decline the level of GSH and inhibit the activity of antioxidant enzymes in renal tissue. Reactive Oxygen Species (ROS) may produce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, denaturation of protein and DNA damage [12].

It has been suggested that CIS-induced oxidative stress through the generation of ROS which leads to decrease the level of enzymatic and non-enzymatic antioxidants and thereby induces normal cell damage [13]. In this regard, CIS injury can be ameliorated by free radical scavengers [14, 15], iron chelators [16], SOD [17], CAT [18], GSH [19], LPO [20], selenium and vitamins [21]. Since CIS elevates the LPO level and decreases endogenous antioxidants levels, free radical scavengers and *in vivo* antioxidants can be effective against CIS-induced toxicities.

Noni (*Morinda citrifolia* L. family Rubiaceae) is one of the traditional folk medicinal plant [22]. The plant has been shown to have potent antioxidant activity both *in vitro* and *in vivo* studies [23]. Noni fruit is rich in phenolic compounds like ellagic acid, gallic acid, quercetin, rutin, rosmarinic acid, caffeic and chlorogenic acid which are highly potent antioxidant. EGCg is a polyphenolic flavonoid antioxidant found in abundance in noni fruit having antioxidant properties which inhibit the quinol oxidase (NOX). NOX enzymes are found in various types of cells and tissues where they react with oxygen to generate ROS, the free radical forms of oxygen that damage the DNA of normal cell [24].

Antioxidants maintain free radicals into balance thus lowering the risk of oxidative stress. It is well documented that many herbal antioxidants reduced the toxicity due to oxidative stress, elicited by several medications and prevent the damage to normal cells [25-27]. There is additionally sensible evidence that antioxidants reversed nephrotoxicity caused by oxidative stress due to one or the other reasons. Reported that antioxidants protected the kidney cells from the toxicity elicited by CIS [28-30].

NJ and DNG has been proven potent antioxidants and used as health tonics can protect the kidney cells by CIS toxicity. So in the light of above reports and evidence, the present study aims to evaluate the possible protective effect of NJ and DNG against CIS-induced nephrotoxicity in mice.

MATERIALS AND METHODS

Chemicals and diagnostic kits

Cisplatin hydrochloride injection 50 mg/50 ml vial was procured from JSS Hospital, Mysuru, India. The kits of LDH, CPK and urea, were purchased from Merck Specialities Pvt. Ltd. India. 1,1-3,3-tetramethoxypropane, 5,5-dithiobis-2-nitrobenzoic acid (DTNB), GSH powder, horseradish peroxidase, N-(1-Naphthyl) ethylenediamine dihydrochloride, o-dianisidine hydrochloride, thiobarbituric acid (TBA), malondialdehyde (MDA), trichloroacetic acid (TCA) tris-hydroxy-methylamino methane was purchased from Sigma-Aldrich (USA).

Noni products

The ripe noni fruits and DNG concentrate were procured from Noni Biotech Pvt. Ltd. Tamil Nadu, India. Fresh NJ was prepared from fully ripped noni fruit by hand squeezing method.

Animals

The inbred Swiss albino mice were procured from central animal house facility of JSS Medical College, Mysuru, India, were used for all the experiments. This experimental study was approved by Institutional Animal Ethical Committee (IAEC) of JSS College of Pharmacy, JSS University, Mysuru. Animal care and handling were done according to the CPCSEA guidelines. The animals were fed commercial nutritional pellets and tap water/*ad libitum*.

Experimental design

Mice were divided into six groups each group contained six mice and subjected to various daily treatment regimens:

Group-I: Normal mice. Group-II (CIS): Mice received CIS (5.0 mg/kg b. wt. i. p) [31] on day one. Group-III (NJ): Mice received NJ (0.35 ml/mouse p. o.) once daily for 14 d. Group-IV (DNG): Mice received DNG (0.35 ml/mouse p. o.) once daily for 14 d. The dose of NJ and DNG were calculated according to the following formula; Human adult dose * body surface area ratio convertible factor of mouse =133 ml * 0.0026 = 0.3458 ml [32, 33] Group-V (NJ+CIS): Mice received NJ (0.35 ml/mouse p. o.) once daily for 14 d+CIS (5.0 mg/kg b. wt. i. p.) on day one after 30 min of NJ administration. Group-VI (DNG+CIS): Mice received DNG (0.35 ml/mouse p. o.) once daily for 14 d+CIS (5.0 mg/kg b. wt. i. p.) on day one after 30 min of DNG administration.

Parameters assessed

After 14 d dosing as represented earlier, on day 15 blood was withdrawn from carotid bleeding and cardiac puncture routes for the estimation of serum biochemical markers (LDH, CPK, and urea) were estimated using commercially available kits (Merck Pvt. Ltd.) in semi auto analyzer. After withdrawal blood, animals were sacrificed humanely using ketamine anesthesia. Animals were then cut opened, and transcardial perfusion was performed with a minimum of 100 ml/mouse using phosphate buffer. The kidneys were dissected out, blotted, dried and weighed for the assessment of nephrotoxicity.

Nephrotoxicity

A part of each kidney were cut and fixed in 10% formalin for histopathological studies. The remaining part was used for endogenous enzymatic and non-enzymatic antioxidant estimation. A 10% homogenate was prepared with ice cold phosphate buffer and used for the estimation of GSH [34], CAT [35], SOD [36], total thiol [37] and LPO [38].

RESULTS

Nephroprotective study

A single dose of CIS (5.0 mg/kg b. wt. i. p.) in group-II, caused significant ($p<0.001$) elevation in the level of serum biochemical markers (LDH, CPK, and urea). Co-administration of NJ and DNG (0.35 ml/mouse p. o.) respectively induced significant ($p<0.001$) reduction in the elevation the above biochemical markers in CIS challenged mice (Group-V and VI). Whereas NJ and DNG respectively (Group-III and IV) showed no significant difference compared to normal (Group-I), (fig. 1).
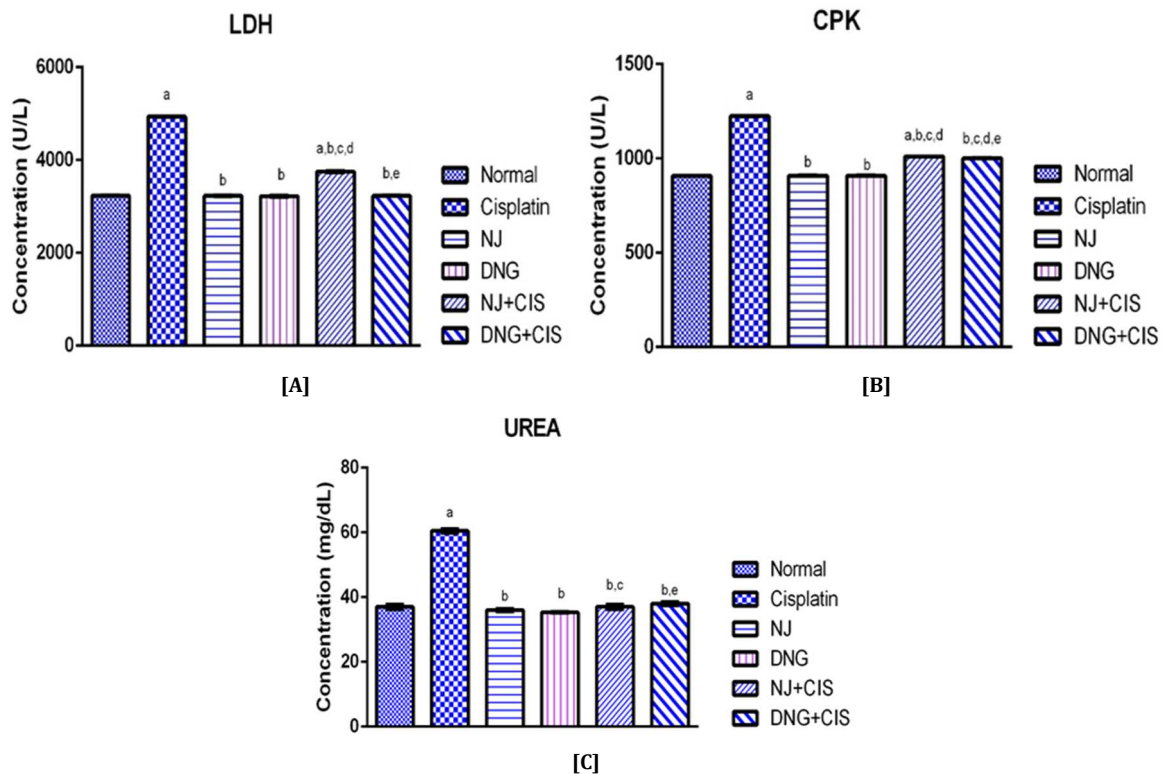

Fig. 1: Effect of NJ and DNG treatment on serum toxicological and diagnostic markers in mice challenged with a single dose of CIS (5.0 mg/kg b. wt.). All the values are mean±SEM of six mice, ***^{a}$p<0.001$ compared to normal, ***^{b}$p<0.001$ compared to CIS, ***^{c}$p<0.001$ compared to NJ, ***^{d}$p<0.001$ compared to DNG, ***^{e}$p<0.001$ compared to NJ+CIS

At the similar dose of CIS also decreased the levels of SOD, CAT, GSH and thiols while LPO level was simultaneously increased.

Co-administration of NJ and DNG respectively at a dose 0.35 ml/mouse significantly (*p*<0.001) decreased elevation in LPO and

maintained SOD, GSH, CAT, and thiols concentrations near to normal in CIS challenged mice (Group-V and VI). In this study, DNG showed a more protective effect when compared to NJ in both serum biochemical markers (fig. 1) and endogenous enzymatic and non-enzymatic antioxidants (fig. 2).

[A]

[B]

[C]

[D]

[E]
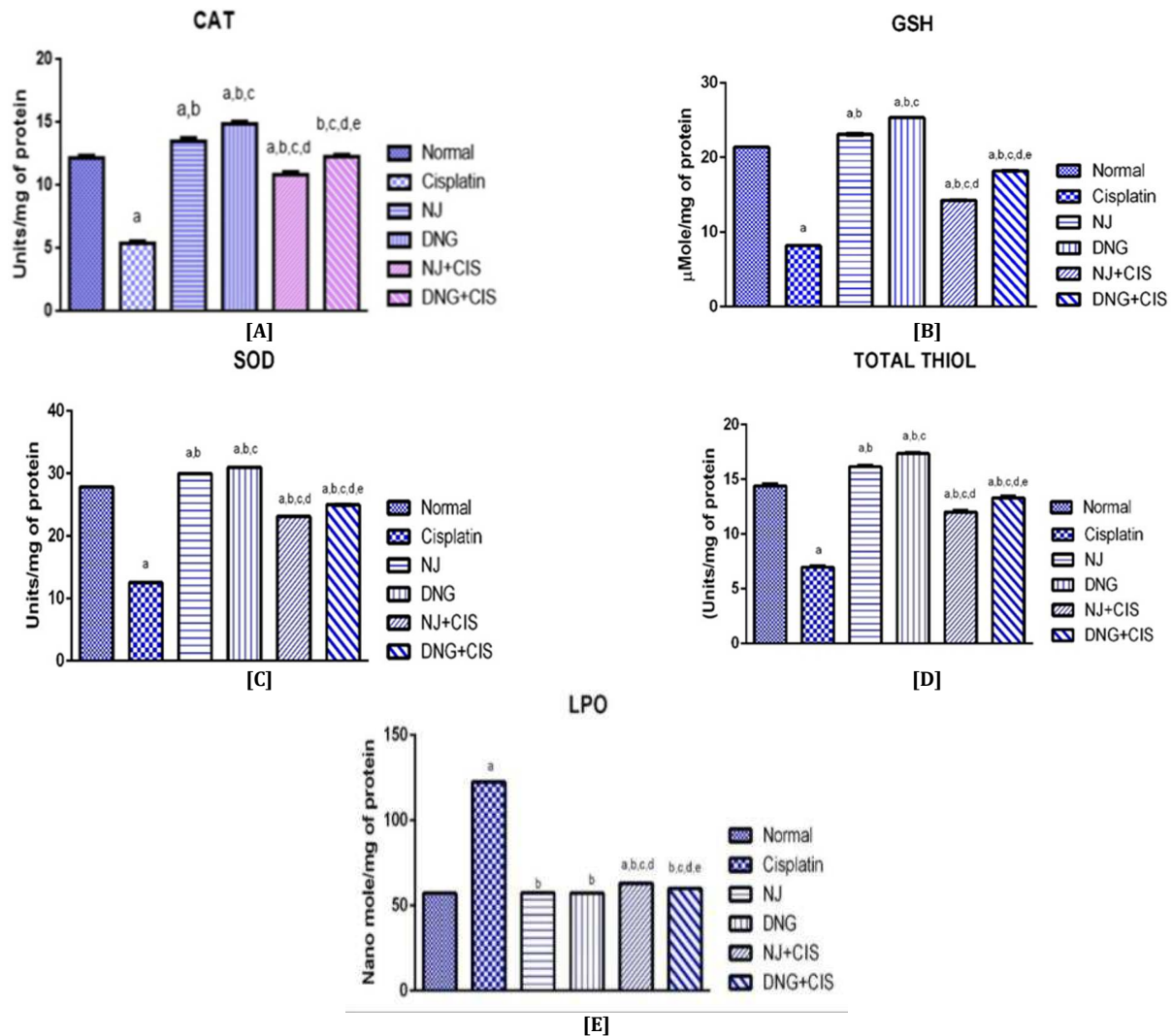
Fig. 2: Status of kidney enzymatic and non-enzymatic antioxidants levels in mice treated with NJ and DNG (0.35 ml/mouse) respectively with CIS (5.0 mg/kg b. wt.). All the values are mean±SEM of six mice, ****a****p*<0.001 compared to normal, ******b****p*<0.001 compared to CIS, ******c****p*<0.001 compared to NJ,******d****p*<0.001 compared to DNG, ******e****p*<0.001 compared to NJ+CIS**

Histopathological study

The normal kidney section (fig. 3; A.) revealed normal histology of glomerulus, distal and proximal convoluted tubules and normal orientation of nephrons. Similar results were obtained in the treatment of NJ and DNG (0.35 ml/mouse p. o.) respectively in normal mice (fig. 3; C, D). Light microscopic observations of CIS at the dose of 5.0 mg/kg b. wt. i. p caused necrosis and thickened blood vessels. The dead and inflammatory cells were increased, also glomerular and tubular congestion was observed (fig. 3: B).

Co-administration of NJ and DNG (0.35 ml/mouse p. o.) respectively induced significant changes, reduced thickened of blood vessels, moderate glomerular and tubular congestion, less necrosis, and inflammatory and dead cells in proximal renal tubules in CIS treated mice was noted as well (fig. 3; E, F).

DISCUSSION

The cytotoxic effect of CIS is believed to result mainly from its interaction with DNA via the formation of covalent adducts between

certain DNA bases and platinum compounds [39]. CIS-induced nephrotoxicity can result in severe renal tubular injury leading to acute renal failure [40]. The CIS concentration in proximal tubular epithelial cells is about 5 times more than serum concentration. The disproportionate accumulation of CIS in kidney tissues contributes to CIS-induced nephrotoxicity manifested by an elevation in serum creatinine, urea and LDH levels [41]. Reported that CIS-induced inflammation, oxidative stress injury and apoptosis which probably clarifies kidney damage [42].

Free radical mediated reactions are responsible for a wide range of chemotherapy-induced side effects, and antioxidants are able to protect non-malignant cells against the destruction by cytostatic agents [43]. The antioxidants can play in protecting against CIS-induced toxicity in mammalian systems [44, 45]. However, little is known about the interaction of antitumor drugs with antioxidants [46]. The results of the estimation of serum biochemical markers and endogenous enzymatic and non-enzymatic antioxidants data clearly revealed that NJ and DNG significantly reduced the nephrotoxic effect induced by CIS which is confirmed by

histopathological study. Natural antioxidants have been broadly used for chemo protection assuming that they detoxify ROS and prevent untoward effects produced by antineoplastic agents and other toxicants [47].

[A]

[B]

[C]

[D]

[E]

[F]
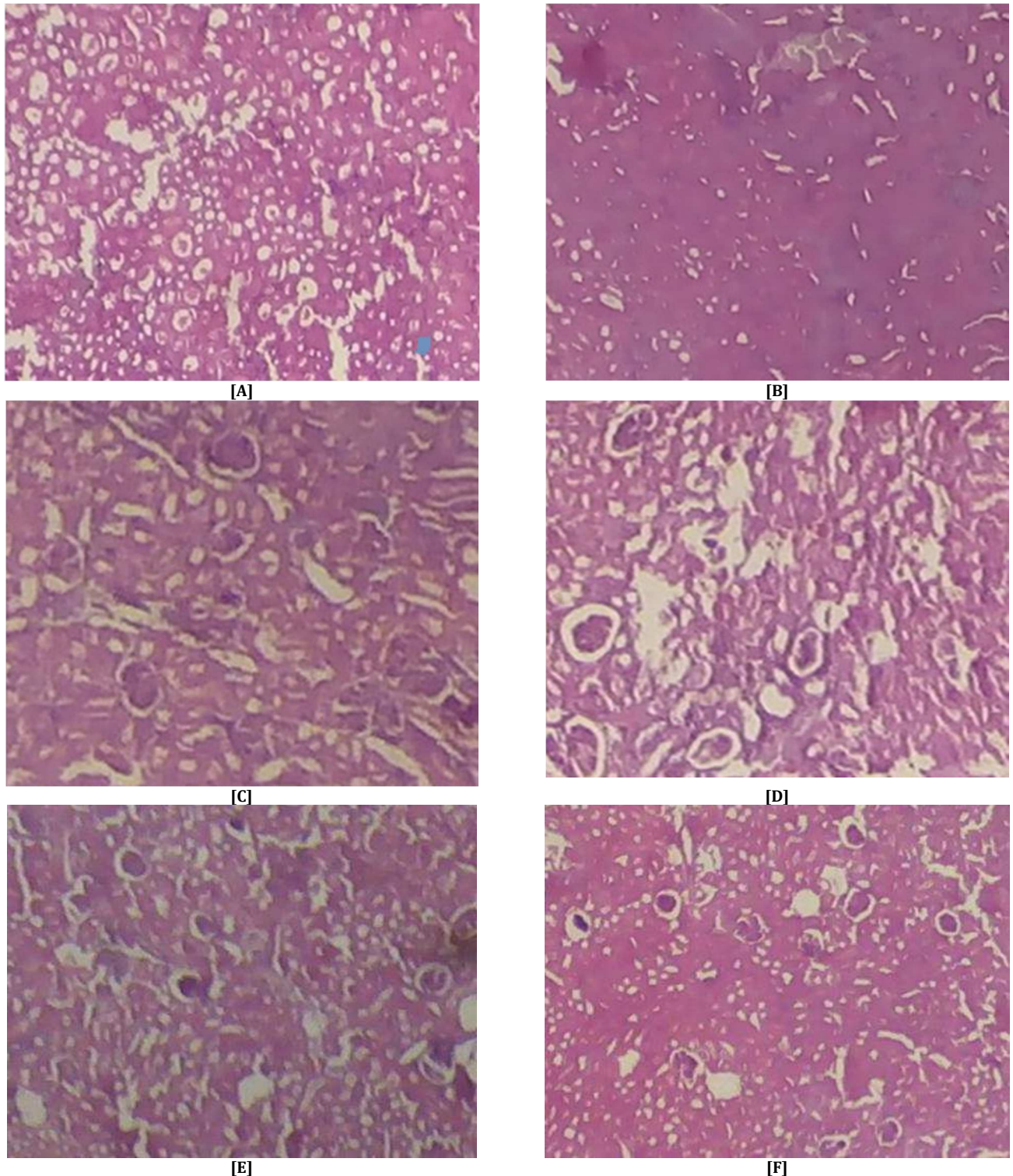
Fig. 3: Histopathological analysis of the kidney [Hematoxylin and Eosin (H and E) stain]. The kidney was mined on day 15 after commencing the treatment. These images are representative of observations made on 6 mice/group. (Scale bar: 5 μm), [A] Normal kidney section is showing the normal renal morphology of predominant tubules, glomerulus, afferent and efferent arterioles, [B] Mice treated with CIS is showing renal tissue with predominant tubular foci, congested tubules, admixed with glomerular distortion foci and thickened and blocked blood vessels, [C] Treated with NJ is showing normal renal tissue with normal, arterioles, tubular and glomerular pattern, [D] Treated with DNG is showing renal tissue with normal tubular and glomerular foci. Fig. [E] NJ with CIS protected kidney tissues and is showing normal glomerular and tubular renal tissues with normal architecture, [F] DNG with CIS protected kidney tissues and is showing predominantly normal renal morphology with normal tubular and glomerular foci

Reported that NJ has a high antioxidant potential along with cytotoxic activity on cancer cells. Consuming 1 to 4 oz (1 oz = 30 ml) of Tahitian Noni Juice (TNJ) daily may reduce the cancer risk in heavy cigarette smokers by blocking carcinogen-DNA binding [48]. Mani and their colleagues reported that NJ treatment significantly increased antioxidant enzymes levels such as CAT, SOD and significantly decreased LPO level in liver and kidney tissues when compared to n-methyl-n-nitrosourea (NMU) induced mammary carcinogenesis in Sprague-Dawley rats. NJ showed a preventive effect against anemia, lymphocytosis, and neutrophilia when compared to NMU control group. Overall they suggest that NJ reduces the adverse effects of NMU carcinogenesis by antioxidant properties [49]. The result of the present study is in accordance with the aforesaid study [48] and [49].

Co-administration of plant extracts with CIS can prevent/minimize the toxicity [50, 51]. Moreover, the decline of SOD, CAT and GSH activities was revealed after CIS (5.0 mg/kg b. wt. i. p.) treatment in the present study, resulting in the abridged ability of the kidney to scavenge toxic H_2O_2, O_2 – and lipid peroxides (Group II). Co-administration of NJ and DNG respectively with CIS were able to maintain SOD, CAT, GSH, thiols and LPO activities in kidney tissues (fig. 2). These results are in agreement with Bae *et al.* [52].

CIS-induced nephrotoxicity was clearly observed through significant elevation of LDH, CPK, and urea levels in CIS treated mice compared with normal which significantly ($p<0.001$) diminished the elevated levels and maintained close to normal when NJ and DNG administered respectively with CIS (fig. 1). This may be attributed to noni components which may stabilize kidney cells and prevent the release of serum biomarkers to the extracellular fluid. Concerning the histopathological changes the kidney damage produced by CIS (5.0 mg/kg b. wt. i. p.) to mice caused the extent of renal tissue with predominant congested tubular foci, admixed with glomerular distortion foci of necrosis and thickened blood vessels (fig. 3; B) which are significantly reduced by co-administration of NJ and DNG respectively with CIS (fig. 3; E and F).

Results obtained in the present *in vivo* study motivated us to initiate the possible protective effect of NJ and DNG against CIS-induced toxicity in experimental animals. Nephroprotective effects of NJ and DNG may be due to the presence of their distinctive phytoconstituents. NJ and DNG are highly rich in phenolic compounds like rutin, quercetin, flavonol glycosides, gallic acid, tannins, sterol, etc. Flavonoids present in noni fruit have been reported to possess both antioxidant and anti-inflammatory activities via free radical scavenging as well as inhibition of oxidases and LPO [53].

In the phytochemical analysis, DNG revealed the presence of more amount of chemical constituents than NJ. DNG is a marketed formulation obtained from noni fruit juice mixed with the extract of garcinia cambogia and glycyrrhiza glabra and mixed with vit. A, B, C, and some minerals that could be one of the reasons for DNG showing more additive and protective effect than fresh NJ. The present study demonstrated that NJ and DNG provided a significant protective effect against CIS-induced nephrotoxicity when administered in combination with CIS and the mechanism of these protective effects of NJ and DNG could be due to their antioxidant, anti-inflammatory and free radical scavenging activities.

CONCLUSION

Oxidative stress plays a major role in CIS-induced nephrotoxicity throughout the conventional clinical regimens of treatment. Antioxidants have evidenced to be effective in ameliorating CIS-induced toxicity in abundant preclinical and few clinical interventions. NJ and DNG have a potent antioxidant activity which is reported in this study i.e. nephroprotective effect. Co-administration of NJ and DNG respectively with CIS provided almost a complete protection in terms of plasma biochemical, endogenous enzymatic and non-enzymatic antioxidants changes, and organs histological changes. The findings of the present study provide an insight and justifies for the use of NJ and DNG as an adjuvant therapy with CIS to attenuate CIS-induced nephrotoxicity.

CONFLICT OF INTERESTS

The authors declare no conflict of interest. The authors themselves are responsible for the content and writing of the paper.

REFERENCES

1. Sanderson BJ, Ferguson LR, Denny WA. Mutagenic and carcinogenic properties of platinum-based anticancer drugs. Mutat Res 1996;355:59-70.
2. Totani T, Aono K, Adachi Y, Komura M, Shiratori O, Sato K. Platinum and other metal coordination compounds in cancer chemotherapy. ed. Nicolini M. Martinus Nijhoff Publishing, Boston; 1988. p. 744-8.
3. Colpi GM, Contalbi GF, Nerva F, Sagone P, Piediferro G. Testicular function following chemo-radiotherapy. Eur J Obstet Gynecol Reprod Biol 2004;113:S2-S6.
4. Atessahin A, Karahan I, Yilmaz S, AO C¸eribasi AO, Princci P. The effect of manganese chloride on gentamicin-induced nephrotoxicity in rats. Pharmacol Res 2003;48:637–42.
5. Sharma SK, Goyal N. Protective effect of heliotropium eichwaldi against cisplatin-induced nephrotoxicity in mice. J Chin Integr Med 2012;10:555–60.
6. Shenberg C, Boazi M, Cohen J, Klein A, Kojler M, Nyska A. An XRF study of trace elements accumulation in kidneys of tumor-bearing mice after treatment with cis-DDP with and without selenite and selenocistamine. Biol Trace Elem Res 1994;40:137–49.
7. Antunes LM, Darin JD, Bianchi Nde L. Effects of the antioxidants *curcumin or selenium* on cisplatin-induced nephrotoxicity and lipid peroxidation in rats. Pharmacol Res 2001;43:145–50.
8. Silva CR, Greggi Antunes LM, Bianchi ML. The antioxidant action of bixin against cisplatin-induced chromosome aberrations and lipid peroxidation in rats. Pharmacol Res 2001;43:561–6.
9. Yamaguchi K, Ishikawa T, Kondo Y, Fujisawa M. Cisplatin regulates Sertoli cell expression of transferrin and interleukins. Mol Cell Endocrinol 2008;283:68–7.
10. Ghosh S, May MJ, Kopp EB. NF-kappa B and rel proteins: evolutionarily conserved mediators of the immune response. Annu Rev Immunol 1998;16:225–60.
11. Widmann C, Gibson S, Jarpe MB, Johnson GL. Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. Physiol Rev 1999;79:143-80.
12. Mora LDO, Antunes LMG, Francescato HDC, Bianchi MDLP. The effects of oral glutamine on cisplatin-induced nephrotoxicity in rats. Pharmacol Res 2003;47:517–22.
13. Kart A, Cigremi Y, Karaman M, Ozen H. Caffeic acid phenyl ester (CAPE) ameliorates cisplatin-induced hepatotoxicity in the rabbit. Exp Toxicol Pathol 2010;62:45–7.
14. Appendroth D, Frob S, Kersten L, Splinter FK, Winnefeld K. Protective effects of Vitamin E and C on cisplatin nephrotoxicity in developing rats. Arch Toxicol 1997;71:677–83.
15. Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and *in vivo* levels. J Pharmacol Exp Ther 2005;314:1052–8.
16. Baliga R, Zhang Z, Baliga M, Ueda N, Shah SV. *In vitro* and *in vivo* evidence suggesting a role for iron in cisplatin-induced nephrotoxicity. Kidney Int 1998;53:394–7.
17. Davis C, Nick H, Agarwal A. Manganese superoxide dismutase attenuates cisplatin-induced renal injury: the importance of superoxide. J Am Soc Nephrol 2001;12:2683–90.
18. Ma SF, Nishikawa M, Hyoudou K, Takahashi R, Ikemura M, Kobayashi Y, *et al.* Cisplatin with cationized catalase decreases

nephrotoxicity while improving antitumor activity. Kidney Int 2007;72:1474–82.

19. Ahmed EM, Mohamed SO, Ahmed MA. *Azadirachta indica* Attenuates cisplatin-induced nephrotoxicity and oxidative stress. BioMed Res Int 2014;1-11. http://dx. doi.org/ 10.1155/2014/647131.

20. Carolina MC, Rita CS, Emerson SL. A simple automated procedure for thiol measurement in human serum samples. J Bras Patol Med Lab 2006;42:345-50.

21. Naziroglu M, Karaoglu A, Aksoy AO. Selenium and high-dose vitamin E administration protect cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. Toxicology 2004;195:221–30.

22. Palu AK, Anne HK, Brett JW, Shixin D, Jarakae J, Leland W. The effects of *Morinda citrifolia* L. (Noni) on the immune system: Its molecular mechanisms of action. J Ethnopharmacol 2008;115:502-6.

23. Gupta RK, Singh N. *Morinda citrifolia* (Noni) alters oxidative stress marker and antioxidant activity in cervical cancer cell lines. Asian Pacific J Cancer Prevention 2013;14:4603-6.

24. EGCg in green tea found to limit the activity of breast cancer cells. Asia Pacific Biotech News 1998;2:562.

25. Ahmed MA, Sajida H Ismail. Protective effect of ginger extracts against cisplatin-induced hepatotoxicity and cardiotoxicity in rats. Iraqi J Pharm Sci 2012;12:27-33.

26. Walaa GH. Effect of hesperidin and rutin on doxorubicin-induced testicular toxicity in male rats. Int J Food Nutr Sci 2012;1:31-42.

27. Raskovic A, Stilinovic N, Kolarovic J, Vasovic V, Vukmirovic S, Mikov M. The protective effects of *Silymarin* against doxorubicin-induced cardiotoxicity and hepatotoxicity in rats. Molecules 2011;16:8601-13.

28. Abdel Moneim AE, Othman MS, Aref AM. *Azadirachta indica* attenuates cisplatin-induced nephrotoxicity and oxidative stress. BioMed Res Int 2014;11. http://dx. doi.org/10. 1155/2014/647131.

29. Haafiza S, Vinoy KS, Renu S, Mohammad A. Chemoprotective effect of turmeric and *spirulina* on cisplatin-induced toxicity in the reproductive system of the male albino rat, *Rattus norvegicus*. Indo-Am J Pharm Res 2013;3:7257-64.

30. Rehman, Muneeb U, Tahir M, Farrah A, Wajhul Q, Lateef A, *et al.* Cyclophosphamide-induced nephrotoxicity, genotoxicity, and damage in kidney genomic DNA of Swiss albino mice: the protective effect of Ellagic acid. Mol Cell Biochem 2012;365:119-27.

31. Seshachary AK, Satyavati D, Subramanian NS, Pradeep HA, Pradeep Kumar C, Deepika GP. Chemoprotective effect of ethanolic extract of *Morinda citrifolia* against cisplatin-induced nephrotoxicity. Pharm Innovation J 2014;3:84-91.

32. Reference. Available from: http://ec.europa.eu/food/ fs/sc/ scf/out151_en.pdf. [Last accessed on 10 Mar 2016].

33. Pandya U, Shah C, Dwivedi RR, Ravishankar B. Pharmacological, and panchbhautik assessment of guru and laghu guna. Daru J Pharm Sci 2016;5:4-9.

34. Moran MA, De PJW, Mannervick B. Levels of glutathione, glutathione reductase, glutathione-S-transferase activities in rat liver. Biochem Biopsy Acta 1997;582:67-1.

35. Aebi H. Catalase *in vitro*. Methods Enzymol 1984;105:121-6.

36. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem 1972;247:3170-5.

37. Miao LH. Measurement of protein thiol and glutathione in plasma. Methods Enzymol 1994;233:380-5.

38. Konings AWT, Driver EB. Radiation effects on membranes. I. Vitamin E deficiency and lipid peroxidation. Radiat Res 1979;80:494-7.

39. Kang KP, Kim DH, Jung YJ, Lee AS, Lee S, Lee SY. Alpha-lipoic acid attenuates cisplatin-induced acute kidney injury in mice by suppressing renal inflammation. Nephrol Dial Transplant 2009;24:3012–20.

40. Nath KA, Norby SM. Reactive oxygen species and acute renal failure. Am J Med 2000;109:665-78.

41. Yao XK, Panichpisal N, Kurtzman K. Nugent, "Cisplatin nephrotoxicity: a review. Am J Med Sci 2007;334:115–24.

42. Weijl NI, Cleton FJ, Osanto S. Free radicals, and antioxidants in chemotherapy-induced toxicity. Cancer Treat Rev 1997;23:209-40.

43. Baldew GS, Van Den Hamer CJA, Los G, Vermeulen NPE, Goeij JJM, McVie JG. Selenium-induced protection against cis-diaminedichloro platinum (II) nephrotoxicity in mice and rats. Cancer Res 1989;49:3020-3.

44. Bogin E, Marom M, Levi Y. Changes in serum, liver, and kidneys of cisplatin-treated rats: effects of antioxidants. Eur J Chem Clin Biochem 1994;32:843-51.

45. Gentile JM, Rahimi S, Zwiesler J, Gentile GJ, Ferguson LR. Effect of selected antimutagens on the genotoxicity of antitumor agents. Mutat Res 1989;402:289-98.

46. Al-Majed AA, Sayed-Ahmed MM, Al-Yahya AA, Aleisa AM, Al-Rejaie SS, Al-Shabanah OA. Propionyl-L-carnitine prevents the progression of cisplatin-induced cardiomyopathy in a carnitine-depleted rat model. Pharmacol Res 2006;53:278–86.

47. Wang MY, Lutfiyya MN, Weidenbacher-Hoper V, Anderson G, Su CX, West BJ. Antioxidant activity of noni juice in heavy smokers. Chem Cent J 2009;3:1-5.

48. Wang MY, Peng L, Lutfiyya MN, Eric H, Vicki WH. Anderson G. *Morinda citrifolia* (noni) reduces cancer risk in current smokers by decreasing aromatic DNA adducts. Nutr Cancer 2009;61:634-9.

49. Mani S, Ram BR, Kuldeep D, Babu LJ, Subramaniyam S, Gopikunte JR. Effects of *Morinda citrifolia* (noni) fruit juice on antioxidant, hematological and biochemical parameters in n-methyl-n-nitrosourea (NMU) induced mammary carcinogenesis in Sprague-Dawley rats. Int J Pharmacol 2014;10:109-19.

50. Xie Y, Sheng W, Miao J, Xiang J, Yang J. Enhanced antitumor activity by combining an adenovirus harboring ING4 with cisplatin for hepatocarcinoma cells. Cancer Gene Ther 2011;18:176–88.

51. Erdem T, Bayindir T, Filiz A, Iraq, Selimoglu E. The effect of resveratrol on the prevention of cisplatin ototoxicity. Arch Oto-Rhino-Laryngol 2012;269:2185–8.

52. Bae EH, Lee JU, Ma SK, Kim IJ, Frøkiær J, Nielsen S. α-Lipoic acid prevents cisplatin induced acute kidney injury in rats. Nephrol Dial Transplant 2009;24:2692–8.

53. Bramorski A, Cherem ADR, Marmentini CP, Torresani J, Mezadri T, Almeida Silva Costa AD. Total polyphenol content and antioxidant activity of commercial noni (*Morinda citrifolia* L.) juice and its components. Brazilian J Pharm Sci 2010;46:652-6.

How to cite this article