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Original Article

Renal Catecholamine Contents in Doxorubicin-Treated Rats Receiving *Morinda Citrifolia* (Noni) Juice

Buranakarl C, Kalandakanond-Thongsong S, Pondeenana S.

ABSTRACT ***Morinda citrifolia* L. or Noni is widely used in many diseases. To determine whether noni juice can modify renal function and catecholamine contents in doxorubicin induced nephrosis, rats were divided into four groups; group 1, control; group 2 noni juice; group 3, doxorubicin (DOX) and group 4, DOX + noni juice. Noni juice was fed in group 2 and 4 daily. Group 3 and 4 were injected with 7.5 mg/kg DOX i.p. at day 15. At day 28, blood chemistries, renal function and renal catecholamine contents were determined. The results showed that rats in group 2 had lower cholesterol and higher plasma albumin concentrations (P<0.05). The renal function and catecholamine contents were unaltered. In group 3 and 4, glomerular filtration rate and packed cell volume decreased while blood urea nitrogen increased significantly (P<0.05). Urinary sodium excretion decreased significantly (P<0.05) whereas protein excretion increased (P<0.05). Renal dopamine and its metabolite, 3, 4-dihydroxyphenylacetic acid (DOPAC), increased significantly (P<0.05) in group 3 and 4 compared with group 1. No change in renal norepinephrine and epinephrine were found. Giving noni juice to group 4 did not modify renal function and renal catecholamine contents compared with group 3. It is concluded that noni juice caused a reduction in plasma cholesterol. Rats receiving DOX had impaired renal function along with compensatory increase in renal dopamine content. Giving noni juice to rats receiving DOX showed no beneficial effect on renal function.**

Key words: **Renal Catecholamine, Doxorubicin, *Morinda Citrifolia* (Noni) juice**

INTRODUCTION

Doxorubicin (DOX) is widely used as an antineoplastic agent in small animal medicine. In animal model, DOX can induce nephrotoxicity and cardiotoxicity. The nephrotoxicity was associated with nephrotic syndrome characterized as proteinuria, hypoalbuminemia, hypercholesterolemia[1,2]. Administration of DOX in rats resulted in hyperlipidemia, proteinuria and increased lipid peroxides, plasma urea and creatinine concentration[3,4]. Moreover, DOX was reported to affect renal sympathetic nerve activity. Enhanced sympathetic activity was proposed in this model due to increased cumulative sodium (Na) balance after DOX injection[5]. The effects were abolished in renal denervated rats. Thus, increased renal sodium retention is dependent on increased efferent renal sympathetic nerve activity in this model. Reduction in renal sympathetic nerve activity after volume expansion or intravenous isotonic saline load was less in DOX-treated animals[6,7]. Therefore, the renal sympathetic nerve activity was expected to be enhanced especially when GFR is reduced immediately. By studying the renal norepinephrine (NE) spillover, resting norepinephrine spillover

Department of Physiology, Faculty of Veterinary Science Chulalongkorn University, Bangkok 10300, Thailand.
Corresponding Author :
Chollada Buranakarl, Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand.

was high in DOX treated animals. Thus, we proposed that renal catecholamine contents (epinephrine (Epi), NE and dopamine (DA)) may be enhanced along with renal Na retention in this model.

The alternative and herbal medicine has been drawn for attention for a last decade although they have been long history of use for many century worldwide. *Morinda citrifolia* L. or Noni plant was used for improving health in many diseases such as cancer, infection, arthritis, diabetes, asthma, hypertension and pain[8]. The benefits of this plant involved various components including the roots, stems, bark, leaves, flowers and fruits. The fruit is being used for health. The anxiolytic effect with alteration of catecholamine levels in brain was demonstrated in rats receiving noni for 15 days[9]. Noni may modulate the autonomic function via decreased central sympathetic outflow. The hypotensive and diuretic activity of noni may be due to many factors including the reduction in Na^+ reabsorption via reduced renal sympathetic or dopaminergic nerve activation. Thus, giving noni in animal receiving DOX may alleviate renal sympathetic activation resulting in less renal catecholamine content and may prevent renal damage.

The objective of this study is to investigate the effect of Noni juice on blood chemistries, renal functions and renal NE contents in normal rats and in rats with doxorubicin-induced nephropathy.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats weighing between 250-300 gm were obtained from National Laboratory Animal Center, Mahidol University, Salaya District, Nakornpathom province. All rats were housed under standard conditions of 12 h of light and dark cycle with free access of water and standard rat laboratory diet containing 24 percent protein by weight. The animals were maintained in the facilities at Faculty of Veterinary Science, Chulalongkorn University for at least 7 days to acclimate to the environmental condition.

Experimental protocol

The experiment was divided into 2 periods, pretreatment (14 days) and post-treatment (14 days) period. The rats were divided into 4 groups (7 rats in each group). Group 1, control; group 2, noni; group 3, DOX and group 4, DOX + noni. On day 14 of experimental period under general anesthesia with diethylether, rats were subjected to intravenous administration of either saline (group 1 and 2) or doxorubicin (DOX) at the dose of 7.5 mg/kg (group 3 and 4). Noni was starting on day 1 of experimental period (14 days before drug administration), while group 1 and 3 received 1 ml-regular drinking water fed orally via feeding tube daily, group 2 and 4 were orally fed with noni juice (99 %) at the dose of 1 ml throughout the experimental period.

A 24 hr urine specimen was collected while they were in metabolic cages, 1 day before experimental period (day 0) and at the end of the experiment (day 28). Urine specimens were stored at -20°C for determination of protein, creatinine and electrolyte concentrations (Na^+, K^+) and osmolarity. On the first day of the experiment following 24 hour urine collection, 0.3 ml blood was collected in heparinized tube by cutting the tip of rat's tail vein for measurement of plasma creatinine concentration. At the end of the experiment (day 28) after removing the rat from metabolic cage, the rat was anesthetized with diethylether. Two ml of blood was drawn from cardiac puncture for measurement of creatinine and electrolyte concentrations, osmolarity, blood urea nitrogen (BUN), albumin, triglyceride and cholesterol. The rats were euthanized by high dose of ether and the abdominal incision was performed. The right kidney was removed for measurement of renal content of catecholamine (NE, E and DA) and its metabolite, 3, 4-dihydroxyphenylacetic acid (DOPAC).

Kidney catecholamine concentrations were determined using high-performance liquid chromatography with electrochemical detector after alumina-batch extraction method[10,11]. In brief, the outer cortex was cut off, and fragments weighing (200 mg) were homogenized in 2 ml of ice-chilled 0.4 M $HClO_4$ containing 1.1 mg/ml reduced glutathione (Merck), 1.7 mg/ml ethylene glycol-bis (β-aminoethyl ether)-N, N, N', N'-tetraacetic acid (EGTA; Sigma), 30 µl of 10 mM $Na_2S_2O_5$ and 120 µl of 3,4-dihydroxybenzyl-amine hydrobromide (DHBA; 0.05 ng ml^{-1}). After centrifugation for 15 min at 5,000 rpm at 4°C, 1 ml of supernatant was added to 25 mg of acid-washed Al_2O_3 (Sigma), and the pH of the sample was adjusted to pH 8.6 by addition of 1 M Tris with 1% Na_2-EDTA. After three washed with distilled water, the

adsorbed catecholamines were eluted from the alumina with 120 μl of 0.2 M $HClO_4$ with 0.1 mM $Na_2S_2O_5$.

An HPLC system with an electrochemical detector with glassy carbon working electrode and amperometric control (Bioanalytical systems, West Lafayette, IN, U.S.A.) was used to measure the concentration of E, NE, DA, DOPAC and DHBA. A Shimadzu Model LC-10 AD pump (Kyoto, Japan) was connected to a Rheodyne (Cotati, CA, U.S.A.) injector equipped with a 20 μl fixed loop, and a 15-cm Phenomenex® column packed with 5-μm particles. The mobile phase solution was composed of 1 mM heptane sulfonate, 100 mM NaH_2PO_4, 1 mM Na_2EDTA, and 5% methanol; adjusted to pH 4.1 with saturated citric acid. Mobile phase was filtered through 0.22-μm filter, degassed by ultrasonic agitation and pumped at a flow-rate of 1 ml min^{-1}. The amperometer was set at a positive potential of 0.700 V with respect to the Ag/AgCl reference electrode, with a sensitivity of 2 nA. The eluate (40 μl) was injected into the HPLC-EC system to separate NE, E, DA, DOPAC and DHBA. Data were collected and analyzed by Delta 5.0 software (Digital Solutions, Margate, QLD, Australia).

The packed cell volume (PCV) was determined by microcentrifugation. The creatinine concentration in the plasma and urine was analyzed by Jaffeés reaction. The blood urea nitrogen was measured by Humalyzer (Human GmbH, Wiesbaden, Germany). Urinary protein was determined using sulfosalicylate. Kidney protein was measured by Lowry et al., (1951)[12]. Sodium and potassium in both plasma and urine were measured by flame photometry (410 C, Ciba Corning Diasnostic Instruments, Halstead, UK). The osmolarity of plasma and urine was determined using osmometer (Osmometer 3D3, Advance Instruments Inc., Norwood, MA, USA). Plasma total protein, albumin, triglyceride and cholesterol were measured by colorimetry.

The glomerular function was calculated using standard clearance of endogenous creatinine clearance. The urinary creatinine was obtained from urine collected in metabolic cage while the plasma creatinine concentration was obtained from blood collected on the next day on day 1 and day 28. The urinary excretion of Na^+ and K^+ was determined by the product of urine volume and concentration of Na^+ and K^+ in the urine. The fractional excretion of Na^+ and K^+ at the end of each experiment was calculated by ratio between clearance of electrolytes and GFR. The urinary excretion was expressed in termed of urinary protein creatinine ratio.

Statistical analysis

Data were expressed as mean ± SEM. Statistics were performed using program Sigma stat. Data between groups were compared with one way ANOVA and Kruskal-Wallis one way ANOVA on Rank. Comparisons between each paired were performed using Student-Newman-Keuls. Difference between data was considered at $P < 0.05$.

RESULTS

Percent increase in body weight was similar in group 1 and 2. Rats in group 3 and group 4 which received DOX showed a significant reduction in body weight compared with both group 1 and 2. The decrease in body weight was started on day 17 until the end of the experiment. The differences were not detected between rats in group 3 and group 4 which received noni with DOX. Noni had no effect on feed intake. After DOX injection in group 3 and 4, feed intake dropped dramatically starting on day 15 (1 day after DOX injection) compared with both group 1 and group 2. In which feed intake was maintained. Noni seemed to decrease feed intake in rats. Water intake was less in group 3 and 4 compared with group 1 and 2 between day 16 to 23. DOX-rats received noni (group 3) had water intake slightly less than DOX-rats without noni.

Effects of noni and DOX on plasma chemistries and packed cell volume

The results of plasma chemistries were shown in Table I. No difference was found in rats feeding with and without noni. For lipid profiles, triglyceride concentrations increased nearly 9 folds in group 3 and 4 in which they received DOX ($P<0.05$). Feeding noni caused no differences in triglyceride level (between group 1 vs 2 and 3 vs 4). Plasma cholesterol in group 2 rats which received noni was significantly lower than control group 1 ($P<0.05$). Injection of DOX caused elevation of cholesterol by 6 folds which was higher significantly from both group 1 and group 2 ($P<0.05$). DOX-rats receiving noni had high cholesterol level similar to rats with DOX injection alone.

Table 1 Effects of noni and DOX on blood chemistries in 4 groups of rats

	Group 1	Group 2	Group 3	Group 4
Triglyceride (mg/dl)	64.71 ± 7.57[a]	62.37 ± 5.04[a]	541.81 ±36.79[b]	518.11 ±43.43[b]
Cholesterol (mg/dl)	81.56 ± 5.09[a]	64.01 ± 1.05[b]	360.56 ±15.53[c]	372.29 ±31.99[c]
Total protein (g/dl)	5.76 ± 0.30	5.26 ± 0.14	5.19 ± 0.07	5.03 ± 0.14
Albumin (g/dl)	3.56 ± 0.12[A]	3.04 ± 0.09[AC]	1.71 ± 0.08[B]	2.43 ± 0.39[C]
P_{Na} (mEq/L)	142.4 ± 1.4	139.9 ± 0.8	141.6 ± 0.9	140.3 ± 0.9
P_{K} (mEq/L)	3.99 ± 0.11[a]	4.17 ± 0.07[a]	4.61 ± 0.22[b]	4.60 ± 0.10[b]
P_{osm} (mOsm/L)	306.3 ± 2.0	304.1 ± 1.9	316.1 ± 2.2	311.3 ± 3.2
PCV (%)	50.43 ± 1.56[A]	50.14 ± 0.88[A]	36.50 ± 0.59[B]	35.86 ± 0.60[B]
BUN (mg/dl)	21.20 ± 1.01[a]	19.90 ± 0.87[a]	49.97 ± 6.23[b]	39.16 ± 3.98[b]
Creatinine (mg/dl)	0.486 ± 0.026	0.443 ± 0.020	0.514 ± 0.026	0.543 ± 0.075

Data are present in X ± SEM; Different superscripts indicate significant differences with P<0.05.
A,B,C compared data in the same row using one way ANOVA; a,b,c compared data in the same row using Kruskal -Wallis one way ANOVA on rank.

Plasma total protein concentrations were not significantly differences among groups. However, the albumin concentrations in rats of group 3 and 4 were significantly lower than control group 1 (P<0.05). Albumin was not difference between group 1 and 2 but it was higher in group 4 compared with group 3 (P<0.05). Plasma Na^+ concentrations were not differences among groups. However, plasma K^+ concentration in rats receiving DOX both with and without noni were significantly higher (P<0.05) than groups 1 and 2 rats which were not injected with DOX. Giving noni had no effect on plasma K^+ concentrations. Plasma osmolarities were not differences among rat groups.

The packed cell volume was decreased significantly in group 3 and group 4 compared with group 1 and 2 (P<0.05). There were no differences in PCV among normal rats and DOX-rats supplemented with and without noni. At 14 days after DOX injection, BUN concentrations were higher significantly (P<0.05) in group 3 and 4 rats which received DOX compared with group 1 and 2 without DOX. There was no difference in BUN level in rats receiving noni (group 2) compared with control group 1 as well as between DOX. DOX-rat receiving noni (group 4) compared with DOX- rats feed water (group 3). Slightly higher plasma creatinine concentrations was also found in group 3 and 4 rats with DOX injection.

Effects of noni and DOX on renal function and urinary excretion of electrolytes and protein

There was no difference in creatinine clearance (CCr) between group on day 0. After 28 days of experiment, CCr in group 3 and group 4 were less than group 1 and 2 rats although not significant (Table II). When compared with day 0, group 1 and 2 had no changes in CCr. However, rats receiving DOX both without and with noni had dramatic reduction in CCr by 47% and 41%, respectively. The osmolar clearance measured on day 28 did not different among groups although a small reduction was found in group 3. The free water clearance in group 3 decreased significantly from other groups. Fractional urinary excretions of Na^+ and K^+ did not differ among groups.

From metabolic cage study, urine flow rates were not significant different among group in all periods of experimental study (Table II).

However, on 28 days of treatment, urine flow rate was decreased dramatically by 45% and 41%, respectively in group 3 and 4 rats which received DOX without and with noni compared with day 0.

The urinary osmolar excretion measured in metabolic cages in group 3 was less than group 1 and 2 significantly (P<0.05). Giving noni in DOX-rats (group 4) slightly increased osmolar clearance although it was still lower than rats without DOX (group 1 and 2). At day

28, the urinary Na excretion in group 3 and 4 was significantly less than group 1 and 2 ($P<0.05$). In contrast to Na excretion, the urinary excretion of K was not different among group. Rats receiving DOX with and without noni had significantly higher protein in the urine compared with group 1 and 2 ($P<0.05$). There were no differences in protein excretion in DOX-rats without and with noni (group 3 vs group 4).

Effects of noni on renal catecholamine contents

The renal catecholamine (NE, Epi and DA) and catecholamine metabolite (DOPAC) were shown in table III. Renal NE concentrations were unaltered between groups of treatment. However, rats injected with DOX with noni showed slightly higher Epi content. The DA increased significantly in group 3 rats and it was still high in group 4. The DOPAC showed significantly higher values in groups 3 and 4 which receiving DOX with and without noni.

DISCUSSION

Rats received DOX lose weight more dramatically compared with control rats in which body weights were maintained. The decreased body weight was correspond to progressive reduction in food intake and water consumption immediately after treating with DOX. The results were similar to our previous report in rats treating with the same dose of DOX[4]. Reduction in weight was due to depressed food intake and may in part due to increased protein lipase in DOX treated rats[13]. Noni had no effect on body weight. Daily weight gain in DOX-rats receiving noni was depressed similar to rats received

Table 2 Effects of noni and DOX on renal functions in 4 groups of rats

	Group 1	Group 2	Group 3	Group 4
C_{Cr} (ul/day/g)	3.072 ± 0.257	3.134 ± 0.343	2.363 ± 0.404	2.627 ± 0.534
C_{osm} (ul/day/g)	0.065 ± 0.007	0.063 ± 0.005	0.045 ± 0.004	0.060 ± 0.008
CH_2O (ul/day/g)	-0.034 ± 0.004^{a}	-0.037 ± 0.006^{a}	-0.026 ± 0.003^{b}	-0.120 ± 0.080^{a}
FE_{Na} (%)	0.289 ± 0.022	0.246 ± 0.039	0.259 ± 0.099	0.146 ± 0.036
FE_K (%)	17.37 ± 1.31	16.26 ± 2.90	26.23 ± 6.21	21.03 ± 2.57
V (ml/day)	18.79 ± 2.95	14.89 ± 2.44	9.87 ± 1.54	10.53 ± 1.09
$U_{osm}V$ (mosm/day)	12.08 ± 1.27^{A}	10.83 ± 0.91^{A}	7.09 ± 0.68^{B}	8.93 ± 1.08^{AB}
$U_{Na}V$ (uEq/day)	776.9 ±109.0^{a}	551.2 ±43.5^{a}	295.6 ±58.5^{b}	202.7 ±28.5^{b}
U_KV (uEq/L)	1257.7 ±108.2	1091.6 ±117.2	1086.9 ±94.7	1074.2 ±105.0
$U_{prot}V$ (mg/day)	25.49 ± 4.28^{a}	23.91 ± 7.83^{a}	491.58 ±38.79^{b}	510.48 ±58.85^{b}

Data are present in X ± SEM; Different superscripts indicate significant differences with P<0.05.
A,B compared data in the same row using one way ANOVA; a,b compared data in the same row using Kruskal -Wallis one way ANOVA on rank.

Table 3 Effects of noni and DOX on catecholamine contents

	Group 1	Group 2	Group 3	Group 4
NE (pmol/mg prot.)	4.962 ± 0.547	5.104 ± 0.457	5.078 ± 0.506	4.501 ± 0.326
Epi (pmol/mg prot.)	0.126 ± 0.059	0.060 ± 0.010	0.096 ± 0.033	0.261 ± 0.182
DA (pmol/mg prot.)	0.198 ± 0.021^{A}	0.260 ± 0.041^{AB}	0.363 ± 0.040^{B}	0.324 ± 0.053^{AB}
DOPAC (pmol/mg prot.)	0.268 ± 0.050^{A}	0.202 ± 0.016^{A}	0.437 ± 0.062^{B}	0.399 ± 0.033^{B}
Data are present in X ± SEM				

Different superscripts indicate significant differences with P<0.05.
A,B compared data in the same row using one way ANOVA

DOX alone. However, water intake in normal (group 2) and DOX-rats feeding noni (group 4) was slightly less than group 1 and group 3 without noni, respectively. However, study in rats receiving noni juice from 0.25 -4 ml/kg once daily for 7-30 days had no effect on body weight, food intake and water intake[9,14] but increased plasma CCK levels[14]).

DOX caused nephrotoxicity characteristic of nephrotic syndrome(1,15,16,2,17,18,13,4). These were characterized by heavy proteinuria, hypoalbuminemia, hypercholesterolemia and increased triglyceride levels. Increased plasma lipids was due to inhibition of carnitine palmitoyltransferase system (CPT1) and lower cytochrome P450 which in turn suppress cholesterol 7 α hydroxylase activity, enzyme in conversion of cholesterol to bile acids[19].

Giving noni in DOX-rats had no preventive effect on plasma lipid profiles. However, giving noni could lower plasma cholesterol in normal rats. Moreover, chemical constituents of noni fruits inhibit copper-induced low-density lipoprotein oxidation which plays an important role in the genesis of atherosclerosis[20]. This may be a beneficial effect of this plant in lowering blood pressure in human[21] and dogs[22-24]. The hypotensive activity was predominantly found using noni root. The fruit juice has been demonstrated to have immunomodulatory polysaccharide-rich substance with antitumor activity. Improved survival time and curative effects occurred when noni was combined with sub-optimal doses of the standard chemotherapeutic agents such as DOX, cisplatin, 5-fluorouracil, mytomycin-C, blemycin, etoposide, camptothecin and vincristine[25].

The plasma albumin in DOX-rats receiving noni was slightly elevated compared with rats receiving DOX alone that may reflect the protective effect on antitumor drug. Although there was a report of hyperkalemia in human consumed noni juice[26], no hyperkalemia was found in normal rats receiving noni[9]. The increased plasma K^+ concentration was found in both groups of rat treating with DOX and the increase was in the same extent whether with and without noni. These increased plasma K^+ may be due to renal K^+ retention. The packed cell volume decreased dramatically in group 3 and 4 which receiving DOX suggesting the effect on erythropoietin production from the impaired kidneys.

DOX caused impaired renal function with insignificant reduction of CCr in group 3 and 4. Impaired renal function could be detected by significantly increased blood urea nitrogen (BUN) and slightly elevated plasma creatinine concentration. Our previous study showed a significant reduction of both glomerular filtration rate (GFR) and renal blood flow (RBF) with significantly increased BUN and plasma creatinine concentrations after DOX injection at the same dose for 16 days[4].

Giving noni in normal rats showed no effects on renal function and solute excretion although root of Morinda citrifolia had diuretic effects[27]. Urine flow rate was unchanged similar to the previous study which received noni up to 4 ml/kg once daily for 7 days[14]. In DOX treated rats, pretreatment with noni caused no beneficial effects on GFR and no changes were found in urine flow rate, protein excretion and blood urea nitrogen compare with group 3 receiving DOX alone. In patients with stage 5 chronic kidney disease, drinking noni was not recommended due to high potassium contents[28]. However, plasma potassium in DOX rats was not further elevated by noni. Noni fruit juice which contained polysaccharide-rich substance (noni-ppt) combined with sub-optimal doses of standard chemotherapeutic agents including DOX improved survival time of inbred syngeneric LLC tumour bearing mice[29]. Noni ppt showed synergistic or additive beneficial effects when combined with DOX for therapeutic potentials against the immunomodulator sensitive sarcoma 180 tumour system[25]. These effects were preferred for tumor treatment. However, dose of DOX induced renal injury may be high and pretreatment of noni showed no preventive effects.

Noni juice had no effects on solute excretion including Na^+ excretion in DOX rats. These data suggested that renal sympathetic activity may be unaltered by the effect of noni. In group 3 and 4 which received DOX, urine flow rate decreased by half. Increased protein excretion was found on 14 days after DOX administration. By determining osmolar excretion in metabolic cages, it decreased significantly in both group 3 and 4. Solute excretions were decreased corresponding to decreased Na^+ excretion but not K^+. These increases in Na^+ reabsorption may be due to the effect of DOX on renal sympathetic nerve activity. Administration of DOX 3.5 mg/kg, iv. in Sprague Dawley rats resulted in less reduction in renal sympathetic nerve activity after vol-

ume expansion[7] or intravenous isotonic saline load[6]. Bilateral renal denervation in DOX treated rats decreased cumulative Na^+ balance[5]. Moreover, the baroreflex renal norepinephrine spillover was shift during development of heart failure due to DOX[30,31]. Therefore, the renal sympathetic nerve activity was expected to be enhanced especially when CCr is reduced immediately due to nephrotoxic agents and certain toxins. However, we found no changes in renal norepinephrine and epinephrine contents from this study.

In rats receiving DOX, no alteration of NE and Epi was found but DA and its metabolite including DOPAC were higher. These data suggest that dopaminergic activity was activated after DOX treatment. Renal DA is mainly synthesized in proximal tubules and independent from innervation, and exerts its effect in an autocrine/paracrine manner through D1 receptor. The activation of D1-like receptors on renal (pre-capillary) vessels causes vasodilation, while the receptors at the tubular cells causes natriuresis by directly inhibition of Na^+-K^+-ATPase and Na^+, H^+-exchanger[32]. The role of kidney DA is to maintain Na+ homeostasis, the DA metabolism was found to be increased in response to increased Na^+ intake[32]. Further, the interaction of DA and angiotensin receptor has been documented, the vasoconstrictor effects of angiotensin II are counteracted by the vasodilator effects of DA. Similarly, these two systems also counteract each other in the paracrine regulation of renal sodium transport[33]. Therefore, in the current study kidney damage following DOX treatment could lead to increase in angiotensin II activity and the increase in DA activity in these two groups (DOX, DOX + noni) was to counteract angiotensin effect.

In conclusion, we found that rats treated with DOX for 14 days had nephrotic syndrome with reduced CCr, loss of urinary protein, hypoalbuminemia and hypercholesterolemia. Although noni juice can reduced plasma triglyceride in normal rats, it cannot modify both renal deterioration caused by DOX and renal catecholamine contents.

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REFERENCES

1. Bertani T, Poggi A, Pozzni R, et al. Adriamycin-induced nephrotic syndrome in rat : sequence of pathology rat. Lab Invest 1982; 46(1):16-23.
2. Milner LS, Wei SH, Houser MT. Amelioration of glomerular injury in doxorubicin hydrochloride nephrosis by methylthiourea. J Lab Clin Med 1991; 118(5):427-34.
3. Montilla P, Tunez I, Munoz MC,et al. Hyperlipidemic nephropathy induced by adriamycin : effect of melatonin administration. Nephron 1997; 76:345-50.
4. Boonsanit D, Kanchanapangka S, Buranakarl C. L-carnitine ameliorates doxorubicin-induced nephritic syndrome in rats. Nephrology 2006; 11:313-20.
5. Herman PJ, Sawin LL, DiBona GF. Role of renal sodium retention of nephrotic syndrome. Am J Physiol 1989; 256(5 pt 2):823-9.
6. DiBona GF, Herman PJ , Sawin LL. Neural control of renal function in edema-forming states. Am. J Physiol 1988; 254 (6 pt 2):R1017-R24.
7. Neahring JC, Jones SY, DiBona GF. Cardiopulmonary baroreflex function in nephrotic rats. J Am Soc Nephrol 1995; 5(12):2082-6.
8. Whistler W. Tongan herbal medicine. Isle Botanica., Honolulu, Hawaii: University of Hawaii Press 1992; 89-90pp.
9. Kalandakanond S, Pandaranandaga J, Komolvanich S, et al. Anxiolytic-like effects of Morinda citrifolia L. (noni) in rats. Thai J Pharmacol 2004; 26(2):105-12.
10. Anton AH. and Sayre DF . A study of the factors affecting the aluminum oxide-trihydroxyindole procedure for the analysis of catecholamines. J Pharmacol Exp Ther 1962; 138:360-74.
11. Vieira-Coelho MA, Hussain T, Kansra V, et al. Aging, high salt intake, and renal dopaminergic activity in Fischer 344 rats. Hypertension 1999; 34:666-72.
12. Lowry OH, Rosebrough NJ, Farr AL, et al. Protein measurement with the folin phenol reagent. J Biol Chem 1951; 193:265-75.
13. Malarkodi KP and Varalakshmi P. Lipid acid as a rescue agent for adriamycin-induced hyperlipidemic nephropathy in rats. Nutr Res 2003; 23:539-48.
14. Pu HF, Huang WJ, Tseng WM, et al. Effects of juice from Morinda citrifolia (Noni) on gastric emptying in male rats. Clin J Physiol 2004; 47(4):169-74.
15. Bertani T, Cutillo F, Broggini M, et al. Tubulo-interstitial lesions mediate renal damage in adriamycin glomerulopathy. Kidney Int 1986; 24:152-59.
16. Hall RL, Wilke WL ,Fettman MJ. The progression of adriamycin induced nephrotic syndrome in rats and effect of captopril. Toxicol. Appl Pharmacol 1986; 82(1):164-74.
17. Okasora T, Takikawa T, Utsunomiya Y, et al. Suppressive effect of superoxide dismutase on adriamycin nephropathy. Nephron 1992; 60:199-203.
18. Grond J , Weening JJ, vanGoor H ,et al. Application of puromycin aminoglycoside and adriamycin to induce chronic renal

failure in the rat. Contr Nephrol 1998; 60:83-93.
19. Hong YM, Kim HS, Yoon H. Serum lipid and fatty acid profiles in adriamycin -treated rats after administration of L-carnitine . Pediatr Res 2002; 51(2):249-55.
20. Kamiya K, Tanaka Y, Endang H, et al. Chemical constituents of Morinda citrofolia fruits inhibit copper-induced low-density lipoprotein oxidation. J Agric Food Chem 2004; 22(19):5843-8.
21. Abbott IA, Shimaza C. The geographic origin of the plants most commonly used for medicine by Hawaiians. J Ethnopharmacol 1985; 14:213-22.
22. Youngken HW. A study of the root of Morinda citrifolia Linn, I. J Am Pharm Assoc 1958; 47:162-5.
23. Youngken HW, Jenkins HJ, Butler CL. Studies on Morinda citrifolia, L. II. J Am Pharm Assoc 1960; 49:271-3.
24. Moorthy NK and Reddy GS. Preliminary phytochemical and pharmacological study of Morinda citrifolia, Linn Antiseptic 1970; 67:167-71.
25. Furusawa E, Hirazumi A, Story S, et al Antitumour potential of a polysaccharide-rich substance from the fruit juice of Morinda citrifolia (Noni) on sarcoma 180 ascites tumour in mice. Phytother Res 2003; 17(10):1158-64.
26. Mueller BA, Scott MK, Sowinski KM, et al. Noni juice (Morinda citrifolia): Hidden potential for hyperkalemia? Am J Kidney Dis 2000; 35(2):310-2.
27. Asahina AY, Ebesu JS.M, Ichinotsubo D, et al. Effect of okadaic acid (OA) and Noni fruit extraction in the synthesis of tumor necrosis factor-(9TNF-() by peripheral blood mononuclear (PBN) cells in vitro. The Proceedings of the International Symposium of Ciguatera and Marine Natural Products. Hawaii 1994; 8-10:197-205pp.
28. Burrows JD and VanHouten G. Use of alternative medicine by patients with stage 5 chronic kidney disease. Adv Chronic Kidney Dis 2005; 12(3):312-25.
29. Hirazumi A, Furusawa E. An immunomodulatory polysaccharide-rich substance from the fruit juice of Morinda citrifolia (noni) with antitumour activity. Phytother Res 1999; 13(5):380-7.
30. McGrath BP, Sano N, Way D. Shift in the baroreflex-renal noradrenaline spillover curve during the development of congestive heart failure in the rabbit. Clin Exp Pharmacol Physiol 1990; 17(4):303-7.
31. Sano N, Way D, McGrath BP. Renal norepinephrine spillover and baroreflex responses in evolving heart failure. Am J Physiol 1990; 258(6 pt 2):1516-22.
32. Odlind C, Fasching A, Liss P, et al. Changing dopaminergic activity through different pathways: consequences for renal sodium excretion, regional blood flow and oxygen tension in the rat. Acta Physiol Scand 2001; 172:219-26.
33. Jose PA, Eisner GM, Felder RA. Dopamine and the kidney: a role in hypertension?. Curr Opin Nephrol Hypertens 2003; 12:189-94.