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Research Article

AN EVALUATION OF DIURETIC ACTIVITY OF *MORINDA CITRIFOLIA* (LINN) (NONI) FRUIT JUICE IN NORMAL RATS

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ABSTRACT

Morinda citrifolia (Noni fruit) juice, a proven antioxidant when evaluated for nephroprotective effects in a murine model was noted to produce a high volume of urine formation. Hence it was evaluated for its diuretic potential in normal rats. The study was conducted in saline primed Wistar albino rats (n=6) using frusemide (10 mg/kg) as the reference diuretic drug with two oral doses, 5mg/kg and 10mg/kg respectively. Urine volume and electrolytes (Sodium, Potassium and Chloride) excretion was estimated at the end of 24 hours and data was analyzed by Kruskall Wallis and Mann Whitney tests. $P < 0.05$ was considered as statistically significant. Noni fruit juice statistically increased the volume of urine (6.82 ±1.18ml/100g/24hr and 7.87±1.15ml/100gm/24hr) in a dose dependent manner increasing the diuretic index to 2.04 and 2.36 for 5ml.kg and 10ml/kg dose ranges respectively. However, there was a statistical significant decrease in sodium ion excretion (70.1±14.3 m.mol/L at 5ml/kg and 41.97±9.3 m.mol/L at 10ml/kg) when compared to the control (107±5.18 m.mol/L). Though there was a similar decrease in potassium excretion it was not statistically significant. These findings indicate that the probable increase in urine formation might be due an aquaretic action of Noni fruit rather than a natruretic effect and further studies with larger doses and longer duration are warranted.

Keywords: Aquaretic activity, Diuretic, Noni fruit juice, *Morinda citrifolia*

INTRODUCTION

Herbal and natural products of folk medicine have been used for centuries in every culture throughout the world. Scientists and medical professionals have shown increased interest in this field as they recognize the true health benefits of these remedies. "Let food be your medicine and let medicine be your food" was advised by the father of medicine, Hippocrates, over two millennia ago. Among the medicinal plants discovered by the ancestors of Polynesians, *Morinda citrifolia* L (Noni) is one of the traditional folk medicinal plants that have been used for over 2000 years in Polynesia[1]. Noni is a native plant from Southeast Asia to Australia and is cultivated in Polynesia, India, the Caribbean, Central and northern South America[2,3]. It has been reported to have a broad range of therapeutic and nutritional value[4].

Morinda citrifolia Linn (Rubiaceae), also known as Noni or Indian mulberry, Ba Ji Tian, Nono or Nonu, Cheese Fruit, and Nhau in various cultures throughout the world, is a small evergreen tree. It is identifiable by its straight trunk, large, bright green and elliptical leaves, white tubular flowers, and its distinctive, ovoid, "grenade-like" yellow fruit. The fruit can grow in size up to 12 cm or more and has a lumpy surface covered by polygonal-shaped sections. The seeds, which are triangular shaped and reddish brown, have an air sac attached at one end, which makes the seeds buoyant. The mature Noni fruit has a foul taste and odor[5]. It has been reported to have a broad range of health benefits for cancer, infection, arthritis, diabetes, asthma, hypertension, and pain[6]. Several animal studies suggest noni may have anti-cancer[7,8], immune enhancing[9] and pain-relieving properties[10]. Most recently Takashima et al. demonstrated the medicinal uses of new constituents isolated from noni leaves[11]. Furthermore, it has been demonstrated that Noni fruit juice contains some antioxidative or anti-inflammatory ingredients[12].

Morinda citrifolia, has been reported to possess antithrombotic[13], antioxidant[14], analgesic and anti-inflammatory[15] and xanthine oxidase inhibitory[16] activities There are also preliminary studies reporting its blood pressure lowering[17] and vasodilatory[18] properties. On the downside, reports of serious hyperkalemia due to its high content of potassium (56.3 meq/L), which is similar to orange and tomato juices have been published[19].

Since noni fruit has proven antioxidant and hepatoprotective activity (attributed to its antioxidant activity), we decided to explore the nephroprotective effects of noni fruit extract in a murine model of gentamicin induced renal damage. During the course of this study, it was noted that noni fruit juice administered rats produced a high volume of urine formation. So this incidental finding prompted us to evaluate the diuretic potential of noni fruit juice in normal rats.

MATERIALS AND METHODS

Experimental animals

Adult male Wistar albino rats (150-200 g) from our breeding stock were used for the study. They were housed in clean and transparent poly propylene cages with three animals in each cage and maintained at 27□ with 12: 12 h light-dark cycle for a period of 7 days prior to the study. They were fed standard rat chow and water *ad libitum*. The experimental procedures described were approved by the Institutional Animal Ethics Committee.

Drugs

Frusemide (Sanofi Aventis Co.) was used as a reference diuretic drug.

Test drug

The fruit juice of *M. citrifolia* was obtained from the mature fruit grown in Karnataka. Ripe noni fruits washed and air dried, were weighed and placed in a food grade plastic container for 4-5 days. The noni fruit juice dripping from the pulp during this time was collected in the container, decanted (separating the juice from other sediments), filtered, preserved using 10% sodium methyl paraben IP and 5% sodium propyl paraben and was bottled. About 200-250ml of juice was obtained from 1kg of ripe noni fruit. After opening it was kept in a cool dry place and stored at -20°C.

Evaluation of diuretic activity

Each animal was placed in an individual metabolic cage 24h prior to commencement of the study for adaptation. The method of Lipschitz *et al*, [20,21] was employed for the assessment of diuretic activity. According to this method, the animals, deprived of food and water for 18 hours prior to the experiment, were divided into 5 groups (n=6). Group I animals received normal saline (25 ml/kg, p.o.); Group II received the standard diuretic, Frusemide (20 mg/kg, p.o.) and Groups III and IV received the test compound Noni fruit juice (5mg/kg and 10mg/kg) respectively. Before treatment, all

animals received physiological saline (0.9% NaCl) at an oral dose of 5ml/100g body weight to impose a uniform water and salt load[22]. All the drugs were freshly prepared prior to administration.

Immediately after administration, the animals were placed in metabolic cages (each animal per cage), specially designed to separate urine and faeces, kept at 20°C±0.5°C. The volume of urine collected was measured at the end of 24hrs. During this period, no food and water was made available to animals. The parameters noted were body weight before and after test period, total urine volume, and concentration of Na^+, K^+ and Cl^- in the urine. Na^+, K^+, Cl^- concentrations were determined by Ion Sensitive Electrode; Roche Hitachi 917 automatic analyzer and bicarbonate ion was estimated with Blood gas analyzer: AVL compact-3.

Statistical Analysis

The results were expressed as mean ± SD. The data was analyzed by Mann- Whitney test and Kruskall Wallis tests. A value of *P* less than 0.05 was considered as statistically significant.

RESULTS

Effect on urine volume

There was no evidence of dehydration and the animals were found normal at the observed 5hr and 24hr intervals. The reference diuretic frusemide, significantly increased the urine output when compared to control (P < 0.01), the diuretic index being 2.74. The test drug at 5 and 10 mg/kg doses, showed a statistically significant increase in the volume of urine with a dose dependent increase in the diuretic index to 2.04 and 2.36 for 5ml/kg and 10ml/kg dose ranges respectively. However it was less than that of frusemide treated rats. (Tableo 1)

Table 1: Effect of oral administration of noni fruit juice on urinary volume excretion

Group	Urine volume (ml/100g/24hr)	Diuretic index (24 hr interval)†
Control	3.33 ± 0.31	-
Frusemide	9.11± 0.61*	2.74
Noni fruit juice (5mg/kg)	6.82±1.18*	2.04
Noni fruit juice (10mg/kg)	7.87±1.15*	2.36

Values are expressed in mean±SD; *P <0.01 compared with control group (Kruskall Wallis and Mann Whitney test)
†Diuretic index = volume of test group/volume of control group

Effect on urinary electrolyte excretion

As indicated in table 2, the test drug, when compared to the control group, showed a statistical significant decrease in the excretion of sodium, at both the dose levels tested. Though there was a similar decrease in the potassium ion excretion, it was not statistically significant. A statistical significant increase in chloride excretion was noted in the test drug groups though it was less than that of the positive control, Frusemide which significantly increased the excretion of all the electrolytes.

Table 2: Effect of oral administration of the Noni fruit juice on urinary electrolyte excretions

Groups	Na^+ m. mol/L	K^+ m. mol/L	Cl^- m. mol/L	Saluretic index‡			Na/K
				Na	K	Cl	
Control	107±5.18	55±10.1	87.33±5.72	-	-	-	1.95
Frusemide	167.8±17.15*	92.5±5.0*	132.5±4.42*	1.57	1.69	1.52	1.81
Noni fruit juice (5mg/kg)	70.1±14.3*	50.2±8.9	98.5±1.52*	0.66	0.91	1.13	1.39
Noni fruit juice (10mg/kg)	41.97±9.3*	45.33±2.66	99±2.61*	0.39	0.76	1.13	0.93

Values are expressed in mean±SEM; *P <0.01 compared with control group (Kruskall Wallis and Mann Whitney test); ‡Saluretic index = volume of test group/volume of control group

DISCUSSION

In the present study, administration of Noni fruit juice in normal Wistar albino rats failed to show an increase in electrolyte excretion in spite of a marked and significant increase in the volume of urine. These findings indicate that the probable increase in urine formation might be due an aquaretic action of Noni fruit rather than a natruretic effect.

Although the term diuretic denotes all substances which increase urine flow (and in this sense water itself is a diuretic agent), diuretic drugs are designed to increase sodium excretion, since cardiac edema largely results through sodium retention. In contrast, in herbal texts the term diuretic is often loosely or inaccurately applied. In particular, when a herb was taken as a decoction or infusion, as it often was traditionally, the water consumed in conjunction with the herb would have produced an observable diuresis which might have had little to do with any diuretic action of the herb itself; this would partially explain variable results of clinical trials with aquaretic herbs[23].

Those herbs which did exhibit a mild diuretic activity might have done so because of their mineral (electrolyte) content. Confounding the issue, the term diuretic is often used in quite a different context in herbal writings. Herbs which are said to enhance the excretion of metabolic waste from the kidneys are also often described as diuretics. However, a more accurate description is encompassed by the terminology "diuretic depurative." Examples of diuretic depuratives include celery and clivers. Any frank diuretic action of these herbs is probably variable, depending on the individual, and unlikely to be outside normal pbysiological limits[23].

The late pharmacognocist Varro Tyler, PhD, theorized that herbs act only as aquaretics, (agents that increase water excretion without affecting renal handling of electrolytes)[24]. In Europe, phytotherapists have proposed that the term "aquaretic": more accurately describes some herbs which genuinely do increase urine output. The thinking here is that these herbs act on the glomerulus (unlike conventional diuretic drugs which act further along the nephron) to increase water excretion from the body, but their effect on electrolytes such as sodium and potassium is largely neutral. Aquaretics may work by causing dilation of glomerular arterioles, thereby increasing glomerular filtration rate. In other words, aquaretics act by increasing fluid loss from the body in a physiological manner, by increasing the formation of primary urine[23]. Various herbs like *Asparagus officinalis* with *Petroselinum crispum* have been studied in this context. In uncontrolled trials, this combination caused significant weight loss in overweight patients and significantly lowered blood pressure in patients with hypertension, without changing other biochemical parameters[23]. The distinction between an aquaretic and diuretic is critical. Aquaretics are very unlikely to affect edema or hypertension since sodium chloride is the major determinant of extracellular fluid volume and aquaretics do not influence electrolyte levels[25]. They have potential for the treatment of excessive weight, hypertension, congestive heart failure, kidney stones and premenstrual syndrome[23].

The mineral (electrolyte) content of herbs can often underpin any observed diuretic activity. The ratio of potassium to sodium was found to be higher in decoctions of herbs which are traditionally regarded as diuretics, compared to other herbs[26]. A pharmacological study concluded that the high potassium content of dandelion is the

agent responsible for any diuretic activity[27]. It is well known that potassium overloading which occurs when the kidney tubules are incapable of absorbing it, produce urinary excretion of the osmotic type[28]. Since noni fruit has a high content of potassium[19] it can be speculated that increase in urinary volume seen during this study could be an osmotic effect.

Thus it can be concluded that the increase in the volume of urine observed in this study could be due to either aquaretic effect of noni fruit juice or an ormotic effect. Since only two dose ranges were tried in this study and since the possibility of a delayed onset of action exists further studies with larger doses and more prolonged duration are warranted. Evaluation of its activity on vasopressin receptors presents yet another portal of further investigation regarding its mechanism of action as numerous in vivo animal studies have demonstrated the unmistakable aquaretic effect of nonpeptide AVP V2 receptor antagonists[29].

REFERENCES

1. Whistler WA. Traditional and herbal medicine in the Cook islands. J Ethnopharm 1985; 13: 239-80.
2. Dixon AR, McMillen H, Etkin NL. Ferment this: the transformation of Noni, a traditional Polynesian medicine (*Morinda citrifolia*, Rubiaceae). Ecological Botany 1999; 53:51–68.
3. Ross IA. Medical Plants of the World. Chemical Constituents, Traditional and Modern Medical Uses Volume 2. New Jersey: Humana Press; 2001.
4. Singh Y, Ikahihifo T, Panuve M, Slatter C. Folk medicine in Tonga. A study on the use of herbal medicines for obstetric and gynacological conditions and disorders. J Ethnopharmacol 1984; 12:305-25.
5. Swanholm CE, St John H, Scheuer PJ. A survey of alkaloids in Hawaiian plants. Pacific Science 1959; 13: 295-305.
6. Whistler W. Tongan herbal medicine. Isle Botanica, Honolulu, Hawaii; 1992. p 89-90.
7. McClatchey W. From Polynesian healers to health food stores: changing perspectives of *Morinda citrifolia* (Rubiaceae). Integr Cancer Ther 2002; 1: 110–20.
8. Hirazumi A, Furusawa E. An immunomodulatory polysaccharide rich substance from the fruit juice of Noni with antitumour activity. Phytother Res 1999; 13: 380–7.
9. Hiramatsu T, Imoto M, Koyano T, Umezawa K. Induction of normal phenotypes in ras-transformed cells by damnacanthal from Morinda citrifolia. Cancer Lett 1993; 73:161–66.
10. Younos C, Rolland A, Fleurentin J, Lanhers MC, Misslin R, Mortier F. Analgesic and behavioral effects of *Morinda citrifolia*. Planta Med 1990; 56: 430–34.
11. Takashima J, Ikeda Y, Komiyama K, Hayashi M, Kishida A, Ohsaki A. New constituents from the leaves of *Morinda citrifolia*. Chem Pharm Bull 2007; 55: 343–5.
12. Shinichi H, Wakako H, Kohei K, Toshiko S, Junichiro Y and Shogo T. Preventive effect of *Morinda citrifolia* fruit juice on neuronal damage induced by focal ischemia. Biol Pharm Bul 2009; 32(3): 405-9.
13. Ayanblu F, Wang MY, Peng L, Nowicki J, Anderson G, Nowiciki D. Antithrombotic effect of *Morinda citrifolia* (Noni) fruit juice on the jugular vein thrombosis induced by ferric chloride in male adult SD rats. Arteriosclerosis Thrombosis and Vascular Biology 2006; 26: E104.
14. Zin ZM, Abdul-Hamid A, Osman A. Antioxidative activity of extracts from Menkudu (*Morinda citrifolia*) root, fruit and leaf. Food Chemistry 2002; 78: 227-3.
15. Basar S, Uhlenhut K, Hogger P, Schone F, Westendorf J: Analgesic and antiinflammatory activity of *Morinda citrifolia* L. (Noni) fruit. Phytother Res 2010; 24(1):38-42.
16. Palu A, Deng S, West B, Jensen J. Xanthine oxidase inhibiting effects of noni (*Morinda citrifolia*) fruit juice. Phytother Res 2009; 23(12):1790-1.
17. Dang-Van-Ho. Treatment and prevention of hypertension and its cerebral complications by total root extracts of *Morinda citrifolia*. Presse Med.1955; 63(72):1478.
18. Runnie I, Salleh MN, Mohamed S, Head RJ, Abeywardena MY. Vasorelaxation induced by common edible tropical plant extracts in isolated rat aorta and mesenteric vascular bed. J Ethnopharmacol 2004; 92:311-316.
19. Mueller BA, Scott MK, Sowinski KM, Prag KA. Noni juice (*Morinda citrifolia*): hidden potential for hyperkalemia? Am J Kidney Dis 2000; 35(2): 310-312.
20. Lipschitz WL, Haddian Z, Kerpscar A. Bioassay of diuretics. J Pharmacol Exp Ther. 1943; 79: 97-110.
21. Murugesan T, Manikandan L, Suresh KB, Pal M and Saha BP. Evaluation of diuretic potential of *Jussiaea sufruticosa* Linn. Extract in rats. Indian Journal of Pharmaceutical Sciences 2000; 62 (2):150-51.
22. Benjumea D, Abdala S, Hernandez-Luis F, Perez-Paz P, Martin-Herrera D. Diuretic activity of *Artemisia thuscula*, an endemic canary species. J Ethnopharmacol 2005; 100: 205-9.
23. Kerry B. Phytotherapy for recurrent kidney stones-Phytotherapy review and commentary. Townsend Letter for Doctors and Patients. October 2005:51-53.
24. Tyler VE. Herbs of choice: the therapeutic use of phytomedicinals. New York: Pharmaceutical Products Press, Binghampton. 1994.
25. Yarnell E. Botanical medicines for the urinary tract. World J Urol 2002; 20: 285–293.
26. Szentmihlyi K, Kery A, Then M. et al. Potassium sodium ratio for the characterization of medicinal plant extracts with diuretic activity. Phytother Res1998;12: 163- 166.
27. Hook I, McGee A & Henman M. Evaluation of dandelion for diuretic activity and variation in potassium content. Pharmaceutical biology 1993:31(1): 29- 34.
28. Martin-Herrera, Abdala S, Benjumea D, Perez-Paz P. Diuretic activity of *Withania aristata*: An endemic Canary Island species. J. Ethnopharmacol 2007; 113:487-91.
29. Wong LL, Verbalis JG. Vasopressin V2 receptor antagonists. Cardiovascular research 2001; 51 (3): 391-402.