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Antihypertensive Effects of Ethanol Stem-Bark Extract of *Morinda Citrifolia* in Rats

Isaac John Umaru[1], Ameh Godwin Okwori[2], Ocheifa Mathew Ngbede[2], Lubabatu Abdulrasheed[3], Kingsley Iyoko Iseko[4], Tensaba Andes Akafa[5]

[1,5]Federal University Wukari. Taraba State, Nigeria; [2]Consultant Obstetric and Gynaecology, Lily Hospital Warri. Delta State,
[2]Federal Medical Centre, Makurdi, Benue State, Nigeria;

[3]Barau Dikko Teaching Hospital Kaduna, Nigeria;

Limi Hospital Abuja, Nigeria
umaruisaac@gmail.com

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Abstract

The medical term used for blood pressure is Hypertension (HTN). Hypertension is a common problem faced by most people today. The leading danger for many diseases such as CVD (cardiovascular) disorder and stroke is high blood pressure. Major diseases like CHF (congestive heart failure), renal disease and blindness can also be caused by HTN. Awareness of plant-based medication therapeutics is continuously increasing day by day. *Morinda citrifolia* L (Noni) has been used in folk remedies by Polynesians for over 2000 years, and is reported to have a broad range of therapeutic effects. The purpose of this study is to investigate the hypotensive potential of Morinda citrifolia L (Noni) (Family: Rubiaceae) in both normotensive and hypertensive rats. Methods: Aqueous-methanol (70:30) extract of Morinda citrifolia L stem-bark extract at doses of 25, 50, 75 and 100 mg/kg was evaluated for its effect on blood pressure and heart rate using non-invasive blood pressure measuring apparatus. After initial screening, 100 mg/kg dose that produced a maximum effect was selected for the antihypertensive study. Median lethal dose (LD50) and sub-chronic toxicity of the extract were also determined. Various

biochemical parameters and organ weight were measured using standard procedures. Results: The extract produced a significant ($p < 0.01$) decrease in systolic blood pressure (SBP), mean blood pressure (MBP), diastolic blood pressure (DBP) and heart rate of normotensive rats at all test doses with maximum effect at 100 mg/kg. Similarly, a significant antihypertensive and negative chronotropic effect was observed in both hypertensive models. LD_{50} of the extract was 200 mg/kg in mice. The extract also exhibited a reduction ($p < 0.05$) in serum alanine transaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase (ALP), triglycerides and low-density lipoprotein (LDL) levels while a significant ($p < 0.05$) increase in high density lipoproteins (HDL) level was observed. Conclusion: It seems that the aqueous-methanol stem-bark extract of *Morinda citrifolia L* possesses active compounds which may be responsible for the antihypertensive and negative chronotropic effects in rats.

Keywords: Antihypertensive, ethanol, stem-bark, Morinda Citrifolia, Rats, Chronotropic, normotensive, hypertensive, rats

INTRODUCTION

Hypertension, or the state of high blood pressure, is defined as above 140mmHg systolic blood pressure (SBP) and 90 mmHg diastolic blood pressure (DBP). It is one of the most significant causes of mortality worldwide since elevated blood pressure is considered to be the leading risk factor for coronary artery disease and its complications such as heart failure, stroke, renal disease, and diabetes [1]. Hypertension is also regarded as the major risk factor for disability-adjusted life years worldwide according to the Global Burden of Disease study [1, 2]. The World Health Organization predicts that 1.5 billion people will suffer from hypertension by 2025 and that more than 7 million deaths yearly are likely to be caused by hypertension [3]. Owing to the global impact of hypertension, many studies have investigated antihypertensive medications and new therapeutic alternatives [4, 5]. There are various types of antihypertensive medications—such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and calcium channel blockers—owing to the many physiological mechanisms of blood pressure control including cardiac output, peripheral vascular resistance, and circulating blood volume [6, 7]. These antihypertensive drugs are extensively used for the treatment of hypertension and related cardiovascular diseases, but they are reported to have adverse side effects as well [5, 6]. According to Hom et al. [8], ACE inhibitor, angiotensin receptor blockers, and calcium channel blockers cause upper

respiratory track abstraction and angioedema in adults and children. Calcium channel blockers contribute to the development and progression of cancer through the inhibition of vascular cell growth and angiogenic growth factors induced by the increase of apoptosis [9].

Other side effects of antihypertensive drugs, including dyspnoea, cough, hair loss, headache, oedema, and flushes, have been reported as well [10, 11]. Thus, an alternative therapy such as herbal drugs is preferred because natural herbal products using medicinal plants are considered to have fewer side effects [5]. Recently, medicinal plants have been reported to be effective in hypertension and empirically used as antihypertensive agents [12, 13]. The antihypertensive effects of plants are attributed to their antioxidant properties because oxidative stress is considered a risk factor in hypertension and cardiovascular diseases [14, 15]. Oxidant stress is caused by the imbalance between the generation of free radicals such as reactive oxygen and nitrogen species and antioxidant defence mechanisms [15]. Reactive oxygen species (ROS) produced in all vascular cells including endothelial, smooth muscle cells, and phagocytic cells play an important role in the pathophysiology of hypertension by causing vascular damage and reducing the production of nitric oxide (NO), which maintains the vascular tone. As such, excessive ROS is observed in patients with essential hypertension, with a close relationship between blood pressure and some parameters associated with oxidative stress reported. Thus, antioxidants can promote the reduction of high blood pressure by trapping free radicals [15].

An edible and medicinal tropic plant -Morinda citrifolia L (Noni) The ancestors of Polynesians are believed to have brought many plants with them, as food and medicine, when they migrated from Southeast Asia 2000 years ago [15]. Of the 12 most common medicinal plants they brought, Noni was the second most popular plant used in herbal remedies to treat various common diseases and to maintain overall good health [16]. Noni is the common name for Morinda citrifolia L and is also called Indian Mulberry, Ba Ji Tian, Nono or Nonu, Cheese Fruit, and Nhau in various cultures throughout the world. It has been reported to have a broad range of health benefits for cancer, infection, arthritis, diabetes, asthma, hypertension, and pain [17]. The Polynesians utilized the whole Noni plant in their medicinal remedies and dye for some of their traditional clothes. The roots, stems, bark, leaves, flowers, and fruits of the Noni plant are all involved in various combinations in almost 40 known and recorded herbal remedies [18]. Additionally, the roots were used to produce a yellow or red dye for tapa cloths and fala (mats), while the

fruit was eaten for health and food. There are numerous Polynesian stories of heroes and heroines that used Noni to survive from famine. There is one tale of Kamapua'a, the pig god, who loved Pele, the volcano goddess. He taunted Pele with a chant, "I have seen the woman gathering Noni /scratching Noni/pounding Noni." Supposedly, the chant referred to Pele's eyes becoming red, and she became so angry that she plunged into battle with him. A Tongan myth tells of the god Maui being restored to life by having Noni leaves placed on his body [19].

Morinda citrifolia fruit has a long history of use as a food in tropical regions throughout the world. Written documentation of the consumption of this fruit as a food source precedes the twentieth century. Captain James Cook of the British Navy noted in the late 1700's that the fruit was eaten in Tahiti [20]. An 1866 publication in London explained that Morinda citrifolia fruit was consumed as a food in the Fiji Islands [21]. Later publications describe the use of this fruit as a food throughout the Pacific Islands, Southeast Asia, Australia, and India. In Roratonga "the fruit was often eaten by the natives" [20]. Australian Aborigines were reported to be "very fond" of the fruit [22]. In Samoa, Noni fruit was common fare, and in Burma, the fruit was cooked in curries or eaten raw with salt [23]. In 1943, Merrill described Morinda citrifolia L as an edible plant in a technical manual of edible and poisonous plants of the Pacific Islands, in which the leaves and fruits could be used as emergency food [24]. Abbott also reported that Noni had been used as a food, drink, medicine, and colorful dye [25]. The medicinal history and accumulated scientific studies, to date, have revealed and confirmed the Polynesian's claim of the health benefits of Noni. The medical knowledge and pharmacopoeia of the Polynesians is now believed to have been fairly complex and modern scientific and medical communities are beginning to study the plants compiled from this knowledge base.

The Noni plant is a small evergreen tree found growing in open coastal regions at sea level and in forest areas up to about 1300 feet above sea level. The plant is often found growing along lava flows. It's 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. This could explain, in part, the wide distribution of the plant throughout the Polynesian islands. The mature Noni fruit has a foul taste and odor[26]. Morinda citrifolia L is not considered to be at risk in the wild.

A number of major components have been identified in the Noni plant such as scopoletin, octoanoic acid, potassium, vitamin C, terpenoids, alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin1-methyl ether, anthraquinone glycoside), β-sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid, Alizarin, amino acids, acubin, L-asperuloside, caproic acid, caprylic acid, ursolic acid, rutin, and a putative proxeronine[27-38].

A research group led by Chi-Tang Ho at Rutgers University in the US is searching for new novel compounds in the Noni plant. They have successfully identified several new flavonol glycosides, an iridoid glycoside from the Noni leaves, a trisacharide fatty acid ester, rutin, and an asperulosidic acid from the fruit. Two novel glycosides and a new unusual iridoid named citrifolinoside have been shown to have an inhibiting effect on AP-1 transactivation and cell transformation in the mouse epidermal JB6 cell line [39-44]. James Duke listed 23 different phytochemicals found in Noni as well as 5 vitamins and 3 minerals in an authoritative CRC handbook [45].

Xeronine system Retired biochemist, Ralph Heinicke, states that the Noni fruit contains a natural precursor for Xeronine that he named Proxeronine. Proxeronine is converted to the alkaloid, Xeronine, in the body by an enzyme he calls Proxeroninase[38]. His hypothesis is that Xeronine is able to modify the molecular structure of proteins. Thus, Xeronine has a wide range of biological activities. When a protein such as an enzyme, receptor, or signal transducer is not in the appropriate conformation, it will not work properly. Xeronine will interact with the protein and make it fold into its proper conformation. The result is a properly functioning protein. Whenever a problem arises in the cell due to a protein structural problem, Xeronine's presence would be beneficial. His hypotheses may explain why TAHITIAN NONI JUICE (TNJ) can help in many health problems in different ways. He has obtained several patents for Xeronine. He states that the active ingredient in many of the pharmacologically active enzymes and in many of the effective folklore drugs is xeronine. This alkaloid is a critical normal metabolic coregulator. The ailments that he believes to be helped by Noni include menstrual cramps, arthritis, gastric ulcers, sprains, injuries, mental depression, senility, poor digestion, drug addiction, and pain [46].

Dong reported that two glycosides extracted from noni-ppt were effective in inhibiting cell transformation induced by TPA or EGF in the mouse epidermal JB6 cell line. The

inhibition was found to be associated with the inhibitory effects of these compounds on AP1 activity. The compounds also blocked phosphorylation of c-Jun, a substrate of JNKs, suggesting that JNKs are a critical target for the compounds in mediating AP-1 activity and cell transformation [42,59].

Anthelmintic activity an ethanol extract of the tender Noni leaves induced paralysis and death of the human parasitic nematode worm, Ascaris Lumbricoides, within a day [59]. A botanist via Morton reported that Noni has been used in the Philippines and Hawaii as an effective insecticide [23]. Based on these results, we hypothesized that the extract has potential antihypertensive effects. Therefore, we investigated our hypothesis in this study.

METHODS

Experimental

Chemicals and drugs

Glucose and methanol were purchased from Sigma Chemicals Co. All other chemicals and drugs used were of analytical grade.

Animals

Sprague Dawley rats and albino mice weighing 200-350g and 30-40g respectively were used for this study. All the animals were housed in controlled environment (23-25°c) and received human care in accordance with the National Institute of Health (NIH) guide for the care and use of laboratory animals. The study protocol was approved by the institutional Animal Ethics committee Faculty of Pharmacy, University of Sargodha (Approval No.20-A12 IEC UOS). Experiments performed complied with the rulings of National Research Council [10].

Plant material

The stem-bark *Morinda citrifolia* L were collected from district Michika, Adamawa State Nigeria during the month of June, 2024 and was identified and authenticated Faculty of Agriculture Federal University Wukari. By a Botany. A voucher (no. BO115-13) has been deposited in the herbarium, of the Faculty for future reference.

Preparation of extract

Aqueous methanolic stem-bark extract of *Morinda citrifolia L* was prepared using cold maceration process. The grounded plant material (2 kg) was soaked in 5 L of water-methanol mixture (70:30) for 72 h at room temperature. After 72hrs of occasional shaking, the whole material was filtered and the filtrate evaporated under reduced pressure using rotary evaporator. The crude extract was then air-dried to obtain a solid mass with a yield of 25 %. [11].

Determination of hypotensive activity in normotensive rats

Normotensive rats of either sex were randomly assigned into four groups (n = 6). Group 1 and 2 received 25 and 50 mg/kg of the aqueous methanolic extract of *stem-bark extract of Morinda citrifolia L* while animals in group 3 and group 4 received 75 and 100 mg/kg of same extract, respectively. Animals in each group served as their own control. Basal blood pressure and heart rates were measured at 0 hr (Before extract administration). After intraperitoneal administration of various doses of the extract, blood pressure and heart rate of each of these groups were determined from the tails of rats at 0, 2, 4 and 6 hrs using non-invasive blood pressure (NIBP) measuring apparatus (IN125, AD Instruments, Sydney, Australia). Each rat was placed in NIBP restrained and appropriate cuff with sensor was then mounted on its tail and warmed to about 33-35 °C. The tail cuff (MLT 125/R) was inflated to a pressure well above the expected systolic blood pressure, i.e., 200 mm Hg, and slowly released during which the pulses were recorded by using Power Lab data acquisition system and computer running Lab Chart 5.0 software (Ad Instruments, Sydney, Australia). Systolic blood pressure (SBP), Mean blood pressure (MBP) and heart rate were measured directly using pulse tracing while diastolic blood pressure (DBP) was calculated from SBP and MBP as in Eqn 1 [12].

$$DBP = (3MBP - SBP)/2 \quad \text{..... (1)}$$

Determination of antihypertensive activity in hypertensive models

Egg Feed-Induced Hypertensive Rat Model

Wister rats of either sex were divided into two groups (n = 6). Group 1 received orally a special prepared egg feed diet (12 egg yolk mixed with 500 g of normal rat diet) for 21 consecutive days in order to produce cholesterol induced hypertension. Animals in group 2 received egg feed diet and aqueous methanol extract of stem-bark extract of *Morinda*

citrifolia L (150 mg/kg) for the same time period. All animals received saline instead of tap water *ad libitum*. Blood pressure and heart rate of each of these groups were measured on week 0, 1, 2 and 3 by the method described above [12,13].

Glucose-Induced Hypertensive Rat Model

Wister rats of either sex were randomly assigned into two groups (n = 5). Group 1 received 10 % glucose solution instead of tap water for 21 consecutive days. Animals in group 2 were given 10 % glucose solution and an aqueous methanolic extract of stem-bark of *Morinda citrifolia L* (100 mg/kg) for same time period. Animals were fed on standard diet. Blood pressure and heart rate of these groups were measured on week 0, 1, 2, and 3 by the above-mentioned method [12,13]

Acute Toxicity Study

Albino mice of either sex were randomly divided into five groups (n = 2). Group 1 served as control and received normal saline (10 ml/kg) while other groups (2, 3, 4 and 5) were administered the extract in doses of 30, 50, 100 and 200 mg/kg, respectively. Mortality rate was observed for 24 hrs. All the doses were administered by intra-peritoneal route. The highest dose, which did not kill any animal, and the lowest dose, which killed only one animal, were noted. LD_{50} was calculated from the mean of these two doses [14].

Sub-Chronic Toxicity Assessment

Wister rats of either sex were randomly divided into two groups (n = 6). The first group received normal saline (10 ml/kg body weight p.o.) that served as control and the animals in group 2 received 100 mg/kg body weight of the extract daily for 28 days. Food and water intake of animals were observed during this period. On the 29th day, blood was collected from overnight fasted rats of each group by cardiac puncture for the determination of serum biochemical parameters. The rats were sacrificed by cervical dislocation for the study of various organs (heart, liver and kidney) weights [67].

Evaluation of biochemical parameters

For the estimation of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), blood samples were collected in clot activator gel tubes. The serum was separated by centrifuging the blood samples at 2000 rev/min for 10

minutes. Serum biochemical parameters were then measured by using commercially available reagent kits (Abbott Laboratories, USA) [67].

Statistical analysis

The results were expressed as mean ± standard error of mean (SEM) and statistical analysis was carried out by Student's t-test using Graph Pad Prism 5.0. Differences were considered significant at $p < 0.05$.

RESULTS

Hypotensive activity in normotensive rats: The aqueous methanol extract of stem-bark extract of *Morinda citrifolia L* produced a significant decrease in SBP, MBP and DBP of normotensive rats at the doses of 25 and 50 mg/kg. The extract at the doses of 75 and 150 mg/kg also exhibited a highly significant ($p < 0.001$) decrease in blood pressure when compared to control (0 hrs). The maximum hypotensive effect was observed at 150 mg/kg. Similarly, the extract also produced a significant ($p < 0.01$) decrease in heart rate at all the doses with maximum effect at 150 mg/kg (Figure 1 and Table 1).

The extract, at a dose of 150 mg/kg, produced a significant ($p < 0.01$) antihypertensive effect after three weeks of treatments. The extract also demonstrated a remarkable decease in heart rate of egg feed induced hypertensive rats at week 1. At the end of weeks 2 and 3, a significant ($p < 0.01$) decrease in heart rate of hypertensive rats was observed, compared to egg feed control group (Figure 2 and Table 2).

Glucose-induced hypertension: In glucose-induced hypertensive rats, the extract, at a dose of 150 mg/kg, produced a significant ($p < 0.001$) antihypertensive effect after 3 weeks of treatment. Similarly, a significant negative chronotropic effect was observed after weeks 2 and 3 treatments (Figure 3 and Table 2).

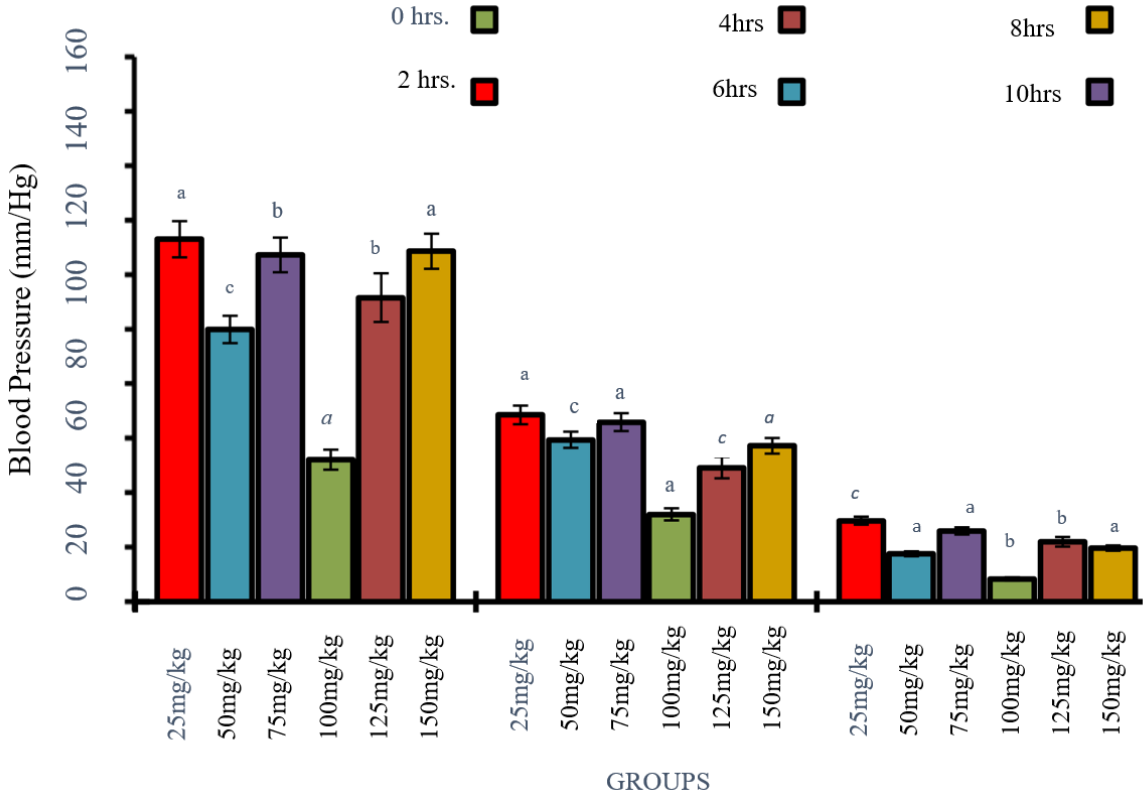

Figure 1: Hypotensive effect of *Morinda citrifolia L* in normotensive rats. ***Key:*** a = ($p < 0.001$), b = ($p < 0.01$) and c = ($p < 0.05$), compared to control (0 h); control = basal blood pressure at 0 hrs (i.e., before extract administration)

Table 1: Effect of stem-bark extract of *Morinda citrifolia L* on the heart rate of normotensive rats

	Normotensive rats (heart beats/min ± SEM)					
	Treatment					
Time	**25mg/kg**	**50mg/kg**	**75mg/kg**	**100mg/kg**	**125mg/kg**	**150mg/kg**
0 hrs	376.0 ± 3.58	361.1 ± 3.59	412.6 ± 2.76	380.2 ± 3.99	370.6 ± 3.86	360.4 ± 3.75
2 hrs	377.6 ± 2.10	357.4 ± 6.40	375.0 ± 5.65[a]	360.6 ± 7.99[a]	352.4 ± 7.99[a]	340.2 ± 6.85[a]
4 hrs	371.0 ± 8.94	355.4 ± 7.37	365.8 ± 8.21[b]	348.4 ± 6.27[b]	337.3 ± 5.27[b]	333.4 ± 5.57[b]
6 hrs	367.0 ± 3.93[a]	344.8 ±5.52[b]	358.0 ± 6.91[b]	330.0 ± 6.56[b]	328.0 ± 5.66[b]	321.0 ± 6.32[b]
8hrs	361.0 ± 4.33[a]	333.7 ±4.12[b]	346.0 ± 4.55[b]	320.0 ± 6.46[b]	316.0 ± 6.76[b]	312.0 ± 6.77[b]
10hrs	349.0 ± 3.93[a]	321.4 ±3.62[b]	329.0 ± 6.87[b]	311.0 ± 6.34[b]	309.0 ± 6.34[b]	298.9 ± 7.36[b]

Note: a = $p < 0.05$ and b = $p < 0.01$, compared to control

Table 2: Effect of stem-bark extract of *Morinda citrifolia L* on the heart rate of hypertensive rats

Hypertensive rats (Heart beats/min, ± SEM)				
	Treatment			
Time	Egg feed control	Extract 150mg/kg	Glucose control	Extract 150mg/kg
0 week	377.7 ± 8.2	375.3 ± 7.3	376.0 ± 8.3	380.6 ± 7.1
1 week	413.4 ± 9.3	358.8 ± 8.2[a]	389.5 ± 8.5[a]	367.5 ± 9.6[a]
2 weeks	433.4 ± 9.2	358.5 ± 1.4[b]	453.3 ± 8.72	358.7 ± 6.9[b]
3 weeks	466.4 ± 9.7	366.0 ± 4.8[b]	467.2 ± 8.43	349.3 ± 6.3[b]

Table 3: Effect of Stem-bark extract of *Morinda citrifolia L* aqueous methanol extract on body weight, organ weight and other biochemical parameters of rats

	Parameter	Control (Normal saline)	Extract (150 mg/kg)
	Liver (g)	5.83 ± 0.11	5.86 ± 0.11
	Kidney (g)	1.37 ± 0.16	1.35 ± 0.12
	Heart (g)	1.45 ± 0.13	1.44 ± 0.13
	Body Weight (g)	283± 5.14	280± 4.49
	ALT (IU/L)	40.12 ± 2.56	36.4 ± 1.70a
	AST (IU/L)	90.11± 1.07	79.36 ± 1.08a
	ALP (IU/L)	70.12± 2.04	57.89± 1.95a
	Triglycerides (mg/dl)	89.17± 1.89	76.0 ± 1.73a
	Cholesterol (mg/dl)	60.6± 1.57	51.0 ± 1.03b
	LDL (mg/dl)	20.15 ± 2.09	15.11 ± 1.07b
	HDL (mg/dl)	33.11± 1.19	45.6 ± 2.11a

Values are expressed in means ± SEM (n=6) where a = $p < 0.05$ and b = $p < 0.01$, compared to control

Acute and sub-chronic toxicity of extract

The median lethal dose (LD50) of the extract in mice was 200mg/kg. All the animals showed signs of respiratory depression and convulsion before death. In sub-chronic toxicity studies, the extract did not cause any significant alteration in food and water intake, body weight and organs weight of rats. The results also revealed that the extract, at a dose

of 150 mg/kg, produced significant reduction in serum ALT, AST and ALP levels. The extract exhibited significant ($p < 0.01$) decrease in total cholesterol, triglycerides and LDL levels but increase in HDL levels was observed (Table 3).

DISCUSSION

It is noteworthy that the aqueous methanol extract of *Morinda citrifolia L* produced a significant reduction in SBP, MBP, DBP and heart rate of normotensive rats indicating a hypotensive effect. Maximum decrease in blood pressure and heart rate was observed at 150 mg/kg. Hence this dose was selected for antihypertensive study in both egg feed- and glucose-induced hypertensive rats. Reduction in blood pressure produced by the extract was much higher in hypertensive rats than in normotensive rats. This is in agreement with previous findings that hypertensive rats appear to have a stronger response to hypotensive agents [60].

In rats, egg feed-induced hypertension has been reported to be largely due to increased cholesterol level while glucose-induced hypertension has been associated with increased reactive oxygen species production as well as reduction in nitric oxide levels [13,61,62]. Cholesterol rich diet and high glucose intake are linked to dyslipidaemia which is considered a major risk factor for hypertension [8,12]. Furthermore, increased sympathetic activity has also been associated with raised blood pressure and a positive chronotropic effect [8]. Thus, the antihypertensive effect of *Morinda citrifolia* stem-bark extract in egg feed- and glucose-induced hypertensive rats might be due to certain hypolipidemic, antioxidant, vasodilator and depressor constituents of the plant extract.

Previously, it has been well documented that various parts *of Morinda citrifolia* contain certain alkaloids, phenols and flavonoids that could exhibit antihypertensive activity. Alkaloids and phenolic compounds also show antioxidant effects which reduce endothelial dysfunction through increased nitric oxide formation, decreased LDL formation, increased prostacyclin formation and enhanced EDHF mediated vasorelaxation [63, 65]. Therefore, the antihypertensive activity of Morinda citrifolia stem-bark extract might be linked to the presence of these antioxidant principles, especially the impotance of alkaloid family has been reported to exert antihypertensive and vasorelaxation effects [65].

In acute toxicity study, all the animals showed convulsions and respiratory depression before death which suggest some effect of the extract on rat nervous system [66]. Sub-

chronic toxicity studies in rats indicate that the extract is safe as no significant signs of toxicity were observed. Food and water intake, body weights and organ weights remained unaltered during the 28 days of treatment with the extract. However, biochemical parameters related to hepatic functions such as ALT, AST and ALP significantly decreased. Reduction in the levels of these enzymes indicate that the extract did not have any toxic effects on both liver and heart tissues [66]. The extract also revealed a significant decrease in serum cholesterol, triglyceride and LDL levels, and increase in HDL levels in rats thus indicating possible reduction in cardiovascular risk factor that could lead to the death of animals, such as the anti-hyperlipidaemic drugs like statins [67].

CONCLUSION

The aqueous methanolic extract of *Morinda citrifolia* most likely contains certain active principles that may be responsible for its antihypertensive and negative chronotropic effects. Further studies are required to isolate these phytochemical constituents and elucidate their possible mechanisms of action.

Conflict of Interests

The authors have not declared any conflict of interests.

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