Research Paper

Antihypertensive, antihyperlipidemia and hepatoprotective activity of ethanolic extract of *Moringa oleifera* leaves

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ABSTRACT

The ethanolic extract of *Moringa oleifera*(EEM) prevented and exerted curative effect on high acute blood pressure induced by L-NAME (10mg/kg). This acute curative effect of EEM (20mg/kg) in acute high blood pressure induced by L-NAME is transitory and reversible. In the subacute hypertension induced by L-NAME (40mg/kg), oral administration of L-NAME causes an increase in blood pressure (BP) (P<0.01) after 4 weeks. Concomitant daily administration of L-NAME and captopril or L-NAME and EEM partially inhibited the increase of BP induced by L-NAME. This decrease in BP was accompanied by a decrease in heart rate (HR). The analysis of some parameters of lipid profile revealed a significant decrease in levels of triglyceride, total cholesterol and atherogenic index in animals treated preventively with ethanolic extract of the plant (200 or 400mg/kg) or captopril (20mg/kg); its was observed against by, an increase in HDL-cholesterol levels in the same groups of animals. The analysis of hepatic and renal function parameters showed a significant decrease in ALT, AST and bilirubin levels compared to animals treated with only L-NAME. Moreover, no significant differences were observed in the total creatinin, total protein and total cholesterol levels, except the group treated with extract 400mg /kg.

Key words: *Moringa oleifera;* L-NAME; Lipid profile; ALT; AST; Bilirubin

INTRODUCTION

High blood pressure is one of the major risk factors for developing cardiovascular diseases, including coronary disease, stroke, peripheral artery disease, renal disease and heart failure (D'Agostino et al., 2008).In sub-Saharan Africa, it would experience a strong growth in all regions and is the predominant cardiovascular disease (Lafay et al.,2006).In Burkina Faso, traditional medicine uses plants in the treatment of various diseases including high blood pressure (Nacoulma-Ouedraogo, 1996).Recently, the use of medicinal plants has gained more interest for the remedy of some ailments. One source is *Moringa oleifera* Lam. (Family-*Moringaceae*), which has the common name drumstick tree (Ampa et al., 2013), also called arzantiiga (tree of heaven) in Mooré, this plant is of warm tropical regions widely used in traditional medicine for its therapeutic and nutritional virtues (Anwar et al., 2007). In the central plateau of Burkina Faso, *Moringa oleifera* is used in the treatment of various diseases

including hypertension (Nacoulma-Ouedraogo, 1996). Many authors have reported antioxidant (Verma et al., 2009), antidiabetic (Jaiswal et al., 2009), anti-inflammatory, anti-diuretic (Caceres et al., 1992), and hypotensive (Gilani et al., 1994) properties of *Moringa oleifera*. But no data was reported in literature egarding sub-acute antihypertensive, antihyperlipidemia and hepatoprotective effects of EEM in this model of HTA. This study aims to evaluate the preventive effects of the ethanolic extract of *Moringa oleifera* on sub-acute hypertension induced by inhibition of NO synthase and its protective effects on the harmful impact related to this endothelial dysfunction in rats.

MATERIALS AND METHODS

Plant material and extraction: The fresh leaves of *Moringa oleifera* was harvested in the southwest of Burkina Faso in July 2010. The plant was identified in the Bio-Info Center where a voucher specimen n°16869 was deposited. The leaves were dried at room temperature and crushed into powder. The resulting powder was macerated and soaked at room temperature in 70° ethanol (10%, g/v) for 72hours. Then, the macerate was filtered and concentrated in a rotary evaporator under reduced pressure in order to extract the ethanol portion. The concentrated aqueous portion remaining was first dried at room temperature under ventilation. After, the doughy residue obtained was dried. The yield was 16.09%.

Effect of ethanolic extract of *M. oleifera* (EEM) on hypertension induced by L-N^G-Nitroarginine methyl ester (L-NAME):

Experimental protocol of acute curative test: The rats were anesthetized using an intra-peritoneal injection of 15% urethane (1.5g/kg of body weight). Hemodynamic parameters were recorded from the left carotid artery via an arterial cannula connected to a pressure transducer (SS13L, Biopac, France). The recorded signal was transferred to an acquisition system (MP35, Biopac) coupled with a computer. 10% heparin (0.1 ml/100 g body weight) was immediately administered in carotid to prevent intravascular blood clotting. The right femoral vein was catheterized with a polyethylene tube filled with a Mc Even solution containing 1% heparin and connected to a syringe for drugs injection. The animals were allowed to stabilize for at least 30 min before administration of the test substance (Dimo et al., 2003). After equilibration period, L-NAME 10mg/kg (0.1ml/100g) was injected through femoral vein in order to induce high blood pressure. Ethanolic extract of *Moringa oleifera* was injected at the maximum level of the blood pressure in order to observe its eventual curative effect on this hypertension.

Experimental protocol of sub-acute preventive test: Five groups of 6 male rats in each group (weight between 200 to 250g), were used for this study. The group1 (control) received the distilled water 1ml/100g body weight (bw). The groups 2, 3, 4 and 5 received the L-NAME (40 mg/kg bw). The group3 additionally received captopril (20mg/kg bw) while the groups 4 and 5 respectively received the ethanolic extract at 200mg/kg and 400mg/kg bw. The rats were then treated daily for four weeks. All products were administered daily and per os during 4 weeks. At the end of the treatment, the rats were anesthetized with urethane 15% (1.5 g/kgbw), and the blood pressure and the heart rate were measured via a catheter placed in the right carotid artery and connected to a pressure transducer coupled to a hemodynamic recorder Biopac Student Lab. (MP35) and to a computer. After that, the rats were sacrificed and the blood collected in glass tubes. After centrifugation (3000trs/min for 15 minutes at 4°C), the serum was collected and stored in eppendorf tubes at -4°C for the determination of lipid profile ,and hepatic and renal function markers.

Analysis of lipid profile parameters: The determination of the lipid profile parameters was performed using standardized enzymatic colorimetric methods by measurement of the optical density of the reaction products at the corresponding wavelength with a spectrophotometer (Genesys 20Thermo Spectronic). Then, total cholesterol (CT), triglycerides (TG) and HDL-

cholesterol (HDL-C) level were determined according to the manufacturer protocols described by Biolabo assay kits (Maizy, France). C-HDL concentration in plasma was determined by the enzymatic method based on specific precipitation of VLDL and LDL in the presence of magnesium ions. Then concentrations were calculated as following:

$$VLLD= Triglycerides/5; HDL\text{-}C= TC\text{-}LDL\text{-}VLDL$$

$$TC \text{ or } TG \text{ (mg/dL)} = \frac{Absorbance \text{ (specimen)}}{Abs \text{ (Etalon)}} \times [\text{ Etalon}] \text{ (mg/dL)}$$

Liver and renal function assays: Cypress diagnostics kits (UV kinetic test IFCC. HBE07 Code) were used for the measurements of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) while creatinin, and total bilirubin (TB) were determined using Fortress diagnostics kits (United Kingdom). The principle of ALT and AST determination was based on the velocity of NADH usage during the enzymatic transformation of α-ketoglutarate to malate or lactate respectively by AST or ALT. The optical density of NADH was measured kinetically with a spectrophotometer (Genesys 20Thermo Spectronic). The activity of AST or ALT (UI/L) was expressed as Δ (optical density)/minute X 1750.

Statistical analysis: Results were expressed as mean±standard error of Mean (SEM). Means were compared one-way ANOVA, followed by Tukey's post-test using Graph Pad Prism software version 5.03 (Graph Pad Software, San Diego, California, USA). The difference was considered significant at $P< 0.05$.

RESULTS

Direct curative effect of Moringa oleifera on L-NAME-induced hypertension in anaesthetized rats: Intravenous administration of L-NAME (10mg/kg) in Wistar rats induces acute hypertension which was partially inhibited at a dose of 20mg/kg by the ethanolic extract of *M. oleifera*. This acute curative effect of EEM (20mg/kg) in acute high blood pressure induced by L-NAME was transient and reversible **(Figure A and B).**
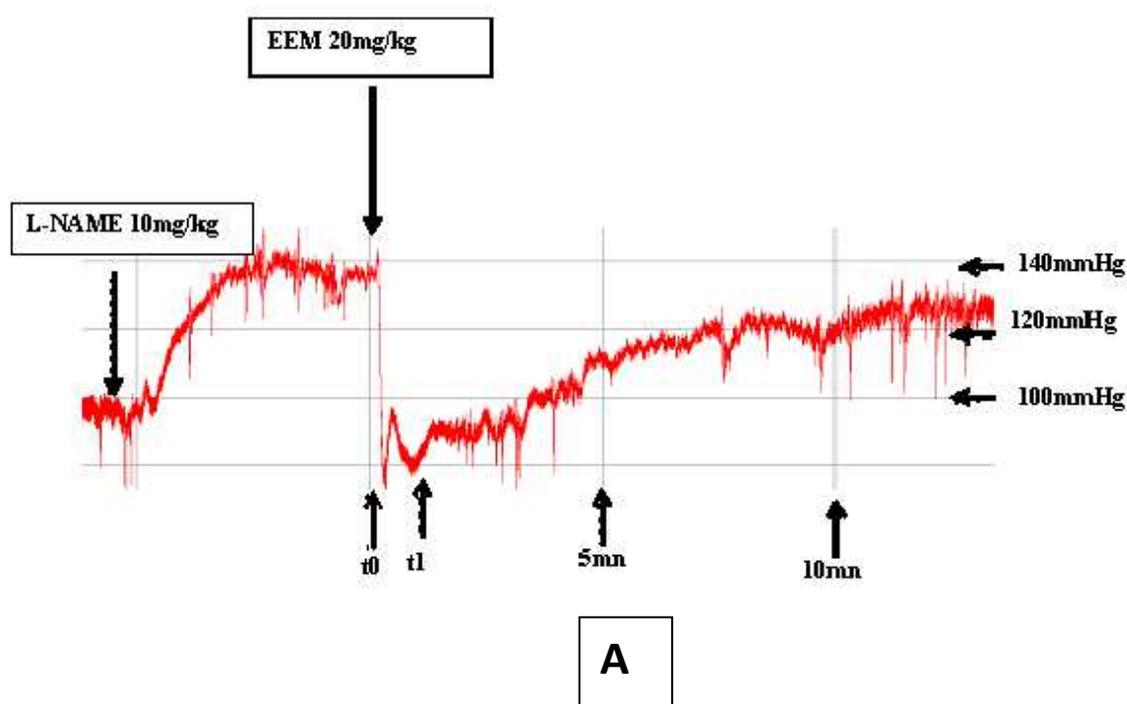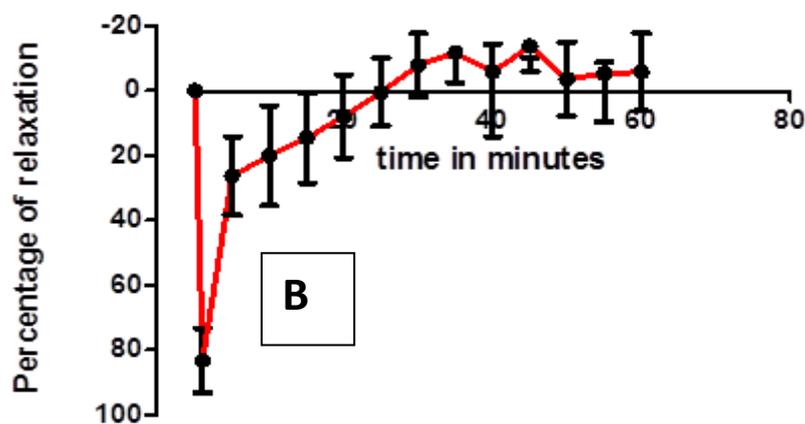
Fig. A & B: Representing lowering of acute high blood pressure induced by L-NAME (10mg/kg) after administration of EEM (20mg/kg) at t0. Maximum of blood pressure (at t0) induced by L-NAME is considered as 0% of relaxation. n =6.

Effects of oral administration of ethanolic extract M. oleifera on L-NAME-induced hypertension in rats: The results of our study showed that oral and daily administration of the inhibitor of NO synthase (L-NAME) at a dose of 40mg/kg results in an increase of systolic blood pressure (SBP) ($P<0.01$) after 4 weeks compared to the control group. Co-administration of L-NAME (40mg/kg)-Captopril (20mg/kg) or L-NAME (40mg/kg)–EEM (200 or 400mg/kg) partially inhibited the increase of HTA induced by L-NAME. This decrease of arterial blood pressure was accompanied by a decrease of heart rate (table 1), which may partially explain the antihypertensive effect observed.

Table-1: Effects of ethanolic extract of *M. oleifera* on hemodynamic parameters.

	DW	L-NAME 40mg/kg	L-NAME 40mg/kg +Captopril 20mg/kg	L-NAME 40mg/kg +EEM 200mg/kg	L-NAME 40mg/kg +EEM 400mg/kg
HR (BPM)	$356.34\pm9.24^{\gamma}$	418.01 ± 5.21^{c}	$374.09\pm11.07^{\beta}$	392.0475 ± 6.85	$383.35\pm4.94^{\alpha}$
SBP (mmHg)	$118.74\pm5.85^{\beta}$	164.10 ± 7.87^{b}	$115,024\pm12.02^{\beta}$	144.355 ± 5.38	$129.21\pm2.68^{\alpha}$

- $^{\alpha}P<0.05$; $^{\beta,b}P<0.01$; $^{\gamma,c}P<0.001$
- b,c significantly different compared to the control rats; α,β,γ significantly different compared to hypertensive rats
- DW: Distilled water 10ml/kg; BPM: Beats/minute. SBP: Systolic Blood Pressure, HR: Heart Rate.

Effects of ethanolic extract of Moringa oleifera on lipid profile:

Table-2: Effects of ethanolic extract of *Moringa oleifera* on some lipid profile parameters.

	DW	L-NAME 40mg/kg	L-NAME 40mg/kg+ Captopril 20mg/kg	L-NAME 40mg/kg+EEM 200mg/kg	L-NAME 40mg/kg+EE M 400mg/kg
Total Cholesterol (mg/dL)	71.60 ± 1.88	83.17 ± 6.28	72.05 ± 5.49	76.20 ± 4.59	$63.10\pm2.22^{\alpha}$
Triglycerides (mg/dL)	55.09 ± 7.67	76.92 ± 6.17	74.32 ± 9.16	$34.11\pm10.92^{\beta}$	$26.86\pm0,97^{\gamma}$
HDL-Cholesterol (mg/dL)	49.22 ± 2.27	30.23 ± 5.03	$62.20\pm5.24^{\beta}$	$72.15\pm6.34^{\gamma}$	$83.97\pm6.94^{a\gamma}$
VLDL (mg/dL)	11.02 ± 1.54	15.38 ± 1.23	14.86 ± 1.83	$6.82\pm2.19^{\beta}$	$5.37\pm0.19^{\gamma}$
Atherogenic Index	1.46 ± 0.04	$3.40\pm0 .00^{a}$	$1.16\pm0.04^{\beta}$	$1.09\pm0.10^{\beta}$	$0.78\pm0.08^{\beta}$

- $^{\alpha,a}P<0.05$; $^{\beta}P<0.01$; $^{\gamma}P<0.001$;
- a,b,c significantly different compared to the control rats; α,β,γ significantly different compared to hypertensive rats;
- DW: Distilled water 10ml/kg.

Effects of ethanolic extract of Moringa oleifera on some parameters of liver and kidney functions:

Table-3: Effects of ethanolic extract of *Moringa oleifera* on some parameters of liver and kidney functions.

	DW	L-NAME 40mg/kg	L-NAME40mg/kg+ Captopril 20mg/kg	L-NAME 40mg/kg+EEM 200mg/kg	L-NAME 40mg/kg+EEM 400mg/kg
ALT (UI/L)	2.30±0.31	4.90±0.30[c]	1.75±0.26[γ]	3.06±0.34[γ]	2.80±0.12[γ]
AST (UI/L)	10.69±1.53	13.77±0.23	9.22±0.74[α]	7.35±0.60[β]	6.271±0.39[aγ]
Total Protein (mg/dL)	7.17±0.25	7,41±0,35	7,22±0.42	6.66±0.21	6.57±0.19
TB (mg/dL)	1.32±0.02	1.25±0.04	1,22±0.05	0.61±0.01[cγ]	0.50±0.04[cγ]
Creatinin (mg/dL)	2.30±0.08	2.30±0.09	2,20±0.10	2.12±0.08	2.10±0.14

- $^{α,a}P<0,05$; $^{β}P<0,01$; $^{γ,c}P<0,001$;
- a,b,c significantly different compared to normal rats; α,β,γ significantly different compared to hypertensive rats;
- DW: Distilled water 10ml/kg;

DISCUSSION

Our preliminary findings showed that intravenous administration of the ethanolic extract of *Moringa oleifera* (20mg/kg) inhibited curatively and transiently the acute hypertension induced by NO-synthase inhibitor, L-NAME (10mg/kg) in Wistar rats. This result suggests that EEM could exert its beneficial effect by stimulating NO production or other antihypertensive mechanism pathways. In this study the oral subacute preventive effects of EEM on oral subacute high blood pressure induced by L-NAME were evaluated on wistar rats. The results of this study showed that the inhibitor of NO synthase (L-NAME) at the dose of 40mg/kg bw resulted in an increase of systolic blood pressure (SBP) (*P*<0.01) after 4 weeks of treatment compared to the control group. The captopril (20 mg/kg) or the ethanolic extract of *M. oleifera* (200 or 400mg/kg) partially inhibited the increase of hypertension induced by L-NAME. These antihypertensive effects of EEM are comparable to those of Metchi et al. (2013) on the same type of hypertension using the extract of *Vitex cienkowskii* at the same doses of 200 and 400mg/kg. Many authors reported that *Moringa* leaf extracts are rich source of phenolic compounds and antioxidant activity (Singh et al., 2009; Verma et al., 2009; Mishra et al., 2011; Vongsaket al., 2013; Matshediso, 2015; Vanajakshi, 2015).

Indeed, polyphenolic compounds are known for their antihypertensive and cardioprotective effects (Afkir et al., 2008; Francisco et al., 2009; Davide et al., 2010). Rupasinghe et al (2011) demonstrated that flavonoids could inhibit angiotensin converting enzyme. Angiotensin II (Ang II) is a key factor that causes vasoconstriction, salt retention and inflammation (Passaglia, 2015). It is also demonstrated that polyphenols rich source are powerful eNOS activators via the Src/PI3-kinase/Akt pathway leading to endothelium-dependent vasodilation in porcine coronary arteries (Kim, 2013). As for the decrease in heart rate, it could be due to a stimulating activity of EEM on the parasympathetic system (Marsac, 2013).

Our results have also shown a significant decrease in triglycerides (TG), atherogenic index (AI), total cholesterol (TC) level and an increase in high density of lipoprotein cholesterol (HDL-C) in rats in the presence of the different doses of EEM. These results corroborate those obtained by Kumar et al. (2010) from a group of hypertensive and normal patients. It has been shown that high concentrations of HDL-C are anti-atherogenic and protective factor against cardiovascular risk (Raghuveer et al., 2008; Marzolini et al., 2004). The increase in HDL-C ratio in the presence of EEM (200mg/kg, *P*<0.01 or 400mg/kg, *P*<0.001) indicates that EEM could have beneficial effects against cardiovascular risks.

HDL-C has anti-atherogenic effects, partly due to its antioxidant and anti-inflammatory activity because of the presence of enzymes such as paraoxonase, able to neutralize pro-inflammatory oxidized lipids (Benaissa, 2012). Hypercholesterolemia and hyper triglyceridemia are often associated with risk factors of hypertension (Youmbissi et al., 2001). The decrease in serum triglycerides in the presence of the extract could be related to the activation of lipases triglycerides or inhibition of acetyl-CoA carboxylase, involved in the hydrolysis of triglycerides to fatty acids (Lutfi et al., 2001). Indeed, hyperlipidemia and hypercholesterolemia promote an expression of molecules and leukocyte adhesion to the vascular blood streams and thus promotes the formation of atherosclerotic plaques (Lebranchu et al., 2000). These results corroborate those of Mansour et al. (2014) who showed that *Moringa* leaf extract induces significant recovery in total cholesterol, triglyceride, HDL-C and LDL-C levels in Gamma-irradiation induced oxidative stress and dyslipidemia in rats. Many authors associate more often the decrease in cholesterol level to the inhibition of the main enzyme of the synthesis of cholesterol, the 3-hydroxy-3-methylglutaryl-CoenzymeA (HGM-CoA) (Belkheiri, 2010; Bouguerne, 2012; Oumarou et al., 2012). In vascular endothelial cells, this inhibition of HMG-CoA reductase leads to up regulation of the expression and activity of endothelial nitric oxide synthase (Laufs et al., 1998; Döndaş et al. 2011) and then leads to NO-dependent vasorelaxation.

In the present study, there is a decrease in serum AST and ALT activity compared to the untreated sick animals which suggest a protective effect of our extract against damage of hepatic cells. These hepatoprotective effects of EEM confirm those of Pari and Kumar (2002) in rat with *Moringa* extract. Ouedraogo et al. (2013) reported that *Moringa oleifera* leaves prevent gentamicin-induced nephrotoxicity in rabbits. Many studies have shown a rise in transaminases during a hypertension induced by inhibition of NO synthesis (Maulood et al., 2013). Indeed, the authors associate the increase of serum transaminases to damage in hepatic,renal and cardiac cells (Gokcimen et al., 2007; Osman et al., 2010; Robert et al., 2011). The extract in reducing transaminase activity, thereby protecting the tissues of these organs against the deleterious effects of subacute endothelial dysfunction imposed on animals. Creatinin is known as a marker of renal function (Lameire et al., 2005). It is a product of the metabolism of proteins. Our sample did not significantly affect the total creatinin levels and the levels of serum total protein, suggesting that it would not interfere with the metabolism of these elements.

CONCLUSION

Our findings indicate that EEM inhibits the sub-acute hypertension induced by endothelial NO-synthase inhibitor, L-NAME. Moreover, our results showed that EEM improves lipid profile, hepatic and renal function parameters and then, indicate that EEM could be used to prevent cardiovascular system against deleterious effects of dyslipidemia, endothelial dysfunction and hypertension. In addition to that, EEM could prevent damage on hepatic and renal systems. These results partly justify the traditional use of *Moringa oleifera* leaves in the management of hypertension in rural environment of Burkina Faso. Subsequent researches will be based on arterial vessels to determine the molecular mechanisms by which EEM exerts its antihypertensive effects.

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