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Research Article

MECHANISMS OF THE HYPOTENSIVE ACTION OF *HARUNGANA MADAGASCARIENSIS* (HYPERICACEAE) STEM BARK AQUEOUS EXTRACT IN RATS

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A B S T R A C T

Harungana madagascariensis (Hypericaceae) is used in the center region of Cameroon for hypertension by traditional healers. Also no scientific works has been undertaken on this pharmacology aspect, the present study was aimed to assess the effects of an aqueous extract of *Harungana madagascariensis* (AEHM) on arterial blood pressure and the involved mechanisms in urethane anaesthetized Wistar rats. Their blood pressure was measured from the left common carotid artery connected to a pressure transducer. The AEHM (5, 10, 15 and 20 mg/kg) was administered via the right femoral vein in a pilot study in 4 groups of 5 animals each. *H. madagascariensis* produced a dose-related hypotension. The dose 20 mg/kg which produced the highest immediate hypotension and bradycardia from the 45th min to the end of the recording period (60th min) was selected for the mechanisms studies. The hypotension produced by 20 mg/kg dose of the extract was significantly ($P<0.05$) inhibited by atropine and yohimbine but not by propranolol, indomethacin or cimetidine. This indicates that H2-histaminergic, β2-adrenergic and cyclooxygenase pathways are not likely to be involved in the hypotension produced by the extract, however, its might contain active compounds possessing cholinergic-receptor agonist action and acting through a reduction of sympathetic outflow and reduction of synaptic norepinephrine. These results may explain the use of this plant by traditional healers to treat hypertension.

INTRODUCTION

Cardiovascular diseases (CVDs) remain the biggest cause of death worldwide. More than 17 million people died from CVDs in 2008. The percentage of premature deaths from CVDs ranges from 4% in high-income countries to 42% in low-income countries (WHO, 2011). Worldwide, raised blood pressure was estimated to cause 7.5 million deaths, about 12.8% of the total of all annual deaths (WHO, 2010). The prevalence of raised blood pressure was highest in the WHO African Region, where it was 46% for males and females combined (WHO, 2011). Effective treatment of hypertension with various classes of antihypertensive drugs has been associated with greater benefits (Turnbull *et al.,* 2008). Apart from the treatment of cardiovascular risk factors with pharmacological agents and the use of antithrombotic drugs, there is growing awareness of the role of dietary factors and herbal medicines in the prevention of CVDs and the possibility of their use in treatment. Proportions of the use of medicinal plants are higher in developing countries due to reduced accessibility to essential medications and a more marked herbalism tradition (WHO, 2003). Herbal medications have become more prominent in cardiovascular medicine among the various medicine specialties (Liperoti *et al.,* 2017). Despite enormous interests in the medicinal uses by consumers, there is still a great deal of confusion and misunderstanding about their identification and effectiveness (Izzo *et al.,* 2005). Therefore, the role of herbal medicines in CVDs still needs more scientific data proving their efficacy and safety.

Harungana madagascariensis is one of the most popular trees in African traditional medicine system, belonging to the Hypericaceae family. It is used as an abortifacient and antiseptic, in the treatment of hypertension (Biapa *et al.,* 2007), anemia, asthma, tuberculosis, fever, angina, diarrhea, dysentery, syphilis, gonorrhea, malaria, parasitic skin diseases,

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and wounds, as a natural source of dermatological agents and cosmetics (Burkill, 1985 ; Tona *et al.,* 1998; Emea, 1999; Erah *et al.,* 2003; Kamanzi *et al.,* 2004), asthma, liver diseases, diabetes, pancreatic and biliary problems (Adeneye *et al.,* 2008; Nicolas, 2012). Studies on bark or leaves revealed antihelminthiase properties (Koné and Kamanzi, 2006), anti-plasmodial (Lenta *et al.,* 2007), antidiabetic (Mangambu, 2014), antimicrobial activities (Etchiké *et al.,* 2011), analgesic and anti-inflammatory activities (Nwodo, 1989). A prenylated 1, 4-anthraquinone isolated from the hexane extract of the stem-bark of *H. madagascariensis* possess α-glucosidase inhibition and antioxidant activities (Kouam *et al.,* 2007).

There is however a need for pharmacological validation of this medicinal plant to justify its usage for the treatment of hypertension. Therefore, the aim of the present study was to investigate the blood pressure lowering effects and possible mechanism of action of an aqueous extract of *Harungana madagascariensis* stem bark in normotensive *Wistar* rats.

MATERIALS AND METHODS

Plant Material Collection and Extraction

Fresh *H. madagascariensis* stem barks were collected at Obobogo, Yaoundé (Center Region, Cameroon) in June 2015. The identification of the plant was done at the Cameroon National Herbarium where voucher sample were deposited under the registration number N° 4224 HNC. Bark pieces were dried under room temperature and powdered with an electrical grinder. Five hundred five grams of powder was introduced into 2 L of distilled water and boiled for 20 minutes. The resulting decoction was filtered through Whatman paper No. 3 and the filtrate was evaporated in an oven at 50°C. A brown extract powder (*H. madagascariensis* extract, 10.1 g) was obtained, giving a yield of 2%.

Experimental Animals

Twelve weeks old male albino *Wistar* rats weighing 200-250 g were obtained from the Animals House of the Department of Biological Sciences at the Higher Teachers' Training College Campus, University of Yaoundé I. They were housed in plastic cages under standard light (12-hour day/night natural cycle) at 25 ± 2°C and fed with standard diet and tap water *ad libitum*. The research was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the US guidelines (NIH publication #85-23, revised in 1985). All procedures were approved by the Cameroon National Ethical Committee (authorization number FW-IRB00001954).

Measurement of Blood Pressure and Heart Rate

The animals were anesthetized with an intraperitoneal injection of 15% urethane (10 mg/kg body weight). A polyethylene catheter was inserted into the right femoral vein for drug administration. Immediately after venous access, a bolus injection of heparin (30 IU) was injected to prevent intravascular blood clotting. The left carotid artery was cannulated and connected to a pressure transducer coupled to a Biopac® recording system, allowing the recording of the systemic blood pressure and heart rate. The animals were allowed for stabilization of the blood pressure for at least 30 min before the administration of any test substances.

Dose Response Effects of Harungana Madagascariensis Extract on Blood Pressure and Heart Rate

After the equilibration period, the dose-response effect of *H. madagascariensis* extract was determined by injection into the right femoral vein. Four doses of the *H. madagascariensis* stem bark aqueous extract (5, 10, 15 and 20 mg/kg) were administered to 4 groups of 5 animals each. These doses were selected following a screening test. The blood pressure and heart rate were again recorded for 1h as previously drescribed (Tom *et al.,* 2011). The extract was dissolved in distilled water.

Pharmacological Antagonist Studies

To study the hypotensive mechanisms of the *H. madagascariensis* extract, 5 groups of 5 rats each were prepared as outlined above. Cholinergic receptor (group 1), α_2-adrenoceptor (group 2), β-adrenoceptor (group 3), histaminergic (group 4) and cyclooxygenase (group 5) blockades were obtained by using respectively atropine (1 mg/kg), yohimbine (100µg/kg), propranolol (100 µg/kg), cimetidine (15 mg/kg) and indomethacin (5 mg/kg). Each drug was given intravenously and allowed to incubate for 5 min before a bolus injection of 20 mg/kg of the *H. madagascariensis* extract was infused. The corresponding blood pressure and heart rate changes were then recorded for 1h.

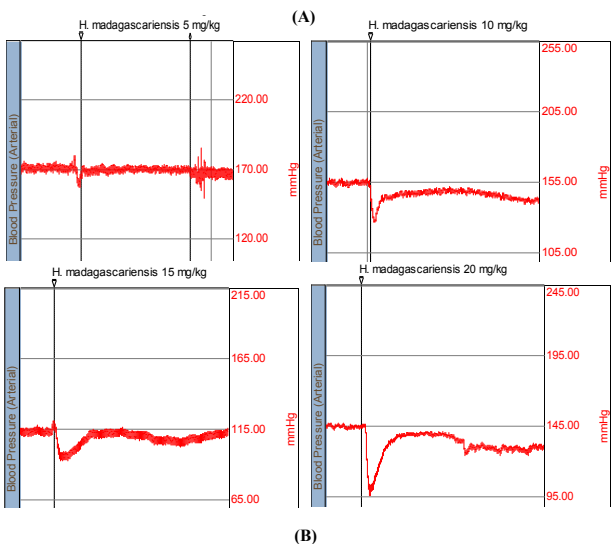
Data Analysis

The results are expressed as mean ± S.E.M. One-way analysis of variance (ANOVA) with Dunnett's post-test was performed using GraphPad Prism version 5.0 (GraphPad Software, San Diego, Ca, USA). The level of significance was defined at $P<0.05$.

RESULTS

Dose Response Effect of Harungana Madagascariensis Aqueous Stem Bark Extract on Arterial Blood Pressure

Intravenous administration of *H. madagascariensis* aqueous stem bark extract (5, 10, 15 and 20 mg/kg) caused an immediate reduction in blood pressure (Fig 1A). The decrease in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure was significant at 10 and 20 mg/kg as compared with the baseline value (Fig 1B). The effect on the DBP was greater than on the SBP.



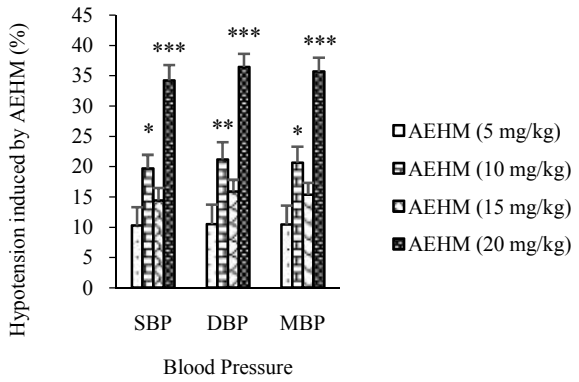


Fig 1 (A)Typical tracing showing the dose-dependent reductions of arterial blood pressure by the aqueous extract of *Harungana madagascariensis* stem bark (AEHM) and (B) the maximal immediate changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) after extract injection in anaesthetized rats. Each bar represents the mean ± S.E.M of five rats $^{*}P<0.05$; $^{**}P<0.01$;$^{***}P<0.001$ when compared to the initial value.

Time Course Effect of the Aqueous Extract of Harungana Madagascariensis on Heart Rate

As shown in Fig 2, the heart rate was not significantly changed during the recording period (60 min) after injection of the extract at doses of 5, 10 and 15 mg/kg. However, the 20 mg/kg dose resulted in a later significant decrease in heart rate from the 45th minute to the end of the recording period. The extract (20 mg/kg) induced a decrease in heart rate of 12.25 ± 2.54% ($P<0.05$), 15.24 ± 4.09% ($P<0.01$), 12.65 ± 3.47% ($P<0.05$) and 10.82 ± 3.62% ($P<0.05$) respectively at the 45th, 50th, 55th and the 60th min.

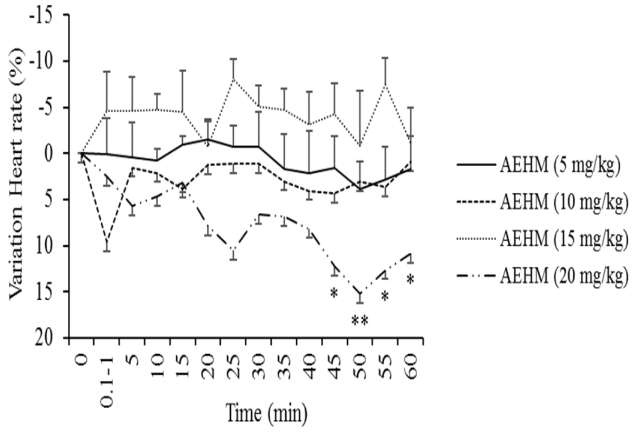


Fig 2 Time course effect of the aqueous extract of *Harungana madagascariensis* (AEHM ; 5, 10, 15 and 20 mg/kg) on the heart rate of anaesthetized rats. The results are present as the mean ± S.E.M of five rats $^{*}P<0.05$; $^{**}P<0.01$ when compared to the initial value.

Mechanism of Hypotensive Effect of Harungana Madagascariensis

The effects of atropine, yohimbine, propranolol, indomethacin and cimetidine on the hypotensive action of the aqueous extract of *H. madagascariensis* (20 mg/kg) were investigated. As shown in Fig 3, the pretreatment of anaesthetized *Wistar* normotensive rats with atropine sulphate (1 mg/kg) or yohimbine (100 µg/kg) significantly ($P<0.05$) reduced the hypotensive effect of the plant extract. However, the administration of cimetidine (15 mg/kg), propranolol (100 µg/kg) and indomethacin (5 mg/kg) did not significantly attenuate the reduction of blood pressure induced the *H. madagascariensis* stem bark extract.

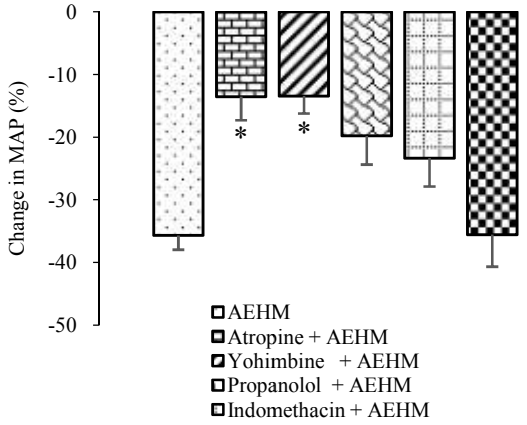


Fig 3 The maximal immediate changes in mean arterial pressure (MAP) after intravenous injection of the aqueous extract of *Harungana madagascariensis* (AEHM, 20 mg/kg) in anaesthetized rats. Some animals received additional pre-treatment of atropine (1 mg/kg), yohimbine (100 µg/kg), propranolol (100 µg/kg), indomethacin (5 mg/kg) or cimetidine (15 mg/kg) 5 min prior to the plant extract administration. Each bar represents the mean ± S.E.M of five rats. $^{*}P<0.05$ vs. the value without antagonist.

Effects of Antagonists on the Bradycardic Response of Harungana Madagascariensis

The late bradycardic response induced by *H. madagascariensis* stem bark extract (20 mg/kg) at the 45th minute was not significantly modified in the presence of of atropine (1 mg/kg), yohimbine (100 µg/kg), propranolol (100 µg/kg), indomethacin (5 mg/kg) and cimetidine (15 mg/kg) (Fig 4).

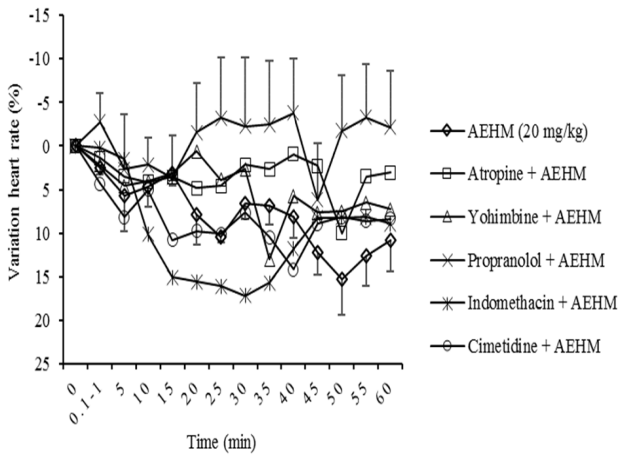


Fig 4 Variation in heart rate induced by the aqueous extract of *Harungana madagascariensis* (AEHM, 20 mg/kg) in anaesthetized rats in the absence and in the presence of atropine (1 mg/kg), yohimbine (100 µg/kg), propranolol (100 µg/kg), indomethacin (5 mg/kg) or cimetidine (15 mg/kg). The antagonists were injected 5 min prior to plant extract administration.

DISCUSSION

The aqueous extract of *Harungana madagascariensis* stem bark (Hypericaceae) (AEHM) induced a dose related decrease in systolic blood pressure, diastolic blood pressure and mean blood pressure on *Wistar* rats. These findings support the traditional use of the plant's stem bark for the treatment of hypertension. In addition, the data indicate that the extract at the highest dose studied (20 mg/kg) induces a significant

negative chronotropic effect from the 45th min to the end of the recording period (60th min). These results suggest that the active compounds of *H. madagascariensis* may be acting on the periphery of the cardiovascular sytem and directly on the heart. However, the hypotensive effect of AEHM was more apparent on the diastolic than on the systolic blood pressure. This is suggestive of a possible mechanism of action, which is mediated via changes in vascular peripheral resistance more than directly influencing the cardiac muscle, since the blood pressure during diastole is more dependent on the peripheral resistance. Future studies on the direct vascular effects of this plant are planned to better elucidate its hypotensive mechanism. In addition, the aqueous extract of *H. madagascariensis* stem bark has been found to contains alkaloids, flavonoids, tannins, triterpenes, phenols and saponins (Biapa *et al.,* 2007). These compounds are known for their cardioprotective and hypotensive activities and could be responsible for the hypotensive effect observed in this study. The hypotension produced by 20 mg/kg body weight dose of the extract was not blocked by propranolol. Even though propranolol is a non-specific β-blocker (Prichard, 1982), it is clear that the compounds present in the extract might not be acting through the β-adrenergic receptors. Indomethacin, because of its potency as an inhibitor of prostaglandin biosynthesis (Romero and Strong, 1977) was used to investigate the involvement of the cyclooxygenase pathway in the hypotensive effect of the extract. Pre-treatment of rats with indomethacin did not modify the blood pressure lowering effect of the extract, suggesting that cyclooxygenase mechanism is also not involved in the hypotension produced by the extract.

Vasodilation is an important aspect of the hypotensive agents. In this study, we evaluated *in vivo* the effect of histamine blocking on the hypotension induced by the plant extract. Vasodilation is by far the most predominant effect of histamine. The H1 and H2-histaminergic receptors mediating vasodilation are distributed throughout the resistance vessels in most vascular beds (Ebeigbe *et al.,* 1989; Leurs *et al.,* 1995). H2- receptors are located mainly on vasuclar smooth muscle cells and the vasodilator effects produced by their stimulation are mediated by cyclic Adenosine monophosphate (cAMP) (Ebeigbe and Talabi, 2014). In our study, H2-blockade was obtained by using cimetidine. Our results show that the effect of the extract remains unchanged in the presence of cimetidine, indicating that the hypotensive action of AEHM is not mediated through H2-histaminergic receptors.

Studies with atropine, the muscarinic blocker of acetylcholine which significantly ($P<0.05$) inhibit the hypotensive response of the extract indicated that it may contain compounds having muscarinic-receptor agonist action. The presence of acetylcholine-like substances in the aqueous extract of *H. madagascariensis* stem bark could therefore be evoked. The intravenous injection of acetylcholine is known to induced an immediate and transient drop in blood pressure resulting from cardiac slowing and vasodilatation. The slowing of the heart is explained by cell hyperpolarization following the opening of potassium channels that are directly related to G proteins (Kurachi and Ishii, 2003; Fleischmann *et al.,* 2004). Peripheral vasodilatation is secondary to the activation of a G protein-coupled to acetylcholine muscarinic receptors. This coupling leads to production of nitric oxide (NO) or a vasodilator substance called Endothelium Derived Hyperpolarizing Factor (EDHF), which has a relaxing effect on vascular smooth muscle (Tekano *et al.,* 2004; Jiang *et al.,* 2005). This could explain the decrease in the heart rate induced by the extract at a dose of 20 mg/kg. However, the direct vasorelaxant effects of this plant extract will be investigated in future studies.

When yohimbine was given, the hypotensive response to the extract was diminished in a significant way ($P<0.05$). Yohimbine inhibits α_2-adrenergic receptors, which increases sympathetic outflow leading to increased synaptic norepinephrine. Yohimbine, therefore, may have additive or antagonistic effects with other drugs that stimulate or inhibit α_2-adrenergic receptors or otherwise affect synaptic norepinephrine concentrations (Horn and Hansten, 2012). Our result means that the α_2-adrenoceptors blockade diminished the hypotensive effect of the extract and therefore suggest that the *H. madagascariensis* extract stimulates α_2-adrenergic receptors and thereby reduces sympathetic outflow and reduces synaptic norepinephrine, acting like clonidine, an α_2-adrenergic agonist whose antihypertensive effect is inhibited by yohimbine (Giovannitti *et al.,* 2015). However, the effect of the extract on the heart rate was not modify by the overall antagonists.

In conclusion, these results suggest that the aqueous stem bark extract of *H. madagascariensis* lowers blood pressure by a mechanism that does not involve H2-histaminergic, β_2-adrenergic, or cyclooxygenase pathways, and that the mechanism of action more likely involves muscarinic receptors activation, reduction of sympathetic outflow and reduction of synaptic norepinephrine. Further studies on the direct vascular effects of *H. madagascariensis* aqueous extract could be done to more understand its hypotensive mechanism.

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