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Preliminary Investigative Study on the Blood Pressure-Lowering Potential of Aqueous Leaf Extract of *Simarouba glauca* (AESG) on Normotensive Adult *Wistar* Rats

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Abstract

Studies have shown that plants possess medicinal properties and compounds are beneficial in managing and treating diseases, including high blood pressure and related cardiovascular conditions. *Simarouba glauca* (SG) has been widely reported to possess antibacterial activity, anti-oxidant, anti-proliferative and hemolytic activity; amongst others. However, there is paucity of data on its effect on blood pressure. Hence, the study research aimed at assessing the hypotensive prospect inherent in the aqueous leaf extract of *Simarouba glauca* (AESG) on normotensive male *Wistar* rats. The study was conducted using adult male *Wistar* rats (n = 3), a urethane/thiopental (1205/20 mg/kg) anesthesia and a chart paper attached to Ugo Basile Uni-recorder Model 400700 data capsule. Under full anesthesia, the rat's trachea and the carotid artery were cannulated for assisted respiration and blood pressure measurement. At stable variables; following the administration of 0.2 mL normal saline, the AESG was administered intravenously via the caudal vein at 2.5 and 5.0 mg/kg body weight dose respectively. The data was recorded on a chart; indicated the characteristic dose-dependent hypotensive effect of AESG on normotensive rats; at doses of 2.5 mg/kg and 5.0 mg/kg, with marked decreases in the systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) from basal levels of 127.83 ± 1.01 mmHg, 91.00 ± 1.00 mm Hg and 103.27 ± 0.99 mm Hg respectively. The outcome of the preliminary investigation indicates that the AESG demonstrated a hypotensive effect on the BP of normotensive male *Wistar* rats dependent on varying doses administered; indicative of further evaluation.

Keywords: Cardiovascular; Caudal Vein; Invasive Blood Pressure; *Simarouba glauca*.

Abbreviations: SG *Simarouba glauca;* AESG: Aqueous leaf extract of *Simarouba glauca;* SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; ACEI: Angiotensin converting enzyme inhibitors; ARA: Angiotensin receptor antagonists.

INTRODUCTION

Hypertension is a public health condition characterized by chronic cardiovascular disease and end-stage renal diseases (Fuchs and Whelton, 2020). Untreated hypertension predisposes risk factors like stroke, myocardial infarction, arteriosclerosis, cardiac arrest, heart attack, cardiomegaly and amongst others (Landazuri *et al*., 2017).

Some allopathic agents applied in the management of hypertension include; adrenergic antagonists (alpha and beta receptor blockers) like prazosin and atenolol, centrally acting sympatholytic agents (alpha-methyldopa, guanabenz and clonidine), calcium channel blockers (nifedipine and amlodipine), diuretics (hydrochlorothiazides), angiotensin converting enzyme inhibitors – ACEI (lisinopril and ramipril), angiotensin receptor antogonists – ARA (losartan and valsartan) and the aldosterone antagonists (spironolactone and eplerenone) have been extensively reported to elicit adverse effects like dry cough, severe hypotension, depressed libido and sometimes erectile dysfunction (Landazuri *et al*., 2017; Olowofela and Isah, 2017; Moke *et al*., 2022); as such, the antihypertensive effect achieved with these agents is always short lived. In addition to the arrays of these side effects, virtually all these antihypertensive agents are cost implicative, creating a huge burden in the purse of affected low-income earners worldwide (Lacy *et al*., 2008; Pr *et al*., 2014). Hence, there is the need to adequately evaluate the anti-hypertensive (hypotensive) potential of cheap and available plants with proven medicinal properties as have been the case in the last four decades (Tabassum and Ahmad, 2011; Pr *et al*., 2014).

There are a number of medicinal plants with folk history that have been applied to treat hypertension; a

few investigations have shown their effectiveness, while others have been disproved by scientific findings (Tabassum and Ahmad, 2011; Kamyab *et al*., 2021).

Literatures have reported vast findings on the ethno-medicinal benefits of *S. glauca* (Patil and Gaikwad, 2011; Ramasamy *et al*., 2022) with no record on the effect on cardiovascular system and blood pressure; hence this study.

MATERIALS AND METHODS

Collection of Plant Material and Preparation of Aqueous extract

Fresh leaves of *Simarouba glauca* were procured from *Cercobela* Farms®, Ubiaja. Fresh plant specimen was authenticated and deposited with voucher specimen No. UBH_S382 at Plant Biology and Biotechnology Department Herbarium, University of Benin. The plant leaves were properly washed with clean water and then dried at room temperature for twenty-eight (28) days. Fine powdery particles were obtained following pulverization of the dried crispy leaves of *S. glauca*. Five hundred grams (500 g) of the leaf powder was macerated in 2.5 L distilled water and stimulated intermittently for forty-eight hours (48 hrs.) to obtain a filtrate. The filtrate was lyophilized with a freeze-drier to obtain the aqueous extract (Osagie-Eweka *et al*., 2016).

Materials for Invasive Procedure

For the invasive procedure, the materials used included the following: An intravenous cannula, eighteen G needles, a surgical table, respiratory tubing (6″ pediatric Ryle's tube may be used). One milliliter tuberculin syringe, 5, 10 ml syringes, small (3″) and medium (5″) c, Adson dissecting forceps (toothed and non-toothed) (5″), artery forceps (5″), small and medium forceps (with teeth, blunt and pointed), a bulldog clamp, a surgical lamp, an insertion needle, a surgical blade, normal saline, a thread, adhesive tape and prepared stock solution of the aqueous extract with appropriate concentrations. Distilled water was used in the preparation of the required stock solution of the aqueous leaf extract of *S. glauca*.

Pressure Transducer Calibration Procedure

Calibration is an imperative step in the experiment; it was conducted with a sphygmomanometer at a specific pressure. The pressure cuff was disconnected from the sphygmomanometer; linked to the transducer with a physiograph data acquisition system. Inflating to a required specific pressure was performed to check the pressure transducer. The mathematical conversion factor to express the blood pressure was established. The calibration between the voltage (millivolts) and pressure in the data acquisition system was previously performed; results were automatically calculated relative to the system calibrated value (Ordodi *et al*., 2005).

Animal Experimental Procedure for Cannulation of the Caudal Vein

Adult male Wistar rats (210 - 220 g) were procured from the rat housing facility of Pharmacology and Toxicology Department, University of Benin. Experimental animals were anaesthetized with urethane/thiopentone (1250/20 mg/kg) (Amaechina and Omogbai, 2007; Wang *et al*, 2013) administered intra-peritoneally. An established protocol for invasive blood pressure assessment (Amaechina and Omogbai, 2007; Wang *et al*, 2013) was used. The caudal vein of the rat was cannulated with a heparinized saline-filled-23 G scalp-vein needle for the administration of extract intravenously and was fastened to the dissecting table dorsally. The cervical region was shaved and dissected open to reveal both the trachea and carotid artery (Plehm *et al*., 2006). The trachea was isolated, cleared of connective tissues and cannulated with a 2 mm diameter polythene tube for assisted respiration (Kramer and Remie, 2005). The carotid artery was isolated, cleared of adhesive tissues, and cannulated with a heparinized saline-filled Teflon polyethylene tube connected to a pressure transducer for the transmission of blood pressure variations to Ugo Basile Uni-recorder (Model: 400700).

An angle poised lamp with a 60 watts electric bulb is positioned over the anaesthetized animal, for the purpose of maintaining the temperature within normal range. When all the measurable variables remained stable as confirmed following the administration of normal saline, AESG was administered to experimental rats intravenously at two varying doses of 2.5 and 5.0 mg/kg respectively. This procedure was conducted in triplicate; the effects of the administered doses were recorded on the Ugo Basile chart recorder.

RESULTS

The data presented in **Table 1** reveal that AESG elicited significant ($P < 0.05$) dose-dependent decreases in the SBP, DBP and MAP at 2.5 mg/kg (122.00 ± 1.15 mmHg, 84.67 ± 2.40 mmHg; 97.10 ± 1.99 mmHg) and 5.0 mg/kg (84.00 ± 2.31 mmHg, 62.67 ± 1.45 mmHg; 69.80 ± 1.73 mmHg) doses respectively; compared to the experimental rat treated with normal saline (127.83 ± 1.01 mmHg, 91.00 ± 1.00 mmHg; 103.27 ± 0.99 mmHg). Likewise, the polygraph presented in Figure 1 indicates marked dose-dependent decreases in the hemodynamic parameters considered at 2.5 and 5.0 mg/kg body weight respectively, when compared to the normal saline group.

Table 1. Effect of AESG on Hemodynamic Parameters of Normotensive Rats.

Parameters	**Systolic Blood Pressure** (mmHg)	**Diastolic Blood Pressure** (mmHg)	**Mean Arterial Pressure** (mmHg)
Normal Saline	127.83 ± 1.01	91.00 ± 1.00	103.27 ± 0.99
AESG 2.5 mg/kg	122.00 ± 1.15	84.67 ± 2.40	97.10 ± 1.99
AESG 5.0 mg/kg	84.00 ± 2.31$^{*\#}$	62.67 ± 1.45$^{*\#}$	69.80 ± 1.73$^{*\#}$

All values expressed as Mean ± SEM, where n=3, all data were analyzed by using one-way ANOVA followed by Tukey's post hoc test. **P<0.05 compared to the normal saline control group;* $^{\#}$*P<0.05 compared to AESG 2.5 mg/kg group.*

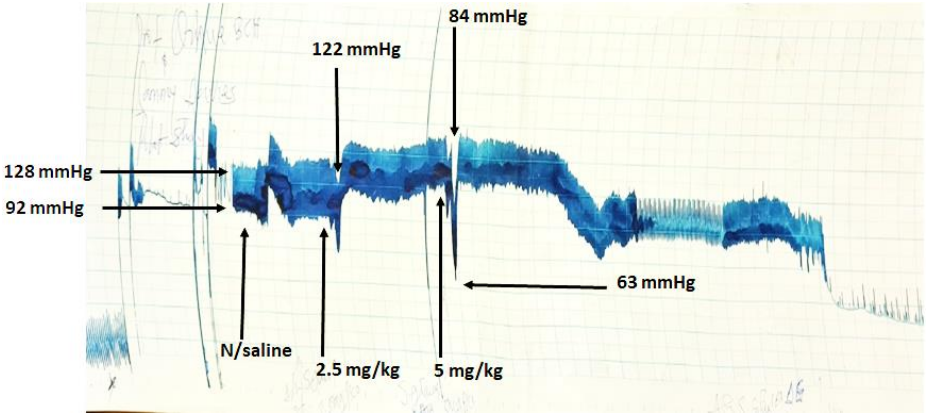

Figure 1. The Effect of AESG on Blood Pressure of Normotensive Rats.

DISCUSSION

The study reveal a 4.6 % decrease in systolic blood pressure (SBP), 7.0 % decrease in diastolic blood pressure (DBP); 6.0 % decrease in mean arterial pressure (MAP) at 2.5 mg/kg compared to the normal saline group of the experimental rats. Furthermore, at 5.0 mg/kg. AESG showed a significant ($P < 0.05$) decrease in SBP (34.29%), DBP (31.13%) and MAP (32.41%) relative to the normal saline group. Additionally, the group treated with 5.0 mg/kg showed 31.15%, 25.98%, 28.12% significant ($P < 0.05$) decreases in SBP, DBP and MAP respectively relative to the group treated with 2.5 mg/kg. The outcome of the study therefore indicate a better and promising blood pressure lowering effect at 5 mg/kg when administered intravenously.

The data presented in **Figure 1** likewise indicate that there was instananeous recovery of the blood pressure to the basal level which may be obviously not unconnected to the reflex compensatory mehanism aimed at restoring the blood pressure to normal after the adminisration anti-hypertensive (Kuogias *et al*., 2010). In the present study, a similar effect was observed at a dose of 5.0 mg/kg. However, the recovery was not sustained as there was a second phase derease in the blood pressure which was more sustained as observed in **Figure 1**. Thus, the outcome and resultant effect on blood pressure suggests that *S. glauca* may possess some promising active principles capable of eliciting hypotensive effect on the cardiovascular system.

In fact, studies have reported the hypotensive and (or) the blood pressure-lowering potentials of several known medicinal plants (Anaka *et al*., 2009; Imafidon and Amaechina, 2010; Amaechina *et al*., 2017; Alawode *et al*., 2021; Kamyab *et al*., 2021) with less adverse effects. However, pharmacologist must continue to conduct systematic inquiry into the therapeutic benefits of plants with hypotensive potentials in the quest to discover the most effective mechanistic treatment approach for hypertension considering the complexities associated with the condition. Accordingly, it is recommended that *S. glauca* may be subjected to detailed and extensive laboratory investigation to ascertain its pharmacological pertinence.

CONCLUSION

The outcome of the preliminary investigative study of AESG (Aqueous Leaf Extract of *S. glauca*) on cardiovascular system indicate a strong blood pressure lowering potential and a promising vaso-relaxant bioactive compound that may be beneficial in managing hypertension related conditions

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All authors have approved the final version of the manuscript.

***Conflict of Interests*:** Authors state that there is no conflict of interest in this research output.

***Ethical Approval*:** The experimental protocols were approved by the Faculty of Pharmacy, University of Benin Ethics Committee with reference number EC/FP/021/11.

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