Original Article

# An Investigation into the Antihypertensive Effects of *Sclerocarya birrea* on Treadmill Exposed Rats

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## ABSTRACT

**Introduction:** High blood pressure (BP) is a common problem experienced by many people world-wide. Medications used to treat it, however, have large side effects profiles. As a result, alternative medicines with less adverse effects are required to treat this illness. *Sclerocarya birrea,* locally available plant, has been used to treat a wide range of illnesses including high BP. This study was aimed at investigating the effects of an aqueous extract of *S. birrea* stem bark (SBE) on BP in treadmill exposed animals.

**Methods:** One kilogram of *S. birrea* stem bark was collected, dried, and extracted using water. It was then filtered and evaporated using a rotary evaporator, and the crude extract was weighed and dissolved in distilled water for use on each day of the experiments. 55 Sprague-Dawley rats were used in the study. Baseline BP readings for each animal used were recorded using tail-cuff plethysmography. Animals were then exposed to exercise on a treadmill for 15 min at 40 m/s. BP was recorded soon after exercise, and either SBE (50-400 mg/kg) or the test drugs (propranolol, nifedipine, or hydrochlorothiazide) were administered. Animals in the control group were given distilled water. BP was subsequently recorded at 15 min intervals for 30 min.

**Results:** SBE significantly ($P < 0.05$) lowered systolic BP, mean arterial BP, and heart rate. Nifedipine lowered systolic BP and mean arterial BP significantly as compared to SBE and the other agents. SBE, however, was the only agent to have a significant effect on heart rate.

**Conclusion:** SBE lowers heart rate, systolic, and mean arterial BP. It can, therefore, be used in patients with high BP. More research, however, will need to be done to determine the exact mechanism by which SBE lowers BP.

**Keywords:** Blood pressure, Cardiovascular, *Sclerocarya birrea*, Tail-cuff plethysmography, Treadmill

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## INTRODUCTION

High blood pressure (BP) is a common disease that is associated with persistent elevated arterial BP (140/90 mmHg).[1] Among cardiovascular diseases, it is the most prevalent[2] with the African region having the highest hypertension prevalence (46% of adults aged over 25 years of age).[3,4] Furthermore, in African populations, the mortality rates from hypertension in the 30-70 year age groups are higher than those in developed countries.[3,5] In Zimbabwe, hypertension has become a major health problem. Statistics released by the WHO (2014) for Zimbabwe and showed that hypertension-related deaths reached 2170 or 1.71% of total deaths in 2014. The age-adjusted death rate is 31.49 per 100,000 people, which ranks Zimbabwe number 21 in the world.[6]

Currently, the use of anti-hypertensive agents in Zimbabwe is extensive. The Zimbabwean Essential Medicines List and Standard Treatment Guidelines book (EDLIZ) recommends the use of beta-blockers and thiazide diuretics as first-line agents to treat and manage hypertension, while angiotensin converting enzyme inhibitors, calcium channel blockers, and alpha-blockers are indicated for use as second-line agents. These drugs, however, are expensive and have large

side effects profiles and might not be ideal to use in patients with other conditions. It is for some of these reasons that herbal medicines for treating hypertension may be needed.

Plant-derived herbal medicines have been used for years by many different cultures around the world for the treatment of many illnesses. This is because these medicines are easily available, and are more harmonious with nature and are cheaper than modern medicines.[7] The folkloric use and anecdotal evidence of some plants have shown great promise in the discovery of novel therapies against many illnesses. *Sclerocarya birrea*, a plant belonging to the Anacardiaceae family, is an example of such a plant that has been used ethnomedicinally for treating hypertension. Various morphological parts of the plant have been used in African folk medicine for the management, control, and/or treatment of many human illnesses, including: Malaria, fever, diarrhea, hypertension, dysentery, stomach disorders, headaches, toothache, backache, dysmenorrhea, body pains, schistosomiasis, diabetes mellitus, and arthritis. Watt and Breyer-Brandwijk,[8] Hutchings *et al*.,[9] Van Wyk *et al*.,[10] and Ojewole[11] reported pharmacological properties of *S. birrea* include: Anti-inflammatory,[11] anti-bacterial,[12] anti-fungal,[13] hypotensive,[14] hypoglycaemic effects,[11,15] use in childbirth,[16] and anti-cancer effects.[17]

The current study was performed to determine the effects of *S. birrea* on BP in normotensive rats subsequent to exercise using a treadmill, and comparing these effects with those of other anti-hypertensive drugs. Gosse *et al*.[18] observed that BP measured at maximal exercise was a better prognostic indicator than resting clinic BP. This is because dynamic stress tests measuring BP are believed to be superior in indicating the patient's BP during ordinary daily activities than BP measurements at rest.[19,20] As a result, exercise testing is supposed to provide accurate estimates of BP response to physical stress.[21,22] In addition, it has been hypothesized that the stress of exercise may unmask a latent tendency toward hypertension.[23]

This study was, therefore, aimed at determining whether exercise-induced changes in BP detected after treadmill stress testing in normotensive rats, could be altered with the oral administration of *S. birrea* or oral anti-hypertensive agents currently used in Zimbabwe.

## MATERIALS AND METHODS

Experimental protocols and procedures used in this study were approved by the Joint Research and Ethics Committee (JREC) of the University of Zimbabwe (JREC 327/13) and conformed to "Handbook of laboratory animal management and welfare."[24]

### Plant Material

Fresh stem bark of *S. birrea* (family: Anacardiaceae) was collected from Plumtree and Gwanda (Zimbabwe) in April 2013. Identification and authentication of the plant's material were done by a taxonomist, and a voucher specimen was stored (reference number SC-CM-04/12).

### Preparation of *S. birrea* Stem Bark Aqueous Extract (SBE)

Amount of 1 kg of fresh stem bark was air-dried at room temperature (26°C ± 1°C) for 2 weeks. The dried stem bark was milled (in a Waring commercial blender) into fine powder, and macerated in 2.5 L of distilled water, with occasional shaking, for 48 h at room temperature (26°C ± 1°C). The powdered stem bark was extracted with 2.5 L of distilled water before being filtered. A rotary evaporator was used to concentrate the aqueous extract by drying it at 60°C ± 1°C. Freeze-drying gave 52.5 g/kg (i.e., 5.25% yield) of a dark-brown, powdery, crude SBE. Aliquot portions of the plant's crude stem bark extract residue were weighed and dissolved in distilled water (at room temperature) for use on each day of the experiments.

### Animals and Animal Husbandry

55 Sprague-Dawley rats (150-200g) were used. The animals were kept and maintained under conventional laboratory conditions of temperature, humidity, and light. They were allowed free access to food (standard pellet diet) and drinking tap water, however, prior to commencing the experiments, animals were fasted for 16 h but had access to drinking tap water. All the animals were adapted to walk on a treadmill for 10 min at 5 m/min daily for 5 days. In addition, the animals were also acclimatized to the procedure of BP measurement by being exposed to the tail-cuff plethysmography machine daily. On the day of the experiment, the rats were warmed up in an animal heating controller (TaII-heating-B-Biopac Systems, Inc.) at 32°C for 30 min, and the baseline BP was recorded using a non-invasive tail-cuff plethysmography (Biopac Systems, Inc., NIBP200A). They were then exposed to exercise by a treadmill at 40 m/s for 15 min (Treadmill Control LE 870-Panlab Harvard Apparatus). The experiment was conducted in two phases with experiment 1 using 25 animals and experiment 2 using 30 animals.

#### *Experiment 1: Determining the in vivo effect of S. birrea extract on treadmill exposed rats*

The animals used for this 1st phase were assigned into the following 5 groups with each group having 5 animals: Group A, Control; Group B, 50 mg/kg; Group C, 100 mg/kg; Group D, 200 mg/kg; and Group E,

400 mg/kg. These doses were chosen based on doses we are currently working within our laboratories. Just after exercise, i.e., at 0 min, each test animal received a single dose of *S. birrea* which was administered through gastric lavage while the control animals were given equivalent volumes of distilled water. BP and heart rate were measured after exercise at 0, 15, and 30 min.

### *Experiment 2: Comparing effects of S. birrea against some of the standard anti-hypertensives prescribed in Zimbabwe*

Animals were separated into 6 groups with 5 animals in each group and were exposed to the treadmill. Just after exercise, i.e., at 0 min, each group of animals received a single dose of either *S. birrea* or the test drugs administered through gastric lavage while the control animals were given distilled water. Doses were administered to the test animal groups as follows; Group 1: Control; Group 2: SBE 200 mg/kg (mean effective dose); Group 3: Propranolol 50 mg/kg; Group 4: Nifedipine 35 mg/kg; and Group 5: Hydrochlorothiazide (HCT) 50 mg/kg.

### Statistical Data Analysis

Data obtained was pooled and presented as means (±standard error mean) and plotted with Graph Pad PRISM5® for graphical representation. In all cases, BP and heart rate readings before the experiment were taken as the baseline values. Statistical differences between the test and control groups were analyzed using one-way analysis of variances and followed by Dunnett's *post-hoc* test. Differences were considered significant if $P \leq 0.05$.

## RESULTS

### Vasorelaxant Effect of SBE

Warming animals in the animal heating controller at 32°C for 30 min non-significantly elevated normal BP readings (6 ± 2 mmHg) in normotensive rats. This resulted in animals starting with a basal systolic BP of 133 ± 10 mmHg ($n = 5$ for each group). Subsequent to exercise exposure, BP was elevated to 146 ± 8 mmHg. Post-exercise administration of *S. birrea* (50-400 mg/kg) lowered the systolic BP with SBE 200 mg/kg and 400 mg/kg showing significant ($P < 0.05$) pressure reductions (Figure 1). Reductions in mean arterial pressure were also observed subsequent to SBE administration. Of the different concentrations of SBE administered, only SBE 400 mg/kg significantly ($P < 0.05$) lowered arterial pressure readings in the test animals versus the control animals (Figure 2). *S. birrea* (100-400 mg/kg) also significantly lowered heart rate. SBE (50 mg/kg) had no significant effects on heart rate (Table 1).

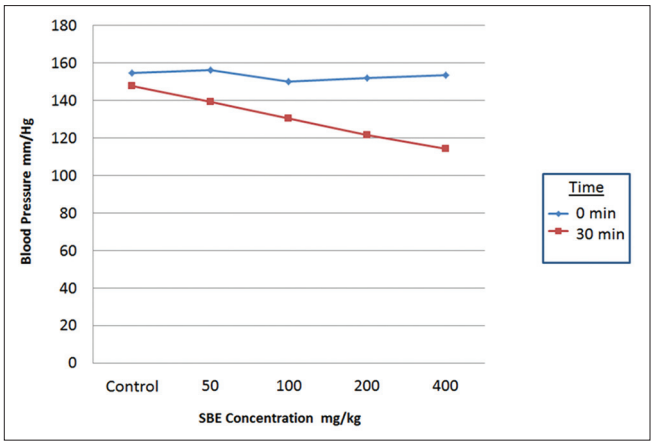


**Figure 1:** Systolic blood pressure (BP). The effect of *Sclerocarya birrea* stem bark aqueous extract (50-400 mg/ml/kg) on systolic BP at 0 min (soon after treadmill exposure) and 30 min versus the control

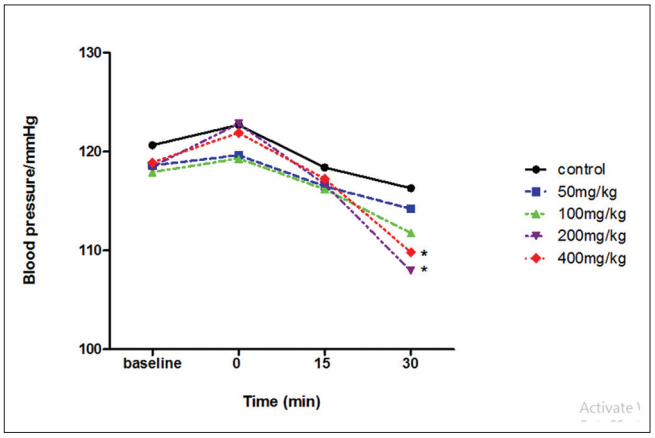


**Figure 2:** Mean arterial blood pressure (BP). The effects of *Sclerocarya birrea* stem bark aqueous extract (50-400 mg/kg) on mean arterial BP versus the control at 0, 15, and 30 min. *$P < 0.05$

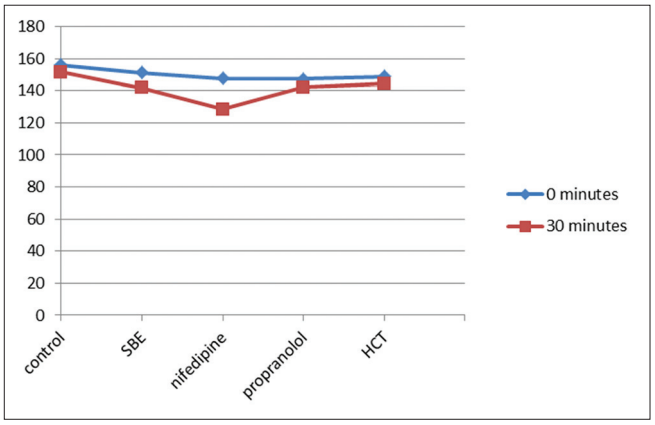


**Figure 3:** Systolic blood pressure (BP). The effects on systolic BP of *Sclerocarya birrea* stem bark aqueous extract (200 mg/kg), nifedipine 35 mg/kg, propranolol 50 mg/kg, and hydrochlorothiazide 50 mg/kg at 0 min (soon after treadmill exposure) and 30 min versus control

### Comparing the Effects of *S. birrea* with Some Commonly used Anti-hypertensives

After 30 min, animals that received nifedipine had the lowest systolic BP reading as compared to those that received SBE, propranolol, or HCT (Figure 3). SBE significantly lowered mean arterial pressure as compared to propranolol and HCT, however, nifedipine had a more significant effect (Figure 4). SBE significantly lowered heart rate, while nifedipine increased heart rate (Table 2).

## DISCUSSION

Our study shows that *S. birrea* (100-400 mg/kg) significantly ($P < 0.05$) lowered systolic BP and heart rate subsequent to increases that occur following dynamic exercise. In addition, SBE (400 mg/kg) also significantly decreased mean arterial pressure versus control. This correlates with data published by Ojewole (2006) which showed the hypotensive effects of SBE leaf extract on hypertensive dahl salt-sensitive rats. The observed *in vivo* results, however, contradict previous results observed in an *in vitro* study conducted in our laboratory,[25] whereby *S. birrea* leaf extracts resulted in a contraction of vascular smooth muscle. The observed differences between the *in vivo* and *in vitro* studies could be as a result of possible metabolic/structural changes that occur to *S. birrea* subsequent to metabolism by digestive enzymes/processes.

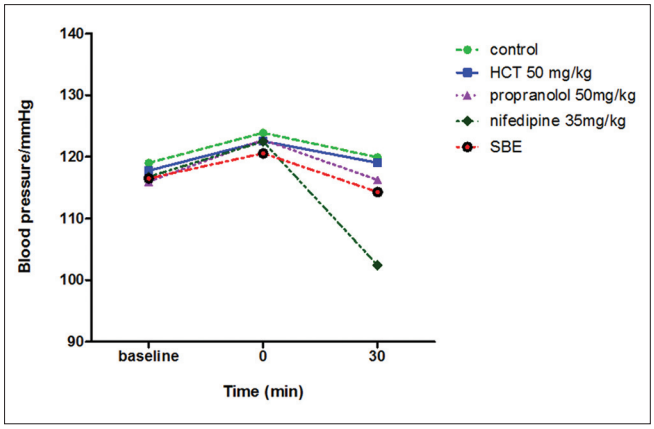


**Figure 4:** Mean arterial blood pressure. The effects on mean arterial pressure of *Sclerocarya birrea* stem bark aqueous extract (200 mg/kg), nifedipine 35 mg/kg, propranolol 50 mg/kg, and hydrochlorothiazide 50 mg/kg versus control

Dynamic exercise can elicit cardiovascular abnormalities not present at rest.[26] It is a preferred method for testing because it puts a volume stress rather than a pressure load on the heart. Systolic BP recorded at maximal exertion during dynamic exercise, or immediately after ceasing the exercise is considered clinically useful as it is an approximation of the hearts inotropic capacity.[26] Systolic BP rises with increasing dynamic work, whereas diastolic pressure remains about the same.[26] Increasing dynamic work increases oxygen uptake during respiration[27] which could result in the formation of reactive oxygen species (ROS). Increases in ROS have been associated with the development of vascular endothelial dysfunction and the development of hypertension.[28]

The formation of ROS could account for the increases in BP observed soon after exercise. Exercise is postulated to generate free radicals by other means, including: (1) Increases in epinephrine and other catecholamines that can produce oxygen radicals when they are metabolically inactivated, (2) production of lactic acid that can convert a weakly damaging free radical

**Table 1: Heart rate**

| Blood Pressure | Control | SBE 50 mg/kg | SBE 100 mg/kg | SBE 200 mg/kg | SBE 400 mg/kg |
|---|---|---|---|---|---|
| Baseline | 389.80±7.0 | 374.93±13.90 | 375.38±13.63 | 375.02±5.85 | 352.76±19.6 |
| 0 min | 402.01±8.86 | 391.48±11.32 | 401.12±13.54 | 392.76±5.20 | 394.68±9.56 |
| 15 min | 394.25±7.79 | 383.99±10.57 | 389.07±14.67 | 377.53±5.32 | 368.72±6.87 |
| 30 min | 388.11±8.14 | 375.88±10.85 | 375.92±14.87 | 365.24±8.55 | 352.54±9.53 |
| BP (mmHg) change | 13.9 | 15.6 | 25.2 | 27.52 | 42.14 |
| % change (BP after treadmill-BP after SBE/water) | 3.46 | 3.98 | 6.28 | 7.01 | 10.67 |
| *P* value versus control | | 0.2794 | 0.0484* | 0.0477* | 0.0443* |

The effects of SBE (50-400 mg/kg) on heart rate versus control. *$P$<0.05. BP: Blood pressure, SBE: *Sclerocarya birrea* stem bark aqueous extract

**Table 2: Heart rate**

| Blood Pressure | Control | Nifedipine 30 mg/kg | HCT 50 mg/kg | Propranolol 50 mg/kg | SBE 200 mg/kg |
|---|---|---|---|---|---|
| Baseline mmHg | 378.60±13.5 | 377.30±18.49 | 423.04±7.85 | 395.918±5.97 | 393.22±9.16 |
| 0 min (mmHg) | 397.31±8.55 | 398.08±17.47 | 436.15±9.98 | 395.16±9.42 | 432.15±9.16 |
| 30 min (mmHg) | 388.51±8.55 | 416.92±17.67 | 425.35±5.89 | 382.68±6.38 | 409.32±9.27 |
| Change in BP (mmHg) | 8.8 (decrease) | 18.84 (increase) | 10.8 (decrease) | 12.48 (decrease) | 22.83 (decrease) |
| % Change in BP | 2.21 | 4.73 | 2.47 | 4.17 | 5.28 |

The effects on heart rate of SBE 200 mg/kg, nifedipine 30 mg/kg, HCT 50 mg/kg, and propranolol 50 mg/kg versus control. SBE: *Sclerocarya birrea* stem bark aqueous extract, BP: Blood pressure, HCT: Hydrochlorothiazide

(superoxide) into a strongly damaging one (hydroxyl), and (3) inflammatory responses to secondary muscle damage incurred with overexertion.[29] Studies by Kumar and Das[30] and Ceriello,[31] observed that the formation of ROS could account for the formation of hypertension. Since SBE has been reported to possess anti-oxidant effects,[32,33] this could account for the possible decrease in BP observed after SBE ingestion. This anti-oxidant effect has been linked with the phytochemicals present in *S. birrea*.

SBE-derived phytochemicals include phenolic catechin derivatives, e.g., epicatechin gallate, gallic acid, and flavonoids, e.g., quercetin and kemferol, proanthocyanidins, and high molecular weight tannins.[34-36] The proanthocyanidins, such as procyanidin oligomers from *S. birrea*, have been postulated to be scavengers of reactive oxygen and nitrogen species.[37,38] Other phytochemicals present in *S. birrea* bark such as the catechins have also been reported to possess anti-oxidant effects.[39,40] The effects of these phytochemicals could possibly account for the observed effects of SBE.

Our study also involved comparing the effects of *S. birrea* with the effects of some of the drugs currently used for hypertensive treatment in Zimbabwe. We observed that *S. birrea* and nifedipine lowered systolic BP versus control when compared to the other agents. This could be because nifidepine rapidly lowers BP as it is rapidly and fully absorbed in the body,[41] which could account for the observed effects. Propranolol and HCT had minimal effects on systolic BP soon after exercise. Propranolol undergoes first pass metabolism resulting in low oral bioavailability which could then result in reduced amounts of drug getting to the target area. In addition, the anti-hypertensive effect of HCT has a slow onset of action which requires up to 2 months for the full expression of these effects.[42] These could account for the observed results.

Heart rate results show that although the heart rate of the animals that were on propranolol and HCT decreased, these decreases were not significant. Animals that were dosed with nifedipine, however, had increased heart rate readings. This is because short-acting calcium antagonists such as nifedipine, cause an increase in sympathetic nerve activation and reflex tachycardia.[43] These changes in heart rate were also not significant when compared with the control.

## CONCLUSION

In summary, *S. birrea* lowers systolic BP, heart rate, and mean arterial pressure. The exact mechanism by which *S. birrea* does this is not yet clear and more research needs to be conducted.

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