Cardiovascular Effects of *Vernonia amygdalina* in Rats and the Implications for Treatment of Hypertension in Diabetes.

Idowu Adewumi Taiwo[1]*, Peter Godwin Chikwenye Odeigah[1], Smith Ishmael Jaja[2], Frank Babatunde Mojiminiyi[3].

1. Department of Cell Biology and Genetics, Faculty of Science, University of Lagos, Lagos 101017. Nigeria.
2. Department of Physiology, College of Medicine, University of Lagos, Idi-Araba, Lagos 101017, Nigeria.
3. Department of Physiology, College of Health Sciences, Danfodio University, Sokoto 840001, Nigeria.

tai_dex@yahoo.com podeigah2003@yahoo.com

Abstract: Cardiovascular effects of aqueous extract of *Vernonia amygdalina* was investigated in normotensive Sprague-Dawley rats weighing 200-250g. Intravenous (femoral vein) administration of the extract at doses of 5.0 and 10.0mg/kg caused a bi-phasic alteration of blood pressure: an initial transient rise in mean arterial pressure which later fell to a considerably lower level than the starting blood pressure. This pattern of response was most clearly noticeable with the dose of 10 mg/kg whereby the mean arterial pressure of 73.7±3.4 mmHg rose to 101.9±4.1 mmHg in the first phase (P<0.01) before it finally fell to 60.2±2.5 mmHg in the second and final phase. Although higher doses (50 and 100mg/kg) caused more significant reduction in mean arterial pressure than the lower doses, the initial temporary elevation in blood pressure was not observed. Cumulative addition of the plant extract to isolated rings of aorta precontracted with noradrenaline produced a dose-dependent relaxation of the aortic smooth muscle. Maximum relaxation of 31.3±3.1% was observed with extract concentration of 2.7 mg/ml. These findings suggest that *V. amygdalina* has antihypertensive effect, and this could be mediated through direct vaso-relaxant mechanism. The implication of these results for the treatment of hypertension associated with diabetes is discussed.
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Key words: aortic rings; cardiovascular; hypertension; *V. amygdalin*a; diabetes.

1. Introduction

There is considerable evidence that the incidence of hypertension and diabetes is rising in both the developed and the developing countries (Swalocki et al, 1989; Wokoma, 2002). This is particularly so in rural and developing communities where there are gradual changes in lifestyles to those of more developed and urban societies. Besides, hypertension has been observed to be highly prevalent in diabetic patients (Swales, 1990; Mbanya, 1993). The association is so close that it is often necessary to screen a newly diagnosed diabetic for hypertension and *vice versa*. Several explanations have been put forward to explain this association: the roles of obesity, insulin resistance, renal factors, and cardiovascular control systems have been discussed in considerable detail in other reports (Fournier et al, 1986; Swales, 1990; Mbanya 1993). Moreover, emerging evidence has indicated an increasing incidence of metabolic syndrome, a cluster of metabolic and cardiovascular disorders including insulin resistance, hypertension, and noninsulin-dependent diabetes ,mellitus (NIDDM).

According to Osuntokun (1992) and some others (Okesina et al, 1996; Wokoma, 2002), the frequency of diabetes complicated with hypertension in Africa, particularly in Nigeria, is 25-42 per cent. In our opinion, this figure does not represent the true prevalence rate because most of the studies were group-oriented and hospital based. These and other available data, though limited, suggest a high frequency of diabetes associated with hypertension in Nigeria. Epidemiological studies are required to ascertain the true prevalence rate of this problem in Nigeria and many other developing countries.

The management of diabetes has been a major problem in tropical Africa including Nigeria (Gill, 1990; Naidu, 1992). Complications with hypertension and other cardiovascular diseases constitute additional difficulties to the management problem. Fortunately, several countries in the world are endowed with plant biodiversity, and there is presently a growing awareness about the importance of native plant remedies in health care delivery system. In many parts of the world especially in the poor countries, efforts are now being directed towards investigating therapeutic efficacy of locally available medicinal herbal products because they are conceived to be safer and more readily available.

Vernonia amygdalina Del. (Astereaceae) is a widely distributed plant used for dietary and medicinal purposes in Nigeria. Its hypoglycaemic effect and possible use in diabetic therapy have been discussed in previous reports (Ogbuokiri et al, 1989). The present investigation was designed to examine the effect of *V. amygdalina* on blood pressure, heart rate, and smooth muscle contractile response in normal rats. The results are expected to stimulate further studies, interest and discussions as regards better understanding, treatment and control of hypertension associated with diabetes in developing countries.

2. Materials and Methods

2.1 Experimental Animals and Plant Extraction

Adult Sprague-Dawley (SPD) rats of both sexes weighing 200-250g were obtained from the Laboratory Animal Centre of the College of Medicine, University of Lagos. They were randomly divided into groups of 5-6 rats per cage for the experiments. Aqueous extract from the powdered dried leaves of *Vernonia amygdalina* was obtained using the Soxhlet extraction procedure.

2.2 Cardiovascular Measurements

The blood pressure and the heart rate were determined using standard procedure as described by previous workers (Obiefuna et al, 1991). In brief, the rats were anaesthetized with a combination of 25% urethane (Sigma) and 1% chloralose (Sigma) by intraperitoneal (i.p.) injection. The trachea was exposed by gentle dissection and immediately cannulated to improve ventilation. The femoral artery and vein were similarly exposed and cannulated. The cannulated artery was used for blood pressure and heart rate measurements while the vein was for administration of graded doses (5.0, 10.0, 50.0 and 100.0mg/kg) of the plant extract. Heparin (500 i.u./kg) was injected intravenously to prevent intravascular clotting. The arterial cannula was connected to a pressure transducer which was coupled to a polygraph for cardiovascular recordings. Heart rate was obtained from blood pressure pulses for 15 seconds and then converted to beats/minute.

2.3 Isolated Tissue Experiment

Contractile responses of aortic smooth muscle to *V. amygdalina* was determined through an *in vitro* study (Obiefuna et al (1991). Briefly, the rats were sacrificed by cervical dislocation after which their thoracic aorta were removed, freed of connective tissue, cut into 2 mm ring segments and placed in a petri dish containing physiological salt solution. The solution was continuously bubbled with 95% O_2. The aortic ring segments were then suspended from a stainless steel rod in a 20ml organ bath containing physiological salt solution containing 5% dissolved CO_2. Varying concentrations of plant extracts (0.1, 0.3, 0.9, and 2.7 mg/ml) were added cummulatively to the bath to determine its effect on the noradrenaline precontracted aortic rings.

2.4 Data Analysis

All results are presented as mean $\pm$ SEM. Blood pressure was expressed as mean arterial pressure (MAP). The mean arterial pressure for each rat was calculated from the systolic and the diastolic arterial pressure (AP) using the formula below (Meyer, 1980):

$$MAP = \text{Diastolic AP} + 1/3(\text{Systolic AP} - \text{Diastolic AP})$$

Differences between means were compared using the student's t test. When the comparison involved more than two groups, one-way analysis of variance (ANOVA) was used. P values less than 0.05 were considered significant in all cases.

3. Results

3.1 Effect of Intravenous Injection of *V. amygdalina* on Blood Pressure and Heart Rate

At lower doses (5.0 and 10.0 mg/kg), the extract of *V. amygdalina* caused a dose-dependent bi-phasic alteration of both the systolic and the diastolic blood pressure. This was most clearly observed with the dose of 10 mg/kg that caused a transient rise in mean arterial pressure from a starting level of 73.7 ± 3.4 mmHg to a higher level of 101.9 ± 4.1 mmHg ($P<0.01$) in the first phase (Figure 1). The mean arterial pressure then fell to a level (60.2 ± 2.5 mmHg) that is significantly lower than the starting ($P<0.05$) and the first phase ($P<0.01$) values respectively. Intravenous injection of 10 ml/kg of normal saline (control) did not significantly affect the blood pressure. At higher doses (50 and 100mg/kg), the temporary hyperglycaemic phase was not noticeable; however, the mean arterial pressure fell significantly below the starting level ($P<0.05$).

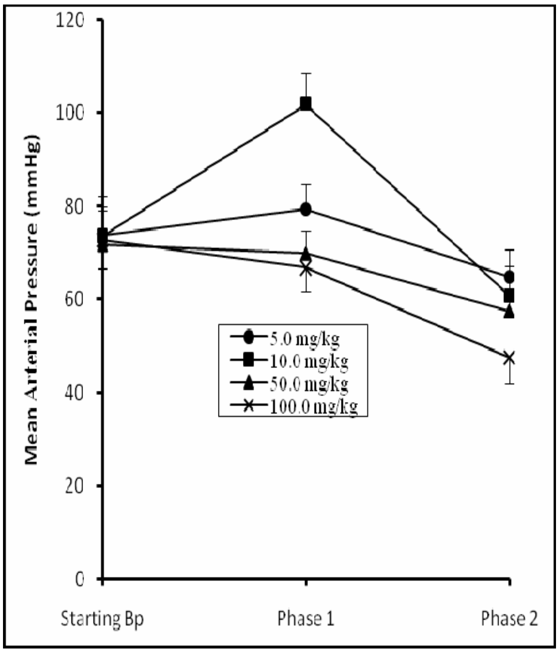

Figure 1. Biphasic Alteration of Mean arterial Pressure after Treating Albino Rats with *V. amygdalina.* Note: Vertical bars represent SEM.

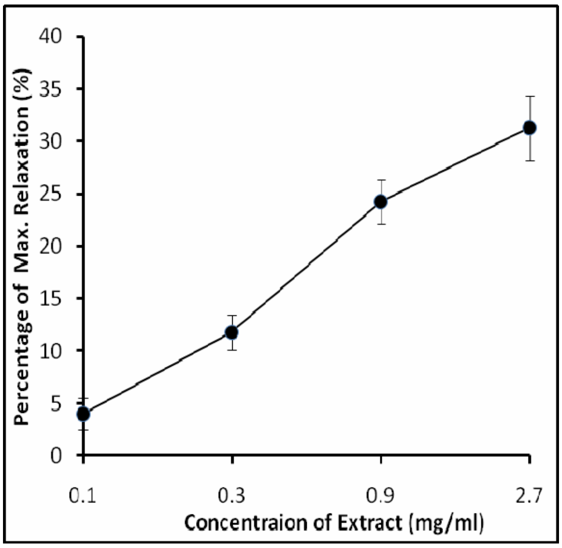

Figure 2: Relaxation Response of Isolated Aortic Smooth Muscle to *V. amygdalin*. Note: Vertical bars represent SEM.

3.2 Relaxation Response of the Aortic Rings to *V. amygdalina*.

Cumulative addition of *V. amygdalina* to noradrenaline precontracted rings of the aorta produced a positive dose-related relaxation of the rings (Figure 2). The extract achieved a maximum relaxation of 31.3$\pm$3.1% of the maximum tension developed to 10^{-7} noradrenaline at the concentration of 2.7mg/ml.

4. Discussion

The data from the present investigation showed that *V. amygdalina*, a plant commonly used for dietary and medicinal purposes, caused an overall blood pressure lowering effect in normotensive rats. The extracts caused bi-phasic alteration of blood pressure at lower doses (5.0 and 10.0mg/kg) but not at higher doses (50 and 100mg/kg). The reason for the difference in blood pressure alteration at lower and higher doses is not yet clear. The observation may imply the presence of a mixture of constituents that lower blood pressure and those that elevate it with the effect of the latter being suppressed at higher doses.

Blood pressure depends on several factors which include heart rate, stroke volume, and peripheral resistance. Agents that lower blood pressure do so via one or a combination of several blood pressure regulatory mechanisms. The results of in-vitro experiment on isolated rat aorta in this study suggested that aqueous extracts of *V. amygdalina* produced a dose-dependent decrease in arterial pressure through vascular relaxation mechanism. It is not possible at this stage to rule out other mechanisms that involve the autonomic nervous system such as sympathetic inhibition or/and parasympathetic stimulation. Experiments are currently in progress to clarify the issues raised above and also to see whether the blood pressure lowering effect of *V. amygdalina* is through acetylcholine or/and histamine mechanisms. Acetylcholine and histamine are known to affect the smooth muscle and cause vasodilatory effect in the body (Obiefuna et al, 1991).

The close association between hypertension and diabetes had long been well established (Naidu, 1992). Adequate control of blood pressure and blood glucose with drugs and other measures like dietary and life style regulations are necessary to retard the progression of cardiovascular complications associated with hypertension and diabetes (Swales, 1990, Mbanya, 1993). Unfortunately, there are compliance problems with recommended drug schedules. This is complicated by the fact that the drug regimes may not be appropriate in developing countries like Nigeria for various cultural and socio-economic reasons associated with poverty and illiteracy. Furthermore the majority of the populations in most of these countries especially those in the rural areas do not have access to conventional medical facilities, so they rely mainly on traditional medicine for their health care needs. The most widely used anti-hypertensive drugs have been criticized, particularly in diabetics, because of their various adverse effects (Mbanya, 1993).

In addition to previous reports that showed that *V. amygdalina* had hypoglycaemic effects in human and animal experimental subjects

(Ogbuokiri et al,. 1989; Gyang et al, 2004; Taiwo et al, 2009), the results of this study further suggests that the plant may also be useful in the treatment of hypertension because of its blood pressure lowering and vasorelaxant effects. The implication is that *V. amygdalina* may be especially useful in those increasing cases of hypertension complicated with diabetes. Recent data from toxicity studies had shown that *V. amygdalina* is safe when consumed in moderate quantities (Ojiako and Nwanjo, 2006).

Extensive phytochemical studies carried out on *V. amygdalina* by previous workers showed that it contains several bioactive compounds (Bohlman et al, 1982). This probably accounts for its widely reported pharmacodynamic nature and its use for the treatment of several diseases. Specific activity-guided phytochemical studies are presently being carried out in our laboratory to determine the active hypotensive and hypoglycaemic constituents of *V. amygdalina* for possible drug formulation and development.

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Correspondence to:
Idowu Adewumi Taiwo
Department of Cell Biology and Genetics, university of Lagos, Akoka, Lagos 101017, Nigeria
Telephone:+234-01-5454891-3,+234-01-4972730-5; Ext. 2331.
Cellular phone: +234-803-326-6013.
E-mails: tai_dex@yahoo.com

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