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Hypotensive and Antihypertensive Effects of *Aframomum melegueta* Seeds in Humans

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Abstract: The current study was designed to determine the effects of the seeds of *Aframomum melegueta* (AM) on the cardiovascular function in both normal and hypertensive human subjects. Normal subjects serving as controls and divided into three groups; A, B and C as well as hypertensive subjects in groups; D and E, were drafted into this study. Baseline Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Heart Rate (HR) values were taken before ingestion of 10, 15 and 20 seeds, respectively in normals and 10 and 20 seeds respectively in hypertensives. Measurements of the above parameters were taken for a duration of 1 h at 10 min intervals post ingestion. Two weeks after, the same protocol was carried out on normal subjects except that group A acted as control (no seeds) and groups B and C took 10 seeds each. Thirty minutes after the start of the protocol, groups A and B were subjected to Vasalva maneuver while group C was subjected to Cold Stress maneuver all for 1 min. An additional 31 min measurement was taken at the end of the procedures. Ingestion of these seeds resulted in the lowering of cardiovascular indices such as SBP, DBP, PP and MAP in normotensives and hypertensives, respectively. All were found to be significantly different from control values ($p<0.01$). Percentage reductions, though similar between normotensives and hypertensives, were however greater for SBP averaging (15-16%) than DBP (9-10%). The results of this study show that seeds of AM exert a potent effect on the blood pressure in both normotensive and hypertensive subjects. The results suggest a central effect but peripheral vasodilatation effect cannot be ruled out probably via the nitric oxide-cGMP pathway. The degree of reduction is within safety limits indicating its potential usefulness in managing hypertension in young and elderly hypertensive patients.

Key words: *Aframomum melegueta*, hypotensive, antihypertensive

INTRODUCTION

Aframomum melegueta (Rose). *K. Schum* (Zingiberaceae) (AM) is a spicy edible fruit that is cultivated and occurs throughout the tropics. It is a perennial herb (Iwu *et al*., 1999) and contains essential oils such as: gingerol; shagaol and paradol and it owes its pungency to these. It has equally been shown to contain alkaloids (piperine), essential oils and resins (Lachman-White *et al*., 1992). The medicinal uses of *Aframomum* include its use as aphrodisiac, in measles and leprosy, for excessive lactation and post-partum hemorrhage, as purgative, galactogogue and anthelmintic and as hemostatic agent (Iwu, 1993). Extracts of AM have been reported to exhibit antioxidant effects on lard and groundnut oil (Gabriel *et al*., 2003). Antidiarrhea activity, which may be as a result of inhibition of prostaglandin formation have been reported by Umukoro and Ashorobi (2003). Umukoro and Ashorobi (2005) reported an anti-inflammatory effect which may be related to a membrane stabilizing activity. Studies also show antimicrobial and antifungal activity against schistosomes (Iwu, 1999) and growth inhibition of *Bacillus cereus* (Gabriel *et al*., 2003). The seeds of the plant are also used for abdominal discomfort, as a carminative and for stomachache (Ajaiyeoba and Ekundayo, 1999) and as a stimulant, principally in veterinary preparations (Lans *et al*., 2000).

In spite of the various effects attributed to the seeds of the plant, to our knowledge, no study has been done to evaluate the effects of this plant on the cardiovascular system. Though ground powder from species of *Aframomum* has been patented for the correction of erectile dysfunction in man (Allas *et al*., 1995) who attributed its effect to that on smooth muscle activity. Since it is generally accepted that vasodilatation of the penile arteries rapidly followed by relaxation of the cavernous smooth muscle are primarily responsible for the initiation of erection (Newman and Northup, 1981), this study was therefore designed to investigate the possible

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effects that the seeds of this plant might have on the cardiovascular function in man bearing in mind the smooth muscle effect of the aframomum genus on the cavernous smooth muscle.

MATERIALS AND METHODS

Determination of dose equivalents: Aframomum melegueta fruits were purchased locally from Bashu village in Boki Local Government Area of Cross River State, Nigeria. The fruits were air-dried and the seeds removed from the papery sheath and pulverized in a blender. Sixty nine point twenty three grams of the resulting powder was subjected to sequential Soxhlet extraction using petroleum ether followed by methanol. The methanolic extract was dried in vacuo and the resulting slurry residue was weighed. One hundred seeds of the plant were also weighed and the mean weight was found to be 120.30 mg. The remaining seeds were kept in a tightly sealed sterile container for the main study. The amount of seeds given to each group in the study falls within the range reported to be routinely ingested based on interview conducted among people who indulge in the use of the seeds. Although it is rarely taken alone; most often with kola nut (*Cola nitida*), we found these amounts to be within the range that can be tolerated by mastication considering its pungency.

The total amount of AM extract obtained from 69.33 g of AM seeds was found to be 3.60 g. This constitutes 5.2%. The mean weight of 100 seeds was determined to be 120 mg, giving an average of 1.2 mg per seed. Though the study involved ingestion of intact seeds by the participants, the equivalent amount of AM extract ingested can be calculated using the following relationship:

$$D_G = \frac{W_s \times N_G}{AV_W} \times E_P \quad (1)$$

Where:
D_G = The calculated dosage per group
W_S = The average weight per seed
N_G = The number of seeds taken per group
E_P = The percentage of extract
AV_W = The average adult weight.

Taking the average adult weight as 70 kg and slotting in the above values, the equation can be simplified to:

$$D_G = N_G \times 8.571E^{-4} \text{ mg kg}^{-1} \quad (2)$$

Study population: Subjects recruited for the study included 18 healthy, non-smoking, non-alcoholic University students (6 men and 6 women, aged 20 to 28 years, mean 23.6±3 years; body weight 61.27±5.1 kg) and 11 hypertensive (Six women and five men, aged 35 to 57 years, mean 50.4±2 years; body weight 63.14±3.7 kg) patients with a well documented history of chronically elevated blood pressure (>145/95 mmHg). Secondary forms of hypertension had been excluded at the outpatient department of the Federal Institute of Industrial Research (FIIRO) clinic. Patients selected were already defaulting on treatment at the time of recruitment to the study. None of them had a history of diabetes, hyperlipidemia, peripheral vascular diseases, coagulopathy, or any disease predisposing them to vasculitis of Raynauld's phenomenon. All subjects were asked to refrain from strenuous exercise a day prior to the study. The study was conducted at the University of Calabar, Cross-River State and the Federal Institute of Industrial Research (FIIRO) clinic, Lagos both in Nigeria through March to May 2006.

Study protocol: Normal (control) subjects were divided into 3 groups A, B and C for the purposes of dosage variation. Baseline SBP, DBP and HR were measured in all subjects prior to the commencement of the test. Shortly after, they were given 10, 15 and 20 seeds, respectively of AM to masticate and swallow. The above parameters were monitored at 10 min interval for a period of 60 min post-ingestion.

A similar procedure was carried out in two groups D and F of hypertensive patients who were given 10 and 20 seeds, respectively and monitored for 60 min.

Vasalva and cold stress measurements: Two weeks after the measurements, the Vasalva and Cold Stress maneuvers were carried out on groups A and B in the normal subjects. Subjects were given 10 seeds after their baseline measurements had been taken as in earlier protocol. However 30 min after ingestion of the seeds, subjects in group A were asked to try to exhale against closed glottis (Vasalva maneuver) while subjects in group B were asked to dip their two hands into ice cold water (Cold Stress maneuver). The two procedures lasted exactly one minute and at the end an additional measurement was taken at the thirty-first minute post ingestion after which the normal time protocol was continued until 60 min.

Blood pressure measurement: Blood pressure was measured manually by trained personnel, using a standard mercury sphygmomanometer according to a protocol adapted from procedures recommended by the American Heart Association (Frohlich *et al*., 1988). Appropriately sized cuff was placed on the subjects' right arm. After the subject had rested 5 min in the seated position, a 30 sec pulse was recorded. The cuff was inflated 30 mmHg above the pulse-obliterated pressure and Korotkoff's auscultatory sounds were used as the basis for measuring both systolic and diastolic blood pressures. The same investigator took all measurements in this study in order to minimize potential errors.

Statistical analysis: One-way ANOVA was used in assessing the homogeneity of the separate dose groups in the normotensive subjects taking into account the values of the parameters at baseline and at the maximal effect. This was achieved with a student's t-test in hypertensives. The probability of chance occurrence of differences in blood pressure, heart rate and other derived parameters as large or larger than those observed was determined by paired or unpaired student's test, where, appropriate. All calculated probability values are two-tailed. P-values of 0.05 or less were considered significant. All statistical tests were carried out using the GraphPad Instat Software, version 2.04a. Numerical values for parameters were recorded as mean±SEM unless indicated otherwise.

RESULTS

Doses ingested by subjects: Based on the numerical relationship expressed above (Eq. 1 and 2), equivalent doses taken in the study were found to be 8.57, 12.85 and 17.14 ng kg^{-1} for 10, 15 and 20 seeds, respectively.

Dose-dependent changes in cardiovascular parameters in normotensives and hypertensives: Figure 1 and Table 1 shows the effect of AM on cardiovascular parameters in normotensives. SBP, DBP, MAP and PP were reduced significantly in all the dosage groups. The reductions were more intense in groups given 8.57 and 12.85 ng kg^{-1} (10 and 15 seeds) compared to those given 17.14 ng kg^{-1} dose equivalents (20 seeds). Within each dosage group, SBP was affected more than DBP in both normotensives and hypertensives. The MAP was reduced to a similar degree in 10 and 15 seed groups while it is less in 20 seed group (Table 1). An inverse relationship between changes in Pulse pressure and the number of AM seeds ingested was observed. A similar pattern was observed in the dose-related effects in hypertensive group (Fig. 2 and Table 1). The percentage decrease in the SBP, DBP and HR were compared between the dosage groups in normotensives and hypertensives using a one-way ANOVA. It was observed that apart from the baseline SBP in normotensives, there were no significant differences in other parameters between subgroups in normotensives and hypertensive. This informed the decision to base other statistical analysis on pooled data in both major groups (Fig. 3).

Effects of AM on systolic, diastolic and mean arterial pressure

Intra-group: Table 2 shows the effects of AM on cardiovascular parameters in pooled data. A reduction of SBP was observed both in normotensive and hypertensive subjects. SBP was reduced significantly in both normotensives ($p<0.0001$) and hypertensives ($p<0.05$). This represents 15.2 and 16.3% reduction

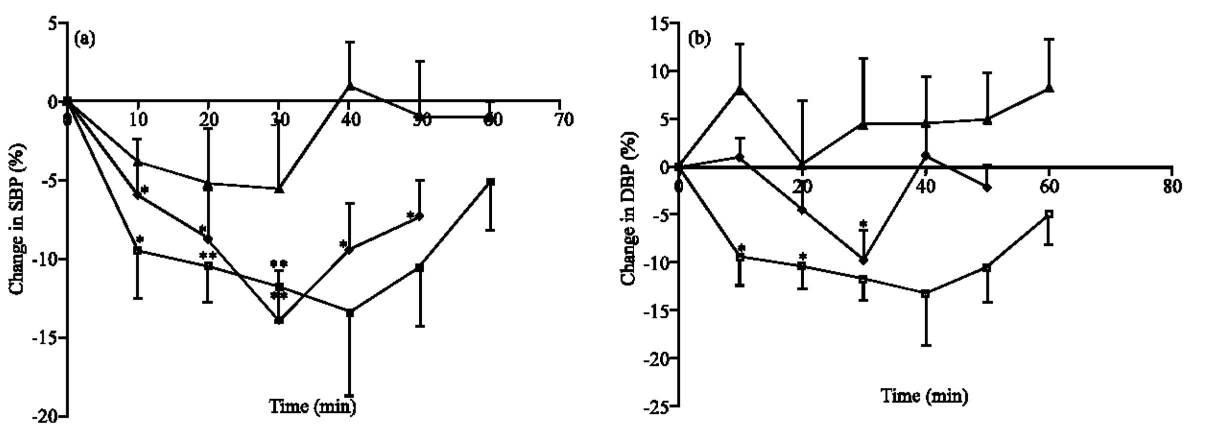

Fig. 1: Effect of *Aframomum melegueta* seeds on Systolic (a) and Diastolic (b) Blood pressure of normotensives. Line graphs show *Aframomum melegueta* (AM)-induced relaxation of Systolic Blood Pressure (SBP) (a) and Diastolic Blood Pressure (DBP) (b) in normotensive subjects given 10 seeds (♦) 15 seeds (□) and 20 seeds (▲). Results are expressed as percent of the initial (Baseline) SBP and DBP values. Each point represents mean±SEM. *: $p<0.05$, **: $p<0.01$

Table 1: Cardiovascular parameters produced by 10, 15 and 20 seeds of *Aframomum melegueta* (AM) in normotensive and hypertensive subjects

	Normotensives			Hypertensives	
Parameters	10 seeds (n = 6)	15 seeds (n = 6)	20 seeds (n = 6)	10 seeds (n = 5)	20 seeds (n = 5)
MAP (mmHg)					
Baseline	84.3±1.7	92.2±2.1	80.0±2.0	116.5±4.7	122.9±7.3
Minimum	72.4±3.1** (14.2)	80.0±2.1** (13.2)	73.2±1.4* (8.2)	101.1±5.5** (13.3)	108.9±5.6** (11.1)
Time to minimum (min)	33.3±4.2	33.3±4.9	16.7±5.6	50.0±4.5	40.0±6.3
PP, (mmHg)					
Baseline (mmHg)	39.5±1.6	41.7±3.2	42.0±2.4	54.4±8.8	66.7±11.3
Minimum (mmHg)	21.0±1.8*** (46.6)	26.7±2.6** (35.2)	29.0±1.7** (30.2)	40.0±8.9** (29.8)	39.5±5.2* (36.4)
Time to minimum (min)	31.7±6.0	30.0±6.8	23.3±6.7	38.0±7.3	35.0±8.5

Data are shown as mean±SEM. Values in parenthesis are percentages. *: p<0.05, **: p<0.01 and ***: p<0.001

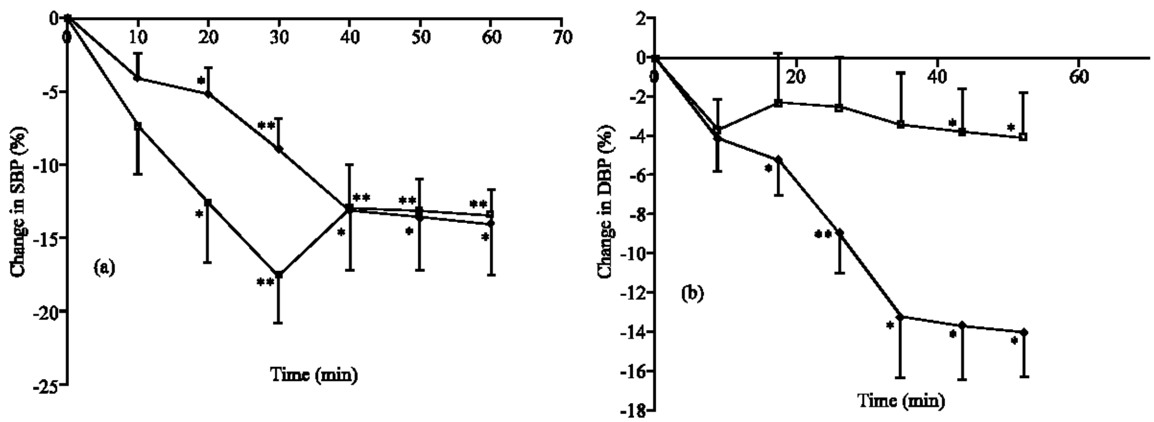

Fig. 2: Effect of *Aframomum melegueta* seeds on Systolic (a) and Diastolic (b) Blood pressure of hypertensives. Line graphs show *Aframomum melegueta* (AM)-induced relaxation of Systolic Blood Pressure (SBP) (a) and Diastolic Blood Pressure (DBP) (b) in hypertensive patients given 10 seeds (♦) and 15 seeds (□). Results are expressed as percent of the initial (Baseline) SBP and DBP values. Each point represents mean±SEM. *: p<0.05 and **: p<0.01

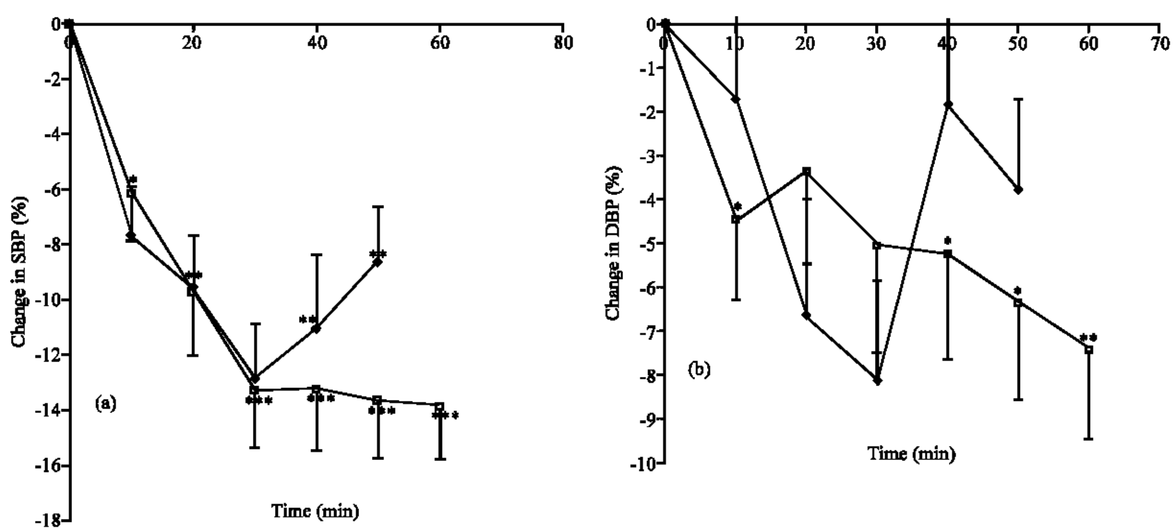

Fig. 3: Effect of *Aframomum melegueta* seeds on Systolic (a) and Diastolic (b) Blood pressure. Line graphs showing AM-induced relaxation of Systolic BP (a) and Diastolic BP (b) in normotensive (♦) and hypertensive (□) subjects. Data for the 10 and 15 seed groups were pooled and results are expressed as percentage of the initial (baseline) values. Each point represents mean±SEM. *: p<0.05, **: p<0.01 and ***: p<0.001

respectively. Reductions were also observed in DBP in normotensives (p<0.01) but not in hypertensives; PP in normotensives (p<0.0001) and hypertensives (p<0.05) and HR in normotensives (p<0.05). In the case of HR however, there was an initial increase in HR in both normotensive and hypertensive subjects (Fig. 4).

Table 2: Cardiovascular parameters produced by *Aframomum melegueta* (AM) seeds in pooled normotensive and hypertensive subjects

Variables	Normotensive	Hypertensive	Probability
SBP			
Baseline (mmHg)	113.6±2.0	160.70±8.1	<0.0001
Lowest (mmHg)	95.9±1.3****	133.80±6.0*	<0.0001
Time to peak SBP (min)	30.5±3.0	41.80±4.0	0.05
Percentage low (%)	15.2±1.5	16.30±2.1	ns
DBP			
Baseline (mmHg)	72.0±1.4	99.60±3.8	<0.0001
Lowest (mmHg)	64.4±1.6**	90.40±3.5	<0.0001
Time to peak SBP (min)	25.5±2.9	27.30±4.1	ns
Percentage low (%)	10.4±1.6	9.10±1.9	ns
PP			
Baseline (mmHg)	41.7±1.4	61.10±7.2	<0.05
Lowest (mmHg)	25.6±1.3****	39.70±4.7*	<0.05
Time to peak PP (min)	28.0±3.4	45.50±3.7	<0.01
Percentage low (%)	37.8±3.2	33.40±5.0	ns
MAP			
Baseline (mmHg)	85.5±1.6	120.00±4.4	<0.0001
Lowest (mmHg)	75.2±1.5***	105.30±3.9*	<0.0001
Time to peak MAP (min)	27.8±3.3	44.50±4.13	<0.01
Percentage low (%)	11.9±1.5	12.10±1.58	ns
HR			
Baseline (mmHg)	71.6±1.3	76.40±7.19	ns
Lowest (mmHg)	66.5±1.9*	69.40±6.82	ns
Time to peak HR (min)	32.9±3.2	46.00±7.48	ns
Percentage low (%)	7.0±2.3	9.14±2.41	ns

Normotensive and hypertensive data were pooled for 10 and 15 seed groups. Data are shown as mean±SEM. Values in parenthesis are percentages. *: p<0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001, ns: not significant

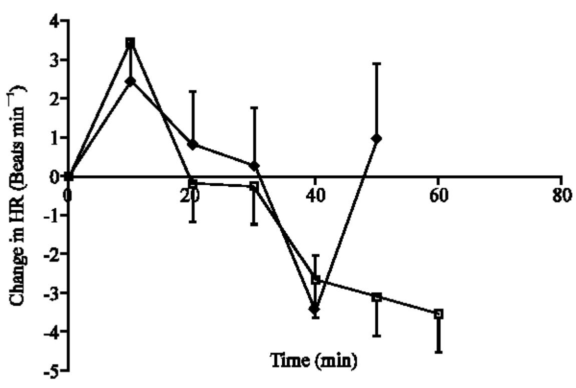

Fig. 4: Effect of *Aframomum melegueta* seeds on heart rate. Line graphs show *Aframomum melegueta* (AM)-induced relaxation of Heart Rate (HR) in Normotensives (♦) and hypertensive (□) subjects. Results are expressed as percent of the initial (Baseline) HR values. Each point represents mean±SEM

Inter-group: Table 2 shows that the baseline values for SBP (p<0.0001), DBP (p<0.0001), MAP (p<0.0001) and PP (p<0.05), are significantly different in normotensives and hypertensives. The HR however did not show any significant difference. The changes in these parameters after ingestion of AM are also different for SBP (p<0.001), DBP (p<0.001) and PP (p<0.05). Changes in HR remained insignificant. The percentage decrease in all parameters however showed no significant different but time taken for the changes to occur differs from SBP (p<0.05), PP (p<0.01) and MAP (p<0.01), while the time was insignificant for DBP and HR.

Effects of AM seeds on vasalva and cold stress response in normotensives: Table 3 shows that for control subjects that were not given the seeds of AM, Vasalava procedure led to an increase in the MAP while a similar increase was observed in the second group who had 20 seeds of AM, the percentage increase due to Vasalva procedure was higher in this group.

In a third group, equally given 20 seeds of AM, Cold Stress procedure resulted in an almost similar percentage increase in MAP. All the groups show similar trend in responses and the decrease in heart rate corresponds to an increase in MAP (Fig. 5).

Table 3: Effects of *Aframomum melegueta* (AM) on MAP in vasalva and cold stress response of normotensives

Groups	Baseline	30 (min)	31 (min)	Increase (%)
Control	86.4±5.2	88.7±5.0	95.8±2.5	8.00
AM1 (Vasalva + AM)	92.2±3.8	86.4±4.4	96.9±2.1	12.4
AM2 (Cold stress + AM)	87.7±1.4	81.3±2.7	92.3±3.3	13.8

Control group are those not given AM seeds but on whom Vasalva response was determined, while AM1 and AM2 groups are those who were given the seeds of AM and on whom Vasalva and Cold Stress procedures were carried out. Percentage increase relates the post-maneuver values to the 30th minute values. Data are shown as means±SEM

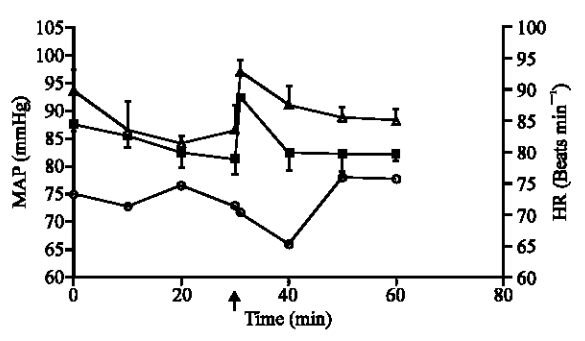

Fig. 5: Effect of vasalva and cold stress maneuvers on *Aframomum melegueta*-induced reduction in MAP and HR in normotensives. Line graphs show *Aframomum melegueta* (AM)-induced changes in MAP and HR in Vasalva (□) and Cold Stress (Δ) groups. Values are mean changes in parameters. (○) represent the point of maneuver

DISCUSSION

The seeds of *Aframomum melegueta* revealed a potent effect on blood pressure in both normotensive and hypertensive subjects but these effects are not dose related, at least at the dose range employed in the study-as shown by the high ANOVA probability values which probably is due to a possible dual effect of the seeds. AM resulted in a sustained decrease in the SBP, DBP, PP and MAP in normotensives and hypertensives. The maximal reductions of these parameters from baseline values are significant in both groups, but the percentage reductions between both groups are similar.

A curious observation is the fact that in spite of the similarities in the degrees of BP reduction, there appears to be a significant difference in the time taken to bring this change about. It took a while longer in hypertensives than normotensives for maximal reduction in SBP ($p<0.05$), PP ($p<0.01$), but not in DBP. Because the effect of AM on BP is shown to be reversed by sympathetic stimulation (Fig. 5), this difference may be as a result of paucity of adrenergic receptors in hypertensives. A previous study had shown that high norepinephrine concentration may cause α-receptor to down regulate (Martinotti, 1991). Izzo *et al*. (1990) also reported in their study that high concentration of norepinephrine can decrease α_1-receptor mRNA level in vascular smooth muscles all of which can make reflex reversal of decreased BP very slow indeed.

Vasalva and Cold Stress maneuvers, which are used as indicators of the patency of the sympathetic system was seen to reverse the decreases in blood pressure which ruled out the involvement of peripheral sympathetic blockade as a mechanism by which the plant exerts its effects on blood pressure. The baseline heart rate appears to be similar in normotensive and hypertensives alike which supports earlier reports by Swales (1994), who noted that manifestations of increased autonomic activity could not be demonstrated in older hypertensives, but only in younger hypertensives (Goldstein *et al*., 1983); implication being that sympathetic activity is similar and normal in both normotensives and hypertensives. It has been shown that agents that decrease both mean arterial pressure and heart rate simultaneously might act via central α_2-receptor mediation as suggested by studies, where central α_2-receptors mediate hypotensive and bradycardic effects (Engelman *et al*., 1989; Jong-Shiaw and Alecy, 1995). This may seem to confer a central role for the seeds in present study where both parameters were observed to decrease together. The transient initial increase in heart rate preceding bradycardia, is most likely a baroreceptor reflex and the tachycardia was caused by the blood pressure effect of the seeds. Other actions of AM however, may contribute to the blood pressure effect; AM may have an antihypertensive and hypotensive effect by acting directly on the peripheral tissues such as the arterial smooth muscles and the cardiac muscle. Its precise mechanism is however not known. The onset of blood pressure reduction is so rapid in this study such that the possibility of Nitric Oxide (NO) synthesis contributing to the initial hypotension and antihypertension effects can be ruled out. Prevention of NO destruction however is a viable possibility since previous studies have shown that patients with essential hypertension have abnormal endothelium-dependent vasodilator function (Clarke *et al*., 1992). Carlos *et al*. (1995) reported that hypertensive patients have an increased destruction of NO by superoxide anions, which normally interact with NO to form peroxynitrite ($ONOO^-$), a shorter-lived and less potent vasorelaxant (Liu *et al*., 1994). Inhibition of superoxide radical on the other hand seems a possible mechanism but argument for this is however weak if cognizance is taken of the fact that in normotensives where the endothelium dependent vasodilator response is apparently normal, similar percentage reductions in SBP and DBP were observed when compared to those in hypertensives. A much more logical explanation of the possible mechanism of the effect can be seen if one moves a step further in the pathway for the NO-dependent vascular muscle relaxation. Drugs like Nitroprusside have been reported to mediate the relaxation of vascular smooth muscles through NO release and NO-cGMP pathway. AM may therefore be acting by preventing the destruction of cyclic nucleotides. There is no reported difference in cyclic nucleotide levels between hypertensives and normotensives, inhibition of hydrolysis in both groups should result in similar effects on vascular smooth muscles as observed in our study. This position is also reinforced by a report on the effects of the seeds on sexual behavior where a significantly increased penile erection index and increased frequencies of intromission and ejaculation in male rats were recorded (Kamtchouing *et al*., 2002). Penile erectants like sildenafil, are known phosphodiesterase inhibitors.

In all, the present study has clearly demonstrated the high potency of the seeds of AM in bringing about a reduction in BP in normotensives and hypertensives; the effects are both on SBP and DBP although more in the former than the latter. The degree of potency can be better appreciated if one considers the low relative dose that exerted these cardiovascular effects in this study 8.57 to 17.14 ng kg^{-1} is far lower than 115 and 20-200 mg kg^{-1} employed by Kamtchouing (2002) and Umukoro and

Ashorobi (2005) for sexual behaviour and antiinflammatory activities, respectively. The importance of this discovery in the potential use in preventing cardiovascular mobidity and pathologies can not be overemphasized. Because both systolic and diastolic pressures are related to Myocardial Infarction (MI) and in the elderly, since Isolated Systolic Hypertension (ISH) is common and is associated with profoundly increased cardiovascular morbidity and mortality (Fang *et al*., 1995), a condition which is rarely found in younger subjects where increased diastolic BP is the commonly accepted guide to cardiovascular risk (Kannel *et al*., 1971) and since a 5mmHg lower DBP is reported to be associated with about one-third lower risk of stroke whereas a 10 mmHg lower DBP is associated with more than one-half risk of stroke (Clarke *et al*., 2001), this recorded dual effect of AM is an advantage, as this may prove beneficial in both younger and elderly hypertensive patients. These findings suggest that it is feasible to apply AM for treating human hypertensive disease in which case the transient reflex sympathetic activation that results can be treated by use of beta-blockers.

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