Pharmacognosy Magazine
ISSN: 0973-1296

PHCOG MAG.
An official Publication of Phcog.Net

PHCOG MAG.: Research Article
Effects of plants popularly used against hypertension on norepinephrine-stimulated guinea pig atria

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ABSTRACT

High blood pressure is often caused by the release of excessive amounts of epinephrine and norepinephrine by the sympathetic nervous system and the adrenal medulla. This condition is associated with an increased vascular resistance and/or cardiac output, the product of cardiac contractility and beating frequency. Thus, an elevated blood pressure can be lowered, among others, by decreasing the contractility and/or beating frequency of the heart. In this study, we used an isolated organ model to investigate whether such a mechanism may play a role in the presumed blood pressure-lowering effects of ten popularly used plant extracts. The plants used in this study were *Annona muricata*, *Artocarpus altilis*, *Averrhoa bilimbi*, *Cocos nucifera*, *Commelina virginica*, *Gossypium barbadense*, *Mangifera indica*, *Momordica charantia*, *Phyllanthus amarus*, and *Solanum melongena*. Aqueous extracts were prepared, and assessed at 0.001 to 1 mg/mL for their ability to reduce the increased relative contractility and/or beating frequency of isolated guinea pig atria caused by 5 x 10^{-6} M norepinephrine. Incubations were in Ringer-Locke buffer, in 100% O_2 and at 30 °C, and were for 3 min with 3-min intervals. Results (means ± SDs; n ≥ 3) were in g/sec and beats/min, and expressed with respect to readings found with Ringer-Locke buffer alone. The extracts from *A. bilimbi* (leaves), *P. amarus* (whole plants), and *S. melongena* (unripe fruits) decreased the contractility of the norepinephrine-stimulated atria by 50 to 100%, but did not affect their beating frequency. In addition, the *S. melongena* extract decreased the contractility of spontaneously beating atria by 90% without affecting the frequency. The remaining samples did not exert any effect under the above-mentioned conditions. The negative-inotropic effects of the *A. bilimbi*, *P. amarus*, and *S. melongena* extracts in the isolated guinea pig atria suggest that reduction of the cardiac output may play a role in their presumed blood pressure-lowering effects. These actions might be associated with alterations in intracellular calcium metabolism and/or phenomena involving the muscarinic receptor, but this must be determined in future studies.

KEY WORDS: Medicinal plants, antihypertensive, isolated guinea pig atria, norepinephrine.

INTRODUCTION

Worldwide, arterial hypertension is one of the leading causes of morbidity and mortality. In industrialized societies, this disorder occurs with a prevalence of 15 to 20% and claims approximately 25 million fatalities each year (1). For instance, in the USA, more than 50 million individuals suffer from hypertension with about 2 million new cases each year (2), and about 800,000 patients die because of complications such as ischemic heart disease, stroke, or renal failure (3,4).

There is increasing evidence that the vast majority of cases of high blood pressure is caused by a stress-induced, hyperactive sympathetic nervous system (5).

This condition leads to the release of excessive amounts of epinephrine and norepinephrine by the adrenal medulla and the sympathetic nervous system (6). The stimulatory effects of these substances on β_1 and α_1 adrenoceptors increase the contractility and beating frequency of the heart, promote constriction of the arterioles, enhance the reabsorption of sodium as well as the release of renine by the juxtaglomerular apparatus in the kidneys, and consequently, enlarge the effective vascular volume. The end result is an increase in cardiac output and peripheral vascular resistance, and elevation of the blood pressure (5).

Not surprisingly, arterial hypertension can be effectively treated with substances that decrease cardiac contractility, beating frequency (both key determinants of cardiac output), peripheral vascular resistance, and/or circulating volume (7,8). Such substances comprise, among others, sympathicolytics and calcium channel blockers, as well as vasodilators, inhibitors of angiotensin-converting enzyme (ACE) activity, and diuretics. They are used either singly or at certain combinations, and act at the level of the central nervous system, the heart, the peripheral vasculature, the renine-angiotensine-aldosteron system, or the kidney (9,10).

In addition to these prescription drugs, a considerable number of traditional medicines, often from plant origin, is popularly used against hypertension. Some examples are given in Table 1, which also summarizes a few other disorders that are treated with these preparations. Of note, interviews with more than one hundred patients with severe hypertension at the Cardiovascular Ward of the Academic Hospital Paramaribo during September and October 2005, confirmed the popular use of these preparations against this condition (unpublished observations).

Currently available information about the mechanisms underlying the presumed blood pressure-lowering efficacy of these folk preparations is scant. Preparations from the leaves of *G. barbadense* and *A. muricata* have been suggested to lower sympathetic tone through (a) central mechanism(s) (11), thereby decreasing cardiac output and/or peripheral resistance (12). Infusions from *C. nucifera* husk fibers, *M. charantia* leaves, and *M. indica* bark may inhibit ACE activity (13). Those from the hardwood of *A. altilis* and the aerial parts of the *Phyllanthus* member *P. niruri* may reduce peripheral vascular resistance, possibly by dilating the arteries (14). The blood pressure-lowering effects of the *A. bilimbi* and the *C. virginica* extracts might involve stimulation of diuresis (15,16), while that of *S. melongena* could be based, in addition, on decrease of the peripheral vascular resistance and/or ACE activity, and/or reduction of cardiac activity (17).

Whether the presumed blood pressure-lowering effects of the above-mentioned plant-derived preparations other than that of *S. melongena* could (also) take place at the level of the heart, is not known. For this reason, we used in the present study an isolated organ model to investigate to which degree the plant extracts may interfere with the increased cardiac activity caused by a hyperactive sympathetic nervous system. Thus, aqueous plant extracts were prepared, which were evaluated for their capacity to reduce the increased contractility and/or beating frequency of isolated guinea pig atria induced by norepinephrine. The results obtained have been discussed against the background of available phytochemical and pharmacognostic information about the plants studied.

MATERIALS AND METHODS

Plant extraction

The plants and plant parts used in this study as well as some relevant details about them are mentioned in Table 1. The plants have been collected in rural areas of Paramaribo, the capital of Suriname. They have been authenticated by the National Herbarium of Suriname in Paramaribo. Collections were only carried out when it was certain that the collection areas had been free of insecticides or other hazardous chemicals during the preceding six months.

After washing with distilled water, the plant material was macerated and extracted with distilled water at a temperature of 45 or 100 °C (Table 1). The plant extracts were filtered, dried under reduced pressure at a temperature not exceeding 45 °C, and divided in aliquots of 3 g which were stored at a temperature of -20 °C until testing. Crude material weighing between 500 and 1000 g typically yielded 15 to 20 g of extract.

Chemicals

Norepinephrine was purchased from Fluka AG (Buchs SG, Switzerland), the β_1 receptor antagonist atenolol from CP Pharmaceuticals (Wrexham, UK). All other chemicals used were from our laboratory stock and were of the highest grade available. The drugs and plant extracts were directly dissolved in an adapted Ringer-Locke perfusate containing NaCl 5 g/L, KCl 0.4 g/L, $CaCl_2$ 0.24 g/L, $NaHCO_3$ 0.15 g/L, and glucose 1 g/L. The final pH of the solution was adjusted to 7.4.

Isolated guinea pig atria

Adult male and female guinea pigs having access to food and water *ad libitum*, were obtained from the animal facility of our institution. For experiments, the

animals were anaesthetized with chloroform in a gassing chamber, the thoracic cavity was opened by a parasternal incision, and the heart was exposed. After excision of the major blood vessels, the heart was quickly isolated, placed in ice-cold Ringer-Locke solution, and the atria were carefully dissected from the rest of the heart.

Subsequently, the preparation was transferred to an organ bath containing 40 mL of Ringer-Locke solution kept at a temperature of 30°C and gassed with pure oxygen. The tip of one atrium was attached to a fixed point in the bath, that of the other to a FT-100 force transducer (CB-Sciences, Dover, NH, USA). The preload was kept at 1 g during the entire experiment. The atria started to contract spontaneously as soon as the operating temperature had been reached, indicating that the pacemaker had not been damaged during the dissection. The isolated organ was allowed to recover in Ringer-Locke buffer for at least 20 min before initiating the experiments. The solution was regularly refreshed during that period of time.

The entire experimental procedure had been approved by the Bioethics Committee of our institution.

Incubations

The isolated guinea pig atria were exposed for 3 min to one of the plant extracts, norepinephrine, or atenolol, either alone or at certain combinations, after which they were washed for at least 2 x 1.5 min with fresh, pre-warmed Ringer-Locke solution. The resulting forces of isometric contraction of the atria were registered by the force transducer and monitored with a desktop computer through a ETH-260 Bridge/Bio amplifier (CB-Sciences, Dover, NH, USA) connected to a Powerlab 400E analog/digital converter (ADInstruments, Castle Hill, Australia). Signals were recorded with the *Chart for Windows 4.2.3* software (ADInstruments, Castle Hill, Australia). The software also displayed the beating frequency of the atria in beats/min, and generated the relative contractility d*F*/dt in g/sec by differentiating forces of contraction. The relative contractility is a well-accepted key parameter of myocyte function (18). All signals were saved on the hard disk of the computer, allowing off-line analysis.

Figure 1 shows representative recordings of the relative contractility and beating frequency of untreated, spontaneously beating atria, and of atria treated with norepinephrine.

Data processing

The relative contractility and beating frequency caused by one of the test substances were derived from the average peak values of their respective recordings, and were expressed with respect to average values registered in the presence of Ringer-Locke buffer alone. The data presented are means ± SDs of at least three independent experiments performed in duplicate or triplicate. p values < 0.05 were taken to indicate statistically significant differences according to the paired two-tailed Student's t test.

RESULTS

Responses of the isolated guinea pig atria to norepinephrine in the absence or presence of atenolol

Exposure of the atria to serial dilutions of norepinephrine between 10^{-9} and 10^{-4} M led to a progressive increase in their relative contractility and beating frequency (Figures 2a and 2b). The contractile response and beating frequency were significantly lower in the presence of atenolol 5 x 10^{-6} M (Figures 2a and 2b). Of note, at this concentration, atenolol itself did not exert a significant influence on the relative contractility and beating frequency of the atria (data not shown). These findings are in agreement with common pharmacological principles (19), and demonstrated that the model responded reliably to variations in the degree of sympathetic stimulation.

Effects of plant extracts on the relative contractility and beating frequency of the isolated atria

The effects of the plant extracts on the increased relative contractility and beating frequency of the isolated guinea pig atria caused by norepinephrine are shown in Tables 2a and 2b. The extracts were used at the concentrations of 0.001, 0.01, 0.1, and 1 mg/mL, norepinephrine at 5 x 10^{-6} M. At this concentration, the norepinephrine-induced relative contractility and beating frequency of the atria were in the linear portions of the dose-response curves (Figures 2a and 2b). The use of the extracts from *A. bilimbi*, *P. amarus*, and *S. melongena* led to a reduction of 50 to 100% in the norepinephrine-stimulated relative contractility of the atria when compared to that caused by norepinephrine alone at extract concentrations of 1.0, 1.0, and 0.1 mg/mL, respectively (Table 2a). However, these plant extracts did not significantly alter the increased beating frequency of the atria caused by norepinephrine (Table 2b). Of note, exposure of untreated, spontaneously beating atria to the *S. melongena* extract alone led to a decrease of approximately 90% in the relative contractility while leaving the beating frequency unaffected (data not shown)

Table 1. *Relevant information about the plant species used in the study*

Botanical name (Popular name, voucher specimen number)	Family	Plant parts used (extraction temperature)	Most cited medicinal uses (references)
Annona muricata L. (Soursop, UVS-17434)	Annonaceae	Leaves (45 ºC)	Hypertension (32) and diuresis (33) Nervousness, anxiety, and insomnia (32-35)
Artocarpus altilis Forst. (Bread fruit, UVS-17805)	Moraceae	Leaves (100 ºC)	Against fever (35)
Averrhoa bilimbi L. (Bilimbi, UVS-17484)	Oxalidaceae	Leaves (45 ºC)	Hypertension (33,34) Jaundice (33)
Cocos nucifera L. (Coconut, UVS-17801)	Arecaceae	Husk fibers (100 ºC)	Hypertension (33,36) (35)
Commelina virginica L. (Virginia day-flower, UVS-17482)	Commelinaceae	Whole plant (45 ºC)	Hypertension (33) Warts and rash of the skin (32,34)
Gossypium barbadense L. (Sea island cotton, UVS-17433)	Malvaceae	Leaves (100 ºC)	Hypertension (35) and diuresis (33,36) Menstrual problems (32,33) (35)
Mangifera indica L. (Mango, UVS-17501)	Anacardiaceae	Leaves (45 ºC)	Hypertension (32,35) Diabetes mellitus (35)
Momordica charantia L. (Bitter cucumber; gourd, UVS-17455)	Cucurbitacea	Leaves (100 ºC)	Hypertension (35) Diabetes mellitus (35,37)
Phyllanthus amarus Schum. & Thonn. (Black catnip, UVS-17432)	Euphorbiaceae	Whole plant (100 ºC)	Hypertension (35), as well as diuresis and edema (38), against anemia (32), and against urogenital disorders (36)
Solanum melongena L. (Egg plant, UVS, 17809)	Solanaceae	Unripe fruits (100 ºC)	Hypertension cardiotonic (37), against abcesses and inflammations of inguinal lymph nodes (35) and against liver ailments (37,38)

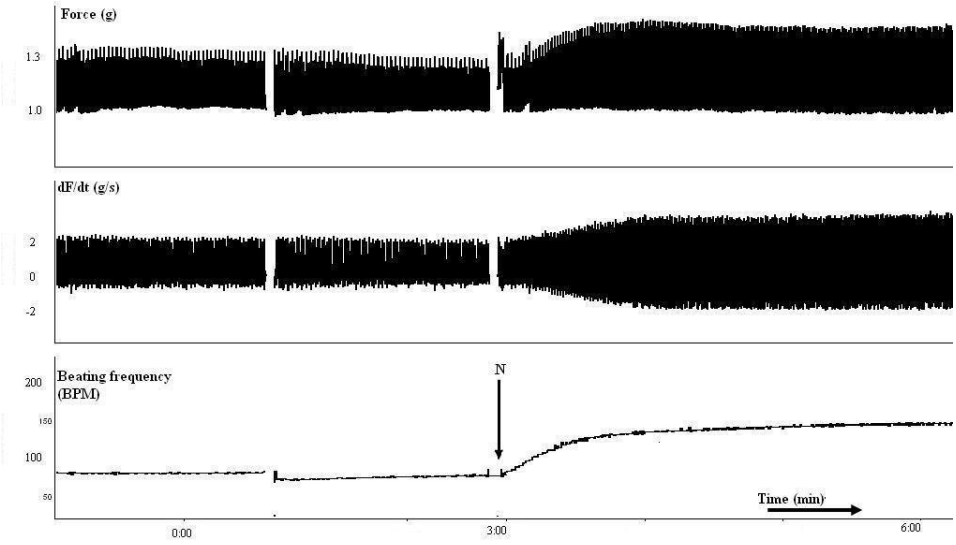

Figure 1. *Representative recording in time of contraction force, dF/dt, and beating frequency of an isolated guinea pig atrium in Ringer-Locke alone and in the presence of 5 x 10^{-6} M norepinephrine at time N.*

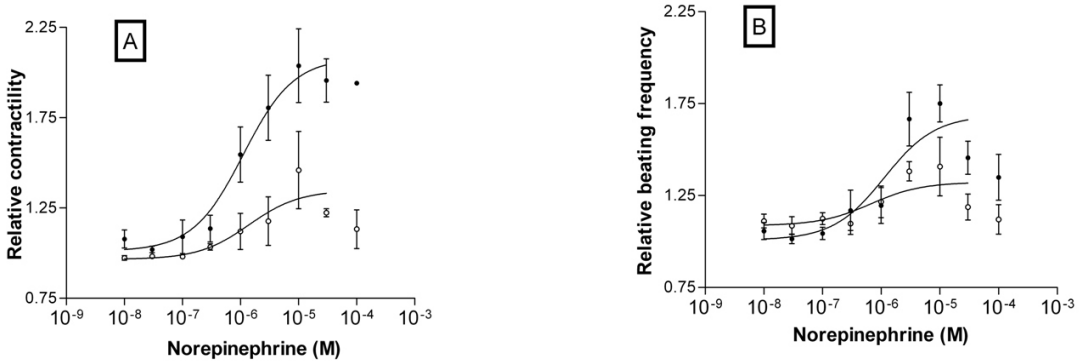

Figure 2. *Effects of norepinephrine in the absence (●) or presence (○) of atenolol 5 x 10^{-6} M on the relative contractility (A) and beating frequency (B) of isolated guinea pig atria. The contractility and beating frequency determined in the presence of norepinephrine with or without atenolol have been expressed relative to those found in the presence of buffer alone. Data are means (data points) ± SDs (vertical bars) of at least three experiments performed in duplicate.*

Table 2a. *Relative contractility (dF/dt) of isolated guinea pig atria upon exposure to plant extracts.*

Plant species	Relative contractility ± SD				
	Extract concentration (mg/mL)				
	0	0.001	0.01	0.1	1
A. muricata	142±21	168±14	173±22	175±18	155±35
A. altilis	178±59	176±36	160±28	175±56	174±43
A. bilimbi	174±10	148±11	151±12	158±6	127±23[a]
C. nucifera	160±31	148±29	154±16	156±31	167±19
C. virginica	128±13	122±17	129±27	121±23	131±31
G. barbadense	171±35	139±38	146±35	142±36	177±18
M. indica	160±4	146±16	133±19	142±20	155±8
M. charantia	155±14	168±10	158±16	165±19	155±23
P. amarus	155±29	135±29	129±8	132±21	111±34[a]
S. melongena	142±19	134±26	125±12	33±23[a]	32±39[a]

[a] *$p < 0.05$; Extract concentrations varied between 0 and 1 mg/mL in the presence of norepinephrine 5 x 10^{-6} M. The values have been expressed relative to base-line values (%). Data are means ± SDs of at least three determinations performed in duplicate or triplicate.*

Table 2b. *Relative beating frequency of isolated guinea pig atria upon exposure to plant extracts.*

Plant species	Relative beating frequency ± SD				
	Extract concentration (mg/mL)				
	0	0.001	0.01	0.1	1
A. muricata	122±16	135±8	136±8	134±15	129±21
A. altilis	135±26	138±10	131±6	129±10	131±4
A. bilimbi	134±2	120±17	118±15	121±18	125±6
C. nucifera	122±13	115±2	114±9	117±10	120±9
C. virginica	118±7	115±3	121±3	120±3	111±3
G. barbadense	144±17	154±19	145±20	158±24	118±8
M. indica	136±13	129±12	139±16	126±9	132±22
M. charantia	123±10	127±3	128±3	128±5	124±8
P. amarus	128±6	126±12	115±7	124±11	97±25
S. melongena	129±10	116±11	120±3	131±24	136±7

Extract concentrations varied between 0 and 1 mg/mL in the presence of norepinephrine 5 x 10-6 M. The values have been expressed relative to base-line values (%). Data are means ± SDs of at least three determinations performed in duplicate or triplicate.

On the other hand, the *A. bilimbi* and *P. amarus* extracts did not alter either the relative contractility or the beating frequency of the spontaneously beating atria (data not shown).

None of the remaining plant extracts elicited a significant influence on the relative contractility and beating frequency of either norepinephrine-stimulated (Tables 2a and 2b) or spontaneously beating isolated guinea pig atria (data not shown).

DISCUSSION

In this study, the aqueous extracts from ten selected plant species that are popularly used against arterial hypertension, have been assessed for their ability to normalize the excessive cardiac contractility and beating frequency that is often seen in patients suffering from this condition (5). It is instigated by a hyperactive sympathetic nervous system, and is associated with constitutive adrenergic overstimulation of the heart (6). Our results suggest that preparations from *A. bilimbi*, *P. amarus*, and *S. melongena* may have the capacity to control such excessive cardiac activity. Thus, this characteristic may play a role in the apparent efficacy of these samples against high blood pressure.

This assumption is based on the observation that these three extracts but not the other seven, significantly reduced the increased relative contractility of the norepinephrine-stimulated isolated guinea pig atria. Indeed, decreasing the relative contractility leads directly to a reduction in cardiac output and, subsequently, to lowering of the blood pressure (9).

There are no immediate indications at hand for the mechanisms that may underlie the apparent negative-inotropic effects of the *A. bilimbi* and *P. amarus* extracts. However, the absence of concomitant negative-chronotropic effects hints towards mechanism(s) involving calcium metabolism (20).

Support for this assumption is provided by the results from studies with several members of the plant genera *Averrhoa* and *Phyllanthus*. Preparations of the former genus contain relatively large amounts of oxalate (21). These may not only lower the blood pressure by promoting diuresis (15), but also by decreasing the cardiac contractility following interference with processes associated with the calcium-induced calcium release in heart tissue (22). The above-mentioned vasodilating effects of preparations from *Phyllanthus* species has been attributed to a decrease in cellular levels of calcium caused by the leaf tannin methyl brevifolincarboxylate (14). Should such a substance be present in *P. amarus* leaves and elicit similar effects on calcium metabolism in the heart, it may also lead to a decrease in cardiac contractility and lowering of the blood pressure.

On the other hand, the reduced inotropic state of the guinea pig atria caused by the *S. melongena* extract could be based on stimulation of the muscarinic receptor. Indications for this supposition come from the observation that blockade of cholinergic activity suppressed the negative-inotropic effect of the aqueous extract from *S. melongena* fruits in isolated rat atria, and that atropine counteracted the hypotensive effect of this preparation in normal laboratory rats (17). Thus, a muscarinic receptor-mediated mechanism might also account for the decreasing effects of the *S. melongena* fruit extract on the relative contractility of both norepinephrine-stimulated and spontaneously beating guinea pig atria noted in the present study. Incidentally, a methanolic extract from *S. melongena* leaves was reported to exert spasmogenic effects in isolated guinea pig trachea rings (23). Whether such an activity is also present in the unripe fruits of *S. melongena* is not known. However, until this question has been answered, the use of *S. melongena* preparations against high blood pressure and other human disorders should be discouraged.

The apparent absence of an effect of the seven remaining plant extracts on the relative contractility and beating frequency of both norepinephrine-treated and untreated isolated guinea pig atria suggests that they do not counteract the effects of sympathetic overstimulation through mechanisms associated with the heart. As mentioned above, these plant extracts may exert their presumed therapeutic efficacy at the level of the central nervous system (the *A. muricata* and *G. barbadense* preparations (11,24,25)) or the peripheral vasculature (the *A. altilis, C. nucifera*, *C. virginica*, *M. indica*, and *M. charantia* preparations (12,13,26-29), or the kidneys (the *A.bilimbi* and *C.virginica* preparations (15, 16)). Studies to investigate these possibilities and to confirm the present results in intact laboratory animals (11), isolated guinea pig aorta rings (30), and isolated rabbit kidneys (31), respectively, are in preparation.

CONCLUSIONS

The results from the present study suggest that the popular use of preparations from *A. bilimbi*, *P. amarus*, and *S. melongena* against stress-induced hypertension may be based, among others, on their capacity to decrease the increased relative contractility of the heart, thereby reducing cardiac

output. The preparations from *A. muricata*, *A. altilis*, *C. nucifera*, *C. virginica*, *G. barbadense*, *M. indica*, and *M. charantia* may exert their presumed antihypertensive effects by acting on sites other than the heart, including the central nervous system, the peripheral vasculature, and the kidneys.

ACKNOWLEDGEMENTS

This work has been performed with equipment donated by the Ministry of Developmental Cooperation of the Kingdom of Belgium, and has been partly supported by a grant from the Research and Development Fund of the Anton de Kom University of Suriname. The authors are also indebted to the staff of the National Herbarium of Suriname for their kind support.

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