STUDY OF THE EFFICACY AND CLINICAL SAFETY OF *ALPINIA SPECIOSA* (JC WENDL.) K. SCHUM CRUDE EXTRACT ON ARTERIAL HYPERTENSION

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ABSTRACT

The crude hydroalcoholic extract of *Alpinia speciosa* (JC Wendl.) K. Schum was administered for six weeks to twenty-two patients, thirteen of which had mild hypertension (stage 1 hypertension) and nine of which had moderate hypertension (stage 2 hypertension). Patients were submitted to the following laboratory tests prior to and after treatment: complete blood count, glucose, serum urea and creatinine, total cholesterol, triglycerides, uric acid, transaminases, bilirubins, alkaline phosphatase, serum sodium and potassium, urinalysis and EKG. Thirteen patients were treated with only one capsule of 250 mg/day containing the crude hydroalcoholic extract of *A. speciosa*. Eight patients were treated with two capsules, and only one was treated with the maximum dose under study, which was six capsules of crude hydroalcoholic *A. speciosa* extract. The biochemical and hematological tests performed showed no statistically significant differences between pretreatment and post-treatment, and the dosing regimen used was effective in significantly reducing blood pressure in stages 1 and 2. Furthermore, there was no report or identification of toxic side-effects, thereby demonstrating good tolerance.

Keywords: *Alpinia speciosa*; crude hydroalcoholic extract; clinical efficacy

INTRODUCTION

The phytotherapeutic agent studied was the crude hydroalcoholic extract of *Alpinia speciosa* (JC Wendl.) K. Schum, a plant species popularly known as 'macassá', 'pacová' or 'colônia', and used in traditional medicine as a diuretic and hypotensive agent.[1] This species is an aromatic herb of Asian origin, but it is widespread in Brazil, where it is cultivated as an ornamental and medicinal plant. It is a rhizomatous perennial grass that forms large growth clumps. It has long broad lanceolated leaves, and its flowers show a pink and white-yellow tinge.[1]

Preclinical pharmacological studies have proven its antihypertensive and mild tranquilizing activities. However, the therapeutic efficacy of derivatives of this plant species needs to be studied in order to provide support for its safe use in phytotherapy.

Alpinia speciosa contains essential oils and other components, but the active principle responsible for the antihypertensive action is not known. Among its fixed constituents, flavonoids and kavalactones have been found. It was determined that the essential oil potentiates barbiturate sleeping time and antagonizes convulsions induced by pentylenetetrazol in mice, indicative of a centralized effect. The essential oil has also shown peripheral analgesic activity[2]. In mice, the aqueous extract of the leaves produced depression of the central nervous system, neuromuscular blocking and both spasmolytic and hypotensive effects,[3] the hydroalcoholic extract also produced hypotension[4] and the ethanolic extract showed antiedematogenic activity[5]. It is possible that at least part of the hypotensive and spasmolytic activities are due to the presence of 4-terpineol[6]. It has been demonstrated that the vasodilatory effect of the hydroalcoholic extract of *Alpinia speciosa* is endothelium-dependent and probably due to the release of nitric oxide (NO) [7]. The Macassá collected in the Northeast seems to be more potent as a vasodilator compared to the plant grown in the Southeast. The observed hypotensive action is due, at least in part, to the presence of flavonoids and kavapyrones in the plant leaves [8].

The chemical constituents of plants of the genus *Alpinia* are mainly sesquiterpenes and flavonoids that are found in almost all species. In the quantitative and qualitative analysis, the leaves of *A. zerumbet* presented an essential oil yield of around 0.3%, containing terpene alcohols (41.4%), terpinene (19.8%) and *p*-cymene (14.6%) as the main constituents. Among the fixed constituents, kavalactones and flavonoids were found in different concentrations in the aqueous extract of Macassá leaves collected in various parts of Brazil.[8]

This study aimed to clinically evaluate the efficacy and tolerance of the crude hydroalcoholic extract of *Alpinia speciosa* in hypertensive patients through a clinical trial protocol.

MATERIALS AND METHODS

Test product

The test product was presented in the form of a 250 mg capsule containing the crude hydroalcoholic extract of *Alpinia speciosa*, which was kindly provided by the

Laboratory Selachii Ltda. in Fortaleza, Ceará, Brazil, and was dispensed to the volunteers included in the study by the Phytotheraphic Division of the Department of Pharmaceutical Care of the Itapemirim Municipal Health Secretariat (Divisão de Fitoterapia do Departamento de Assistência Farmacêutica da Secretaria Municipal de Saúde de Cachoeiro de Itapemirim), Espirito Santo, Brazil.

Collection of the crude hydroalcoholic extract

The crude hydroalcoholic extract was obtained from the leaves of *Alpinia speciosa* collected in Fortaleza-CE, which were dried at room temperature and macerated with a 70% hydroalcoholic solution for 15 days. The extract obtained was concentrated under reduced pressure to provide the crude extract. This extract was standardized based on the concentration of flavonoids, which was 2.5%.

Selection of volunteers

Patient selection was performed through medical consultation, including thorough history and physical examinations in the outpatient clinic of the Municipal Health Center, as well as laboratory tests and medical procedures detailed below. Once evaluated, the subjects were submitted to a free interview to evaluate the emotional condition of the participants in the investigation. Subjects were informed about the trial and signed a free informed consent form approved by the Ethics in Research Committee of the Alfenas University, Minas Gerais, Brazil, to participate in the study. Twenty-two patients, sixteen of whom were women and six were men with a mean age of 48 ± 2.3 years, were selected and followed over an estimated period of six weeks, returning every two weeks for medical evaluation. After the study, the whole routine was conducted again (medical consultations, medical procedures and laboratory tests).

Criteria for inclusion in the study

The following criteria were applied for patient inclusion in the study: diagnosis of stage 1 hypertension (mild) or 2 (moderate) according to the VI Joint (NIH, 1997); a systolic pressure between 140-180 mmHg; diastolic pressure between 90 to 110 mmHg; no use of antihypertensive in the last 30 days; older than 35 years and body mass index under 27; patient freely signed the consent form after all the essential elements of the protocol had been made clear prior. In the pre-study medical evaluation, of the twenty-two selected patients, thirteen were classified as mildly hypertensive and nine as moderately hypertensive.

Exclusion criteria

The following criteria were used to exclude patients from participation in the study: history of secondary hypertension; renal insufficiency; cardiopathy (CHF, left ventricular hypertrophy, arrhythmia requiring medical treatment, infarction); patient participated in any experimental study in the three months prior to the study; patient was hospitalized for any reason within the eight weeks preceding the study; had a history of alcohol abuse (more than 30 ml of ethanol, 720 ml of beer, 300 ml of wine or 60 ml of whisky per day for men or half that amount for women) or drugs; presented any other condition that the investigator judged relevant to non-participation in the study.

Clinical and laboratory tests

Patients underwent the following laboratory tests: complete blood count, glucose, serum urea and creatinine, total cholesterol, triglycerides, uric acid, transaminases, bilirubins, alkaline phosphatase, serum sodium and potassium, urinalysis and EKG. The results of medical examinations and laboratory tests were recorded in spreadsheets for each patient.

Treatment regimen

A capsule containing 250 mg of crude hydroalcoholic extract of *Alpinia speciosa* Schum was administered orally in the morning. When necessary, in the case of no response by the patient, the dose was increased by one capsule (when blood pressure levels were maintained) to 6 capsules (if the blood pressure increased) in the afternoon and/or at bedtime. The total treatment period was 6 weeks of there was no discontinuation of treatment. Of the twenty-two patients treated, thirteen patients took only one capsule, eight took two capsules and only one took the maximum dose, six capsules of crude hydroalcoholic extract of *A. speciosa*.

Data collected

The data collected from the clinical protocol consisted of the medical assessment, blood pressure measurements, adverse events reported every two weeks on return of the patient and the results of laboratory tests and electrocardiograms performed before and after the study period.

Target blood pressure

The target blood pressure in this study was a systolic blood pressure <140 mmHg and a diastolic blood pressure < 90 mmHg. As a secondary target, we aimed to obtain a significant reduction in systolic and/or diastolic blood pressure. After a six-week period, at the conclusion of the study, the patients were again evaluated (Post-Study) according to the routine at the initial assessment.

Discontinuation of Study Medication

Patients could withdraw from the study for medical reasons, in the case of persistent high blood pressure even after a medication dose increase, upon the occurrence of adverse events, or for breach of protocol. In the case of persistent high blood pressure, other antihypertensive medications were prescribed after careful medical evaluation.

Clinical Evaluation

The researcher provided adequate information regarding any findings that suggested significant risks,

contraindications, side effects or precautions relevant to the safety of the medication under study.

Adverse Events

Included in the "adverse events" was one of the following that possibly developed or increased in severity during the study:

a) any suspected signs or symptoms related or not to the study conditions;

b) any clinically significant laboratory abnormality;

c) any abnormality detected during medical evaluation.

Signs and symptoms

Signs and symptoms were classified as mild, moderate or severe by investigators according to the following definitions:

a) mild: not causing limitation of normal activities;

b) moderate: causing some limitation of normal activities;

c) severe: causing inability to perform normal activities.

Serious adverse events

A serious adverse event was defined as any event that suggested a significant risk, contraindication, side effect or precaution. A serious adverse event included any event that was fatal or life threatening, was disabling, required hospitalization or was an overdose.

Statistical analysis

For statistical analysis, variance analysis (ANOVA, one-way) was applied followed by the Tukey-Kramer test for multiple comparisons of blood pressure values before, during and after treatment. Results with $p<0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

The first piece of data to note from this study was the fact that the twenty-two hypertensive patients who received one to six capsules containing 250 mg of crude hydroalcoholic extract of *Alpinia speciosa* did not report unpleasant side effects from this treatment regimen, indicating that the tolerability was good. There was one patient withdrawal, but it was unrelated to the treatment.

Hypertension, in general, is an asymptomatic disease in its early stages. The best way to detect it early is by routinely measuring blood pressure. In some cases of hypertension, the initial symptom is headache, especially occipital and in the morning.

In this study, seventeen patients presented with headache as a symptom. The crude hydroalcoholic extract of *A. speciosa* was effective in reducing headache within the first follow-up (second week) in all patients who experienced lowered blood pressure. These patients also showed improvement in insomnia and agitation, slept better and felt more relaxed, indicative of central effects, in accord with the preclinical study in mice by Maia et al.[2]

The results showed that the crude hydroalcoholic extract of *Alpinia speciosa* was effective at reducing blood pressure in stages 1 and 2 of the hypertension classification (Figure 1, Tables 1 and 2). The results obtained demonstrated the efficiency after six weeks of treatment in reducing systolic blood pressure in twenty of the twenty-two patients. Only one patient showed no change (patient 02) and another withdrew from the experiment (patient 22), complaining of undefined malaise that was not correlated with laboratory tests or electrocardiography (Table 1).

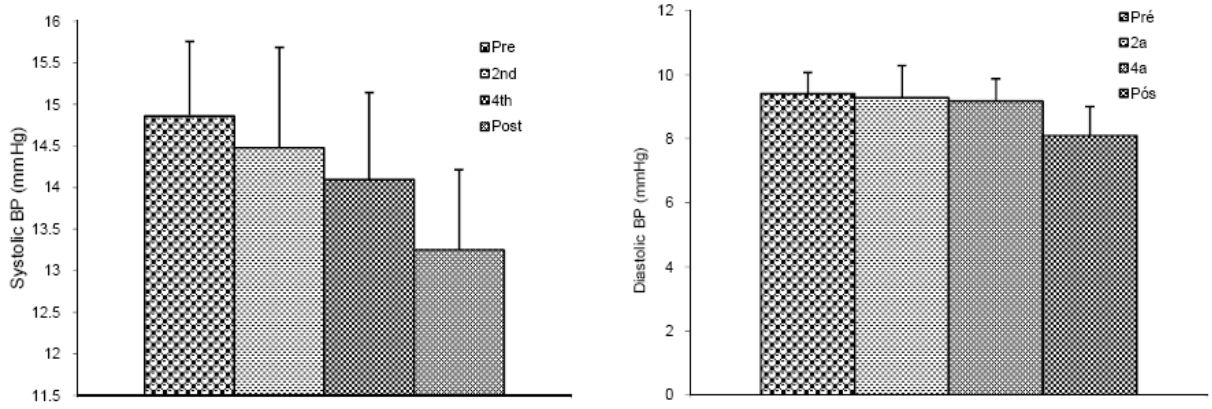

Figure 1: The effect of 6 week treatment with the crude hydroalcoholic extract of *Alpinia speciosa* on systolic and diastolic blood pressure (mmHg) in hypertensive patients. The bars represent the mean ± SD of measurements taken pre-treatment (pre), after two weeks of treatment (2^{nd}), after four weeks of treatment (4^{th}) and post-treatment (6 weeks). * $P<0.05$.

Table 1: Systolic blood pressure of patients undergoing treatment for 6 weeks with the crude hydroalcoholic extract of *Alpinia speciosa*.

Patient	Pre Study	Week		Post Study
		2nd	4th	
01	17	14	13	13
02	14	14	14	14
03	15	14	13	13
04	16	15	14	13
05	15	18	15	14
06	15	14	14	14
07	14	13	13	13
08	15	14	13	14
09	14	13	14	13
10	15	16	16	12
11	15	14	14	12
12	14	14	14	13
13	14	14	14	13
14	16	16	16	14
15	14	14	14	12
16	14	13	12	12
17	16	15	16	14
18	14	14	14	12
19	14	14	14	13
20	16	16	16	12
21	15	15	14	13
22	15	16	15	16
Mean	14,864	14,476	14,095	13,250
SD	0,889	1,209	1,044	0,967
Variance	1	1	1	1

F Test - (a result of p> 0,95 indicates equal variance).				
Pre Study	Week		Post Study	
	2nd	4th		
0,09	0,958	0,572	0,264	
Week	Pre Study	Week		Post Study
		2nd	4th	
2nd	0,151	!	!	!
4th	0,342	0,621	!	!
Post Study	0,625	0,339	0,643	!
t-Test	Pre Study	Week		Post Study
		2nd	4th	
2nd Week	0,33	!	!	!
4th Week	**0,029**	0,305	!	!
Post Study	**0,000**	**0,000**	**0,002**	!
One-tailed Test	Pre Study	Week		Post Study
		2nd	4th	
2nd Week	0,165	!	!	!
4th Week	**0,014**	0,153	!	!
Post Study	**0,000**	**0,000**	**0,001**	!

Table 2: Diastolic blood pressure of patients undergoing treatment for 6 weeks with the crude hydroalcoholic extract of *Alpinia speciosa*.

Patient	Pre Study	Week		Post Study
		2nd	4th	
01	10	9	9	9
02	9	9	9	9
03	9	8	9	9
04	9	10	9	8
05	10	8	9	8
06	9	8	9	8
07	9	9	8	8
08	9	9	9	8
09	9	8	9	8
10	9	10	9	8
11	9	9	9	7
12	9	9	9	7
13	10	10	10	8
14	10	10	9	6
15	10	10	10	9
16	9	9	8	8
17	11	10	10	9
18	9	9	9	8
19	9	8	9	8
20	11	11	11	9
21	9	11	10	7
22	9	11	9	10
Mean	9,409	9,286	9,190	8,100
SD	0,666	1,007	0,680	0,912
Variance	0	1	0	1

F-Test (p>0.95 result indicates equal variance)				
Pre Study	Week		Post Study	
	2nd	4th		
0,06	0,749	0,063	0,744	
Week	Pre Study	Week		Post Study
		2nd	4th	
2nd	0,073	!	!	!
4th	0,991	0,071	!	!
Post Study	0,194	0,611	0,191	!
t-Test	Pre Study	Week		Post Study
		2nd	4th	
2nd Week	0,724	!	!	!
4th Week	0,264	0,596	!	!
Post Study	**0,000**	**0,000**	**0,000**	!
One-tailed Test	Pre Study	Week		Post Study
		2nd	4th	
2nd Week	0,362	!	!	!
4th Week	0,132	0,298	!	!
Post Study	**0,000**	**0,000**	**0,000**	!

Table 4: Clinical and laboratory results of patients undergoing treatment for 6 weeks with the crude hydroalcoholic extract of *Alpinia speciosa*.

22 Patients			Mean		Standard Deviation	
Tests			Pre	Post	Pre	Post
Haemogram	W BC	. Leukocytes	6.850	6.673	1.763	3.295
		. Basophils	-	-	-	-
		. Eosinophils	2	2	2	3
		. Myelocytes	-	-	-	-
		. Metamyelocytes	-	-	-	-
		. Mast cells	4	2	1	3
		. Neutrophils	55	54	6	6
		. Lymphocytes	37	38	6	7
		. Monocytes	2	4	1	1
	RBC	. Hematology	4	4	0	0
		. HGB	13,1	13,3	1,4	1,4
		. HCT	38	40	4	4
		. HGM	30	30	2	3
		. VGM	90	91	6	6
		. CAGH	33	33	1	1
		Hematoscopy				
Blood biochemistry		. Glucose	108	108	56	57
		. Urea	21	23	7	5
		. Creatinine	0,8	0,8	0	0
		. Cholesterol	200	194	48	45
		. Triglycerides	191	144	61	212
		. Uric Acid	5	5	1	1
		. TGO	31	23	8	13
		. TGP	26	22	10	16
		. Bilirubin	1,0	1,0	0,2	0,3
		. BD	0	0	0	0
		. BI	1	1	0	0
		. FA	147	153	39	39
		. Sodium	139	137	2	3
		. Potassium	4,1	3,8	0,3	0,4
Urine contents	General Characteristics	. Density	1.024	1.022	3	5
		. PH	5,3	5,9	0,5	0,5
		. Volume	47	39	15	11
		. Color				
		. Reaction				
		. Deposit				
	Abnormal elements	. Proteins				
		. Ketone bodies				
		. Bile salts				
		. Reducing salts				
		. Bilirubin				
		. Hemoglobin				
	Sedimentoscopy	. Pyocytes				
		. Erythrocytes				
		. Desquamated cells				
		. Crystals				
		. Cylinders				
		. Protozoans				
		. Yeast				
		. Bacterial flora				
EKG		. CR				
		. SAP				
		. SAQRS				
		. SAT				
		. PR interval				
		. QRS duration				
		. QT				
		. HR	68	68	8	10
		. Conclusion				
		SPS Abnormality				

The efficiency of the crude hydroalcoholic extract of *Alpinia speciosa* in reducing diastolic blood pressure was also demonstrated in nineteen of the twenty-two patients after six weeks of study (Figure 1, Tables 1 and 2). Two patients did not show a reduction in diastolic blood pressure (patient 02 and 03), and another experienced increased blood pressure (patient 22) after having withdrawn from the study (Table 2).

Table 3: Heart rate of patients undergoing treatment for 6 weeks with the crude hydroalcoholic extract of *Alpinia speciosa*.

Patient	Pre Study	Week		Post Study
		2nd	4th	
01	80	80	80	86
02	90	90	80	90
03	80	80	80	80
04	84	84	80	80
05	80	80	84	84
06	84	84	80	80
07	80	80	92	80
08	89	89	80	89
09	86	86	80	86
10	89	84	89	89
11	80	80	80	80
12	84	84	84	84
13	86	86	86	86
14	82	82	82	80
15	82	82	82	82
16	89	89	89	89
17	80	80	80	80
18	80	80	80	80
19	86	86	86	86
20	84	84	84	84
21	76	76	76	86
22	84	84	84	84
Mean	**83,409**	**83,143**	**82,667**	**84,150**
SD	**3,775**	**3,651**	**3,954**	**3,573**
Variance	**14**	**13**	**15**	**13**

In preclinical studies, Soares de Moura et al.[9] showed that the antihypertensive effect of the crude hydroalcoholic extract of *Alpinia speciosa* may be due to a direct action on vascular smooth muscle, and Emiliano et al.[7] demonstrated that the vasodilatory effect of the hydroalcoholic extract of this plant is endothelium-dependent and is probably due to the release of nitric oxide (NO). Should the same effects occur at the clinical level, we propose that the antihypertensive action of the crude hydroalcoholic extract of *Alpinia speciosa* occurs through vasodilatation. Based on this hypothesis, one can correlate the antihypertensive action of *Alpinia* to that of synthetic antihypertensive drugs of the class of direct vasodilators whose mechanism of action is correlated.

Other effects related to the mechanism of action of direct vasodilators, such as reflex tachycardia and polyuria, could also be observed in this study. The difference was that in relation to the action of the crude hydroalcoholic extract of *Alpinia speciosa,* these effects presented with decreased intensity. However, on outpatient evaluation, the results showed an initial drop in heart rate (Table 3), which was sustained until the end of the study, at which point a slight increase in HR was observed, possibly a reflex mechanism to maintain homeostasis. Polyuria was also observed by most patients in the study, with reports of a transitory increase in urine volume and frequency. This effect can also be attributed to the diuretic action of direct vasodilators through the increase of renal plasma flow and consequent increase in diuresis of the glomerular filtrate.

After completing the treatment period with the crude hydroalcoholic extract of *Alpinia speciosa*, the hematological and biochemical tests performed showed no statistically significant differences (Table 4), demonstrating no toxicity at the hematological and biochemical levels during the study period. However, in animals treated with the tea and hydroalcoholic extract, an increase in transaminases and HDL was observed.[4]

It is noteworthy that one patient showed significant improvements in the results of several laboratory parameters after completion of the study, with an emphasis on leukocytes and triglycerides. The post treatment urinalysis did not show results that could be considered abnormal, and the results were similar to those performed before treatment. Additionally, the electrocardiograms performed before and after the study revealed no significant changes. Changes in pre-study EKG remained practically unchanged after completion of the study.

A 46 year-old patient who was treated with a dose equivalent to 1.5 g per day of crude hydroalcoholic extract of *Alpinia speciosa* showed the best results in post-study laboratory tests. This patient drew clinical attention not only due to the laboratory test results resulting from a drop in blood pressure at the end of the study but also due to the excellent clinical response. The patient showed improvement of symptoms of hypertension (headache) and menopause (hot flushes) and showed visible improvement of varicose veins, insomnia and anxiety.

These results suggest that the use of the crude hydroalcoholic extract of *Alpinia speciosa* in cases of hypertension can be a useful therapeutic alternative. This species showed no side effects, indicative of its safety, and most importantly, is inexpensive when compared to current treatments. Moreover, the species is abundant throughout Brazil and would therefore not require an import investment.

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