Evaluation of *Phyllanthus emblica* extract on cold pressor induced cardiovascular changes in healthy human subjects

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ABSTRACT

Background: Acute and chronic stress is a risk factor for the development and progression of coronary artery disease. Increased arterial stiffness is an independent marker for cardiovascular disease. Cold pressor test (CPT) is known to be associated with substantial activation of the autonomic nervous system. **Objective:** The aim of this study was to evaluate the effect of *Phyllanthus emblica* extract on cold pressor stress test induced changes on cardiovascular parameters and aortic wave reflections in healthy human subjects. **Materials and Methods:** This was a double-blind, placebo-controlled, crossover study. Participants were randomized to receive either two capsules of *P. emblica* extract 250 mg (containing aqueous extract of *P. emblica,* highly standardized by high-performance liquid chromatography to contain low molecular weight hydrolysable tannins emblicanin-A, emblicanin-B, pedunculagin and punigluconin) or two capsules of placebo twice daily for 14 days. Pharmacodynamic parameters such as heart rate, augmentation pressure, augmentation index (AIx), subendocardial viability ratio (SEVR), radial and aortic blood pressure (BP) were recorded before and after CPT at baseline and end of treatment. After washout period of 14 days, subjects crossed over to the other treatment and the same test procedure was repeated again. Safety assessments were done at baseline and at the end of treatment. **Results:** A total of 12volunteers completed the study. Compared with baseline and placebo, *P. emblica* extract produced a significant decrease of mean percent change in the indices of arterial stiffness (AIx, radial and aortic BP) and increase in SEVR, an index of myocardial perfusion with CPT. Both treatments were well-tolerated and no serious adverse events were reported. **Conclusion:** Proprietary *P. emblica* extract, showed a significant decrease in cold pressor stress test induced changes on aortic wave reflections.

Key words: Augmentation index, cardiovascular disease, cold pressor test, *Phyllanthus emblica*

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INTRODUCTION

The human body is in a state of dynamic equilibrium, also known as allostasis.[1] Stress is the state of threatened homeostasis provoked by psychological, physiological or environmental stressors.[2] The stress response is initiated when external and internal forces, the stressors challenge this allostasis. The sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis are the main mediators of stress response, which might negatively affect the cardiovascular system by alterations in blood pressure (BP) and lipids.[3] Most allostatic mediators have a biphasic role with protective effects in the short run and damaging effects under chronic stress. Experimental studies have found that acute stress leads to pathophysiological changes in cardiac risk profile and thereby more directly explain a link to cardiovascular disease.[3] Stress releases free radicals which results in oxidative stress damage, resulting in imbalance between oxidant/antioxidant systems. Generation of free radicals is an integral feature of normal cellular functions. In contrast to excessive generation, inadequate removal results in destructive and irreversible cell damage.[4]

Antioxidants play an important protective role against reactive oxygen species.[5] Research indicates that

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there is an inverse relationship between the dietary intake of antioxidant rich foods and the cardiovascular morbidity.[6] *Phyllanthus emblica*, also known as *Emblica officinalis* (Family: *Euphorbiaceae*) is used in Ayurveda as potent rasayanas, a class of plant derived drugs reputed to promote health and longevity by improving defense against diseases.[7] *P. emblica* is a rich source of vitamin C, which plays an important role in scavenging free radicals, thus attenuates stress induced cardiovascular changes through its antioxidant action.[8] *E. officinalis* has been reported to reduce arterial BP and heart rate (HR) in rats with deoxycorticosterone acetate/1% sodium chloride high salt-induced hypertension.[9]

The present study was undertaken to evaluate the effect of *P. emblica* on cold pressor stress test induced changes on cardiovascular parameters and aortic wave reflections in healthy human subjects. We hypothesized that cold pressor stress test would result in increased central BP, wave reflection and aortic stiffness.

MATERIALS AND METHODS

This was a prospective, randomized, double blind study conducted after approval of the Institutional Ethics Committee of Nizam's Institute of Medical Sciences (NIMS), Hyderabad, India. The study was registered in the Clinical Trial Registry of India (2013/05/003656). All subjects gave written informed consent prior to participation in the study. The cold pressor stress test model equipment used in the present study was designed and validated by the department of clinical pharmacology and Therapeutics, NIMS, Hyderabad.[10]

Study participants

The 15 healthy male participants aged between 20 and 30 years, were screened following a full medical history, physical examination, hematological, hepatic, renal, biochemical, electrocardiogram and chest X-ray. Urine drug screening was done, for drug of abuse. The volunteers were selected from departmental database, which includes some of them working with the institute and some with private firms. Volunteers were excluded if there was any evidence of physical illness, drug abuse or abnormal laboratory parameters. Subjects were trained on the test procedure on two prior occasions so as to introduce them to the test procedure and to make them familiar with the testing device. All the recordings were carried out in the morning between 7.30 am and 10:00 am after a light breakfast.

Study medication

Each CAPROS® 250mg capsule,is an aqueous extract of the edible fruits of Phyllanthus emblica (Amla), containing not less than 60% of low molecular weight hydrolysable tannins comprising Emblicanin-A, Emblicanin-B, Punigluconin and Pedunculagin as the bioactives. Each placebo capsule contains microcrystalline cellulose (49.7% w/w), lactose (49.5%) and magnesium stearate (0.69% w/w). Both study medications were supplied by Natreon, Inc. USA.

Study procedure

The study was a double-blind placebo controlled crossover design. All eligible subjects were randomized to receive either two capsules of proprietary *P. emblica* extract 250 mg twice-a-day or two capsules of placebo twice-a-day for 14 days. Subjects were housed in the department and after an overnight fast and abstinence of caffeine containing beverages, alcohol and smoking for at least 12 h, the study procedures were initiated. Before any testing, each subject rested in a supine position for 20 min in a quiet, temperature-controlled (26°C ± 1°C) room. Subjects were asked to breathe normally and to remain at rest during the cardiovascular measurement. Subjects were permitted to listen to music and to read, except during periods of cardiovascular measurement. After stabilizing in an ambient environment the baseline arterial stiffness was recorded with sphygmocor, after which cold pressor test (CPT) was performed as described below. Then the arterial stiffness was again recorded within 2 min of performing CPT. Then the subject was given study medication and asked to take two capsules twice-a-day of the study medication allocated to them as per prior randomization schedule with 240 ml of water. The same procedure was repeated after 2 weeks of treatment. A washout period of 14 days was given between the treatments. Subjects then crossed over to receive the second formulation two capsules twice daily for 2 weeks. All the same test procedures were repeated before and after treatment.

Recording of vital parameters

Brachial BP and HR were measured with an automated digital BP monitor (OMRAN, SEM-1) and a mean of three readings was taken. All readings were taken with cuff placed on the subject's non-dominant arm positioned at heart level with the forearm resting on a table.

Cold stimulation technique

The recording was performed in a temperature controlled room at 24°C. After 10 min of rest, subject's BP was recorded. Then the subject placed his non-dominant hand up to the wrist with fingers wide apart in a temperature controlled hot water bath at 35°C for 2 min. 15 s before transferring the arm into cold water bath, the BP cuff was inflated to 20 mm Hg below subject's diastolic BP. Then the subject was asked to keep his hand in cold water bath up to the wrist with fingers wide open maintained at 1°C ± 0.5°C, until he was able to sense unbearable pain (indicated by raising the

finger of dominant hand). Then the subject was then asked to immerse his hand again in hot water bath maintained at 35°C for 1 min for normalization of temperature.[10]

Measurement of wave reflection indices

Arterial stiffness was measured by using a validated, commercially available system (SphygmoCor; AtCor Medical, Australia) that employs the principle of applanation tonometry and appropriate acquisition and analysis software for non-invasive recording and analysis of the arterial pulse.[11-13] Augmentation index (AIx) and augmented pressure of the central (aortic) pressure waveforms were measured as indices of wave reflections. The AIx (defined as augmented pressure divided by pulse pressure and expressed as a percentage) is a composite measure of the magnitude of wave reflections and arterial stiffness, which affects timing of wave reflections. The subendocardial viability index, an indicator of myocardial workload and perfusion (O_2 supply vs. demand) was calculated as the ratio of the integral of diastolic pressure and time to the integral of systolic pressure and time.[14]

Statistical analysis

As this is a pilot study, the test has been carried out in 15 healthy volunteers. ANOVA and paired *t*-test was used for evaluation. Two-way ANOVA was used for the analysis. $P < 0.05$ was considered to be statistically significant. All statistical analysis was performed using GraphPad Prism 4, Sandiego, CA, USA.

RESULTS

A total of 15 male volunteers were screened and three were excluded due to abnormal laboratory results (two volunteers had abnormal elevated Serum glutamic pyruvic transaminase (SGPT) and one had mildly elevated BP). The remaining 12 volunteers were randomized to receive either *P. emblica* or placebo capsule in crossover manner. All the randomized subjects completed the study and were evaluated for cardiovascular measurements. The mean age of the study participants was 25.62 ± 2.32 years and mean body mass index 22.42 ± 2.32 kg/m^2.

In healthy human subjects, CPT is known increase BP. In the present study, the CPT produced marked increase in cardiovascular parameters when compared to baseline in both groups. It has been suggested that increased sympathetic activation and BP in response to cold exposure may contribute to cardiovascular changes.[15,16] Sympathetic activation could lead to an increase in peripheral arterial stiffness via vasoconstriction, resulting in increased BP.[17] The present study also showed significant increase in BP after CPT compared with baseline. The BP response to CPT was attenuated after 2 weeks of treatment with *P. emblica* extract, contributing to decrease in mean systolic and diastolic BP compared with baseline and placebo [Table 1]. CPT also increases arterial stiffness, which results in increase in aortic augmentation pressure and AIx as measured by sphygmocor. The increase in AIx produced by CPT was also significantly reduced by *P. emblica* extract [Table 1], resulting in 7% decrease in AIx compared with baseline and placebo [Figure 1].

Sub-endocardial viability ratio (SEVR) is an indicator of myocardial perfusion, which is reduced by CPT as compared to baseline [Table 1]. The present study also showed 14% increase in SEVR on treatment with *P. emblica* extract, which was significant compared to baseline and placebo. Further no significant changes were observed in the evaluated parameters in placebo group [Figure 2].

Both study medications were well-tolerated with two volunteers reported mild adverse effects, abdominal discomfort in *P. emblica* extract and one with headache

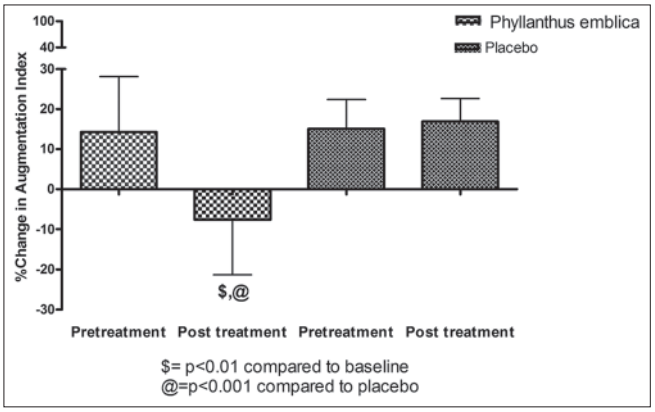

Figure 1: Mean percent change in augmentation index induced by cold pressor test after treatment with *Phyllanthus emblica* and placebo

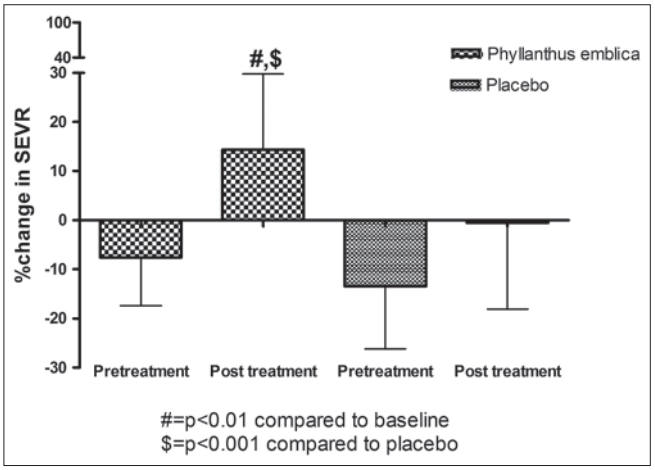

Figure 2: Mean percent change in subendocardial viability ratio induced by cold pressor test after treatment with *Phyllanthus emblica* and placebo

Table 1: Effect of Phyllanthus emblica and Placebo on cold pressor induced changes in wave reflections

	Phyllanthus emblica 250 mg				Placebo			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
	Baseline	Within 2 min of hand immersion	Baseline	Within 2 min of hand immersion	Baseline	Within 2 min of hand immersion	Baseline	Within 2 min of hand immersion
HR (bpm)	7.58±5.48	72.67±6.15	74.38±7.26	68.88±4.24*	68.60±3.03	72.15±10.44	66.71±2.22	72.71±9.08
AAP (mmHg)	2.08±4.94	4.17±5.61	1.42±4.44	1.17±3.78*	3.0±3.65	5.40±4.09	2.33±2.74	4.92±1.98
AIX (%)	104.08±16.33	118.0±16.25	113.75±17.56	104.0±14.34†,‡	100.75±5.50	115.83±6.89	100.25±3.89	117.24±7.62
SEVR (%)	160.22±10.94	147.72±15.61	146.39±17.79	165.13±9.07§,‖	162.14±13.21	139.76±20.20	148.46±18.70	146.38±15.67
RSBP	113.58±3.15	126.00±2.73	123.42±4.03	120.58±2.27†,**	112.83±2.33	121.50±4.17	117.17±4.78	124.50±4.17
RDBP	69.92±4.96	77.50±5.47	76.00±5.48	70.50±7.09§,‡	69.67±2.50	76.25±3.39	70.25±2.83	78.25±2.67
RMAP	84.48±5.13	93.45±4.87	91.59±4.95	87.08±6.70§,#	83.90±1.86	88.70±4.52	84.55±3.40	91.50±6.47
RPP	43.67±4.64	48.50±6.24	47.58±7.01	50.83±5.98*	43.17±3.59	48.92±5.95	46.25±7.05	47.33±5.16
ASBP	98.96±7.92	109.92±6.39	107.67±5.26	103.58±6.75#,‡	96.04±3.03	106.58±5.20	99.75±4.79	109.75±3.91
ADBP	71.29±6.16	77.46±6.17	75.54±5.09	70.75±7.23§,‖	68.17±5.94	76.33±6.24	72.42±4.72	79.21±3.66
AMAP	82.28±6.55	90.15±6.06	88.12±6.05	83.88±7.62§,**	76.92±4.15	82.73±6.54	81.69±4.20	89.47±3.54
APP	27.67±7.24	32.46±5.10	32.13±2.87	34.42±9.89*	28.08±4.23	31.30±7.99	28.72±5.08	32.79±5.44

HR=Heart rate; AAP=Aortic augmentation pressure; AIx=Augmentation index; SEVR=Subendocardial viability ratio; RSBP=Radial systolic blood pressure; RDBP=Radial diastolic blood pressure; RMAP=Radial mean arterial pressure; RPP=Radial pulse pressure; ASBP=Aortic systolic blood pressure; ADBP=Aortic diastolic blood pressure; AMAP=Aortic mean arterial pressure; APP=Aortic pulse pressure. Data (expressed in mean±SD)*Non-significant compared to baseline and placebo; †$P<0.001$ compared to baseline; ‡$P<0.01$ compared to placebo; §$P<0.01$ compared to baseline; ‖$P<0.001$ compared to placebo; #$P<0.05$ compared to baseline;**$P<0.05$ compared to placebo; SD=Standard deviation

in placebo group and none of the subjects discontinued the drugs because of these adverse effects. There was no significant change in safety lab parameters at the end of treatment when compared to baseline.

DISCUSSION

In the present study, CPT was used as a model to produce the stress induced cardiovascular changes in healthy volunteers. Increased aortic stiffness, enhanced wave reflection, increased systolic pressure and pulse pressure (and especially central pulse pressure) have been identified as independent components of cardiovascular risk.[18] *E. officinalis* has been reported to produce cardiovascular adaptation by augmenting endogenous antioxidants and protects heart from oxidative stress in animal models.[19] The antioxidant and cardioprotective effect of *E. officinalis* was also elaborated by Bhattacharya *et al.*, in animal models.[20]

Cold pressor stress is an experimental stress paradigm based on a short-term painful stimulation by immersing the hand into ice-cold water. This paradigm has been frequently used in stress research and is known to be associated with substantial activation of the autonomic nervous system as well as mild to moderate activation of the HPA axis.[21,22] Studies have shown that CPT model can be used to examine the cold induced sympathetic activation on vascular function. The cold exposure results in sympathetic activation, vasoconstriction and increased systolic and diastolic BP and also increases aortic augmentation index (AIx), a measure of wave reflection, leading to augmented central systolic pressure.[23-26] The increase in AIx induced by CPT in the present study was significantly reduced on treatment with *P. emblica* extract.

Tapas *et al.*, in their study demonstrated that immersion of the right hand up to the wrist in 4°C cold water for 60 s stressed the healthy subjects. Stress exerted through the CPT for a minute stimulated the sympathetic nervous system and produced an acceleration of the HR and rise in BP, both systolic and diastolic, in comparison to those recorded before the foregoing test in all the normotensive volunteers.[27] Our study observations are in agreement with these published reports. In the present study, there was increase in, radial and aortic systolic and diastolic BP after CPT. These stress induced changes on cardiovascular parameters were attenuated on treatment with *P. emblica* extract, whereas the placebo group did not show any significant change in response to CPT induced stress. The effect of CPT on HR response and BP is less well-defined, more variable on an individual basis and not homogeneous for the entire CPT period as reported by Mourot *et al.*,

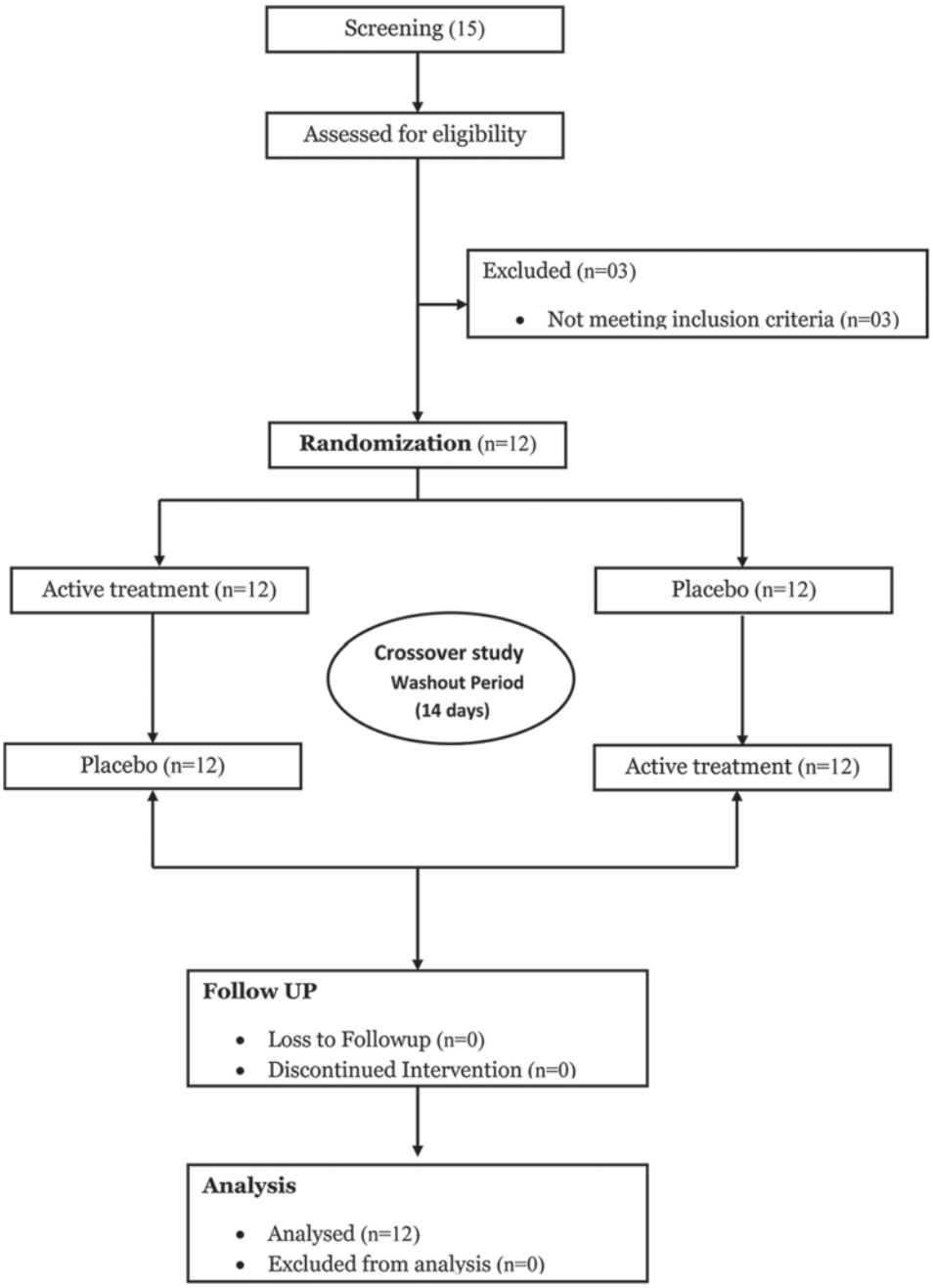

Chart 1: Consort flow chart

in normal subjects and the similar variations in HR and BP in response to CPT was also observed in the present study.[28] This explains the variability in vascular reactivity in response to cold pressor stimulation in healthy volunteers.

SEVR is an index of myocardial oxygen supply and demand. Low SEVR has been shown to be associated with coronary artery disease, severity of Type I and Type II diabetes, decreased renal function and a history of smoking.[14] Estimation of SEVR by using applanation tonometry may provide a reliable tool for the assessment of coronary microcirculation in essential hypertensives with indications of myocardial ischemia and normal coronary arteries. The decrease in SEVR observed in the present study after cold pressor induced stress, is due to vasoconstriction and decreased myocardial perfusion.

Oxidative stress has been implicated in the pathophysiology of stress and associated cardiovascular changes. Thangaraj *et al.*, investigated the antioxidant property of *E. officinalis* during restrain stress in albino rat. Administration of *E. officinalis* (500 mg/kg body weight for 30 days) significantly prevented the restrain-stress-induced oxidative stress and elevation in lipid peroxidation levels.[29] In another

recent study, the antihypertensive effect of administration of hydro-alcoholic lyophilized extract of *E. officinalis* given in different doses (75, 150 and 300 mg/kg/day) for 5 weeks caused reduction in arterial BP in rats. Increased thiobarbituric acid substances and decreased endogenous antioxidants including glutathione s- transferase and superoxide dismutase activity in serum, heart and kidney tissues of hypertensive rats were also normalized.[13] Gopa *et al*., demonstrated that Amla therapy given in the dose of 500 mg capsule once daily at night for 42 days produced reduction in BP in hypertensive patients.[30] The well-established antioxidant and cardio protective actions of *E. officinalis* explains the possible mechanism of *P. emblica* extract in reducing cardiovascular changes produced by CPT.

CONCLUSION

Proprietary *P. emblica* extract used in the present study showed significant decrease in cold pressor stress test induced changes on aortic wave reflections, suggesting the beneficial effects of this formulation in reducing stress induced cardiovascular changes. Further clinical studies are warranted to evaluate the beneficial effects of *P. emblica* in patients with other associated diseases and in those residing in cold climatic conditions.

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