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EVALUATION OF THE EFFECT OF A STANDARDIZED AQUEOUS EXTRACT OF THE FRUITS OF *EMBLICA OFFICINALIS* ON MENTAL STRESS INDUCED CARDIOVASCULAR CHANGES IN HEALTHY HUMAN SUBJECTS

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Keywords:

Augmentation index, Mental stress test, Cardiovascular disease, Arterial wave reflections, *Emblica officinalis*

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ABSTRACT: Introduction: 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. The present study was undertaken to evaluate the effect of *Emblica officinalis* versus placebo on mental stress induced changes in cardiovascular hemodynamic parameters and arterial wave reflection properties in healthy human subjects. **Materials & Methods:** In this randomized, double-blind, placebo-controlled, crossover study, participants received either two capsules of standardized *Emblica officinalis* fruit extract 250 mg or placebo daily for 2 weeks, as per prior randomization schedule. Pharmacodynamic parameters were recorded before and after a standardized mental stress test, at baseline and at the end of treatment. After a 2 week washout, participants crossed over to receive the other treatment. **Results:** A total of 12 volunteers completed the study. Compared to baseline, *Emblica officinalis* fruit extract produced a statistically significant decrease in Aortic augmentation pressure (from 6.6±2.15 to 4.6±2.02); ($p< 0.01$) and in Augmentation Index AIx (from 120.1±12.80 to 116.2±12.63); ($p< 0.05$). There was a reduction in Radial and Aortic systolic (SBP) and diastolic (DBP) pressures and an increase in Sub Endocardial Viability Ratio (SEVR), which was however not statistically significant. **Conclusion:** Acute mental stress results in temporary increase in arterial stiffness and wave stiffness. Standardized *Emblica officinalis* fruit extract decreased the mental stress induced changes on aortic wave reflections in normal healthy subjects. These results suggest the beneficial effect of *Emblica officinalis* in mitigating the effects of stress, thereby reducing the risk of acute cardiovascular morbidity.

INTRODUCTION: Stress has been defined as "A state, in which a set of events modify steady state conditions so as to activate adaptive mechanisms."[1] According to Dr. Hans Selye, a pioneer stress researcher in the 1930s, stress includes not only the body's response to physical and psychological demands, but also to the mental and emotional demands.

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In the general population, individuals who lead a stressful lifestyle and show "type A" behavior are recognized to be at risk for coronary heart disease (CHD). [2] Mental stress is more characteristic of the present day life and demands an active coping mechanism causing elevated sympathetic responses. This can increase the heart rate and arterial stiffness and thus increase the blood pressure of the individual. Several studies have documented that cardiovascular risk factors have an unfavorable impact on arterial function, including decreased endothelial function, increased arterial stiffness, and central blood pressure (BP), all of which are predictive of all cause cardiovascular mortality.[3 - 6]

Chronic mental stress can lead to atherosclerosis and coronary artery disease, thereby having a negative impact on cardiovascular health .[7, 8] Acute hemodynamic reactions to mental stress among healthy adults are determined in part, by the arterial stiffness and the sensitivity of arterial baroreflex. [9] Prolonged impairment of endothelium–dependent relaxation may result even after a brief episode of mental stress; this may represent an important link between repeated or chronic stress and acceleration of atherogenic process.[10, 11]

At present, there are only a few pharmacological agents which could reduce the arterial stiffness. However, new and more effective treatments with fewer side effects are highly desirable. Further, there is a paucity of studies using the herbal formulations on reversal of the effect of mental stress on haemodynamic parameters. The approach ideally needs to be oriented directly to arterial function and represent a simple preventive approach to the same. Ayurvedic systems of medicine have used *Emblica officinalis* Gaertn. Or *Phyllanthus emblica* Linn. commonly known as the Indian gooseberry or "Amla", in the treatment of a wide range of diseases like jaundice, leucorrhea, inflammation, diarrhea, cerebral insufficiency and mental disorders and atherosclerosis[12, 13, 14].

It has been reported to be a rich source of polyphenolic compounds, which play an important role in scavenging free radicals. *Emblica officinalis* extract has been tested for various pharmacological activities. The fruit extract is known to possess hepato-protective, chemo-preventive, anti-atherogenic, anti-proliferative, cardio protective, hypo-lipidaemic, anti-inflammatory, antidiabetic, analgesic and antipyretic and adaptogenic activities. [15] It has been shown to attenuate the ischemic injury and improve the contractile function of the myocardium.[16] *Emblica officinalis* has been described by Ayurveda as an important revitalizing medicine which helps to adapt to various types of stress.[15]

Therefore, the present study was undertaken to assess the effect of *Emblica officinalis* on the mental stress induced changes in cardiovascular pharmacodynamic parameters and aortic wave reflections in healthy human subjects.

MATERIALS AND METHODS:

Study Medication: Identical looking test product and placebo product capsules were supplied by Natreon, Inc., New Brunswick, NJ, USA. Each capsule of the test product, CAPROS®, contained 250 mg of an aqueous extract of the edible fruits of *Emblica officinalis*, standardized by HPLC to contain not less than 60% of low molecular weight hydrolysable tannins, comprising Emblicanin-A, Emblicanin-B, Pedunculagin and Punigluconin as bio-actives. The Placebo capsules contained the same excipients as in the test product, namely, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, talc and magnesium stearate. The HPLC chromatogram of CAPROS® is shown in **Fig. 1.**

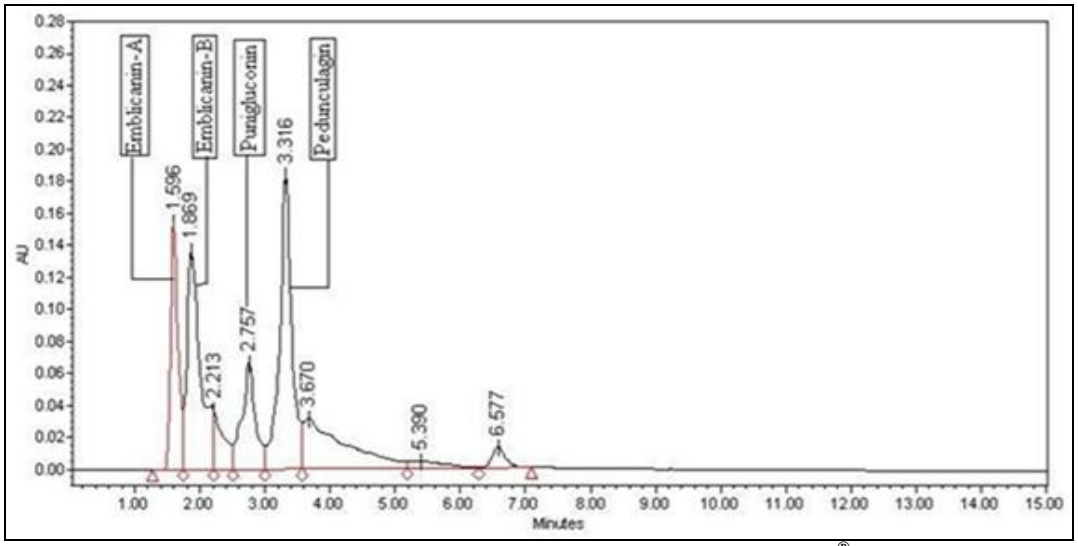

FIG. 1: HPLC CHROMATOGRAPHY OF CAPROS®

Study population: A total of twenty healthy male participants aged between 20-30 years, body mass index (BMI) between 18 - 24.9 kg/m^2 and nonsmokers were screened for the study. A full medical history was taken and physical examination, including hematological and biochemical screening, and an electrocardiogram was done during the screening process. Participants who were willing to comply with the requirements of the study and give written informed consent and those who were able to operate and perform basic tasks on a computer were included in the study. Participants who had any evidence of physical illness, smoking, drug abuse or abnormal cardiac, hepatic, renal functions, and those who had used CNS stimulant drugs in the past two weeks were excluded from the study.

After screening, a total of 12 eligible subjects were enrolled in the present study and randomized to study medications. All the participants were trained on the study procedure on at least two occasions prior to the study to introduce them to the study procedure and make them familiar with the testing device.

Study Methodology: This randomized, double blind, placebo-controlled, crossover study has been conducted during January - June 2016 at Nizam's Institute of Medical Sciences (NIMS), Hyderabad, India after approval from the Institutional Ethics Committee. The study was registered with the Clinical Trials Registry-India (CTRI) and the reference number is REF/2016/08/012073.

Participants were randomized by block randomization. They were divided into 3 blocks of 4 participants each and allocated to treatment and placebo groups in 1:1 ratio to receive either *Emblica officinalis* two capsules of 250mg each or two capsules of placebo twice daily for 2 weeks. Both the investigator and patient were masked to the treatment received by identical looking drug and placebo tablets. The subjects arrived at the laboratory following an overnight fast and abstinence from caffeine containing beverages or alcohol for the past 24 hrs. confirmed by a questionnaire at the beginning of the session. Before any procedure was started, each subject rested in supine position for 20 min in a quiet, temperature-controlled (26°±1°C) room.

Brachial Blood Pressure (BP) and Heart Rate (HR) were measured with an automated digital BP monitor (OMRON®) and a mean of 3 readings was taken. All the readings were taken with cuff placed on the subject's non-dominant arm positioned at heart level with the forearm resting on a table. The arterial stiffness was recorded using a tonometric device, SphygmoCor (AtCor Medical, Australia). Then the mental stress tests were assessed using a battery of tests of psychomotor performance. The blood pressure and arterial stiffness were recorded again within 2 minutes of performing the stress test. Subjects then received the given study medication and were asked to take the capsules as per the prior randomization schedule for 14 days. All the measurements were recorded 3 hrs. post drug administration on Day 15.

After a washout period of 14 days, the subjects were crossed over to the other treatment group and the test procedures were repeated. Any adverse reaction was noted in the case record form. Safety lab investigations for hematological, hepatic and renal biochemical parameters were conducted before and at the end of the study and also as and when required (in case of any adverse drug reaction (ADR). Compliance to therapy was assessed by pill count method.

Mental Stress Test: In healthy subjects, induction of mental stress causes a temporary and reversible endothelial dysfunction and arterial stiffness and serves as a model for studying the effect of drugs. In the present study, mental stress was induced by instructing the participants to perform computerized psychometric performance tests like Choice Discrimination Test (CDT), Digit Symbol Substitution Test (DSST) and Digit Vigilance Task (DVT) as quickly and as accurately as possible for three times. [17] The total duration of the mental stress test was 5 min. During the test, a metronome was played loudly with headphones, as a distracter. This also acted as a source of mental stress.

Measurement of Wave Reflection Indices: The indices of wave reflections were measured as Augmentation Index (AIx) and Augmented Pressure of the central (aortic) pressure waveform. Augmented Aortic Pressure (AP) represents the pressure, which is added to the incident wave by the returning reflected wave. The left ventricle has

to cope with this pressure boost which is caused by the wave reflection.[18] The AIx is expressed as a percentage (defined as augmented pressure divided by pulse pressure). Larger values of AIx indicate increased magnitude of wave reflections from the periphery due to increased pulse wave velocity (due to increased arterial stiffness).[19] Because the AIx is influenced by changes in heart rate (HR), it was corrected accordingly. The AIx was measured by using a validated system (SphygmoCor), that employs the principle of applanation tonometry and appropriate software for non-invasive recording and estimating central aortic pressure.[20]

Central (aortic) arterial pressure has been derived from radial artery recordings, with the use of a generalized transfer function, which has been shown to give an accurate estimate of the central arterial pressure waveform and its characteristics. Because there is practically negligible pressure pulse amplification between the brachial and the radial artery, the waveforms of radial pressure were calibrated according to sphygmomanometric systolic and diastolic pressures which were measured in the brachial artery. The Sub Endocardial Viability Index (SEVR), an indicator of myocardial workload and perfusion (O_2 supply *vs*. demand), was calculated as a pressure-time integral ratio (the ratio of diastolic pressure and time integral to the systolic pressure and time integral). [21]

Statistics Analysis: The study has been carried out in 12 healthy volunteers as a pilot study. All data were presented as Mean±SD and the results were tabulated. The mean % change for each individual pharmacodynamic parameter between the two treatments (*Emblica officinalis* fruit extract and Placebo) was calculated. For statistical significance paired t-test was done. Statistical significance was at $p<0.05$. Data analysis was performed using GraphPad Prism software, Version 7 (Graph Pad Software Inc., USA).

TABLE 1: EFFECTS OF *EMBLICA OFFICINALIS* ON MENTAL STRESS INDUCED CHANGES IN WAVEFORM REFLECTIONS (n=12)

		***Emblica officinalis* fruit extract 500 mg BID**				**Placebo**			
		Pre Treatment		**Post Treatment**		**Pre Treatment**		**Post Treatment**	
		Baseline	**Within 2 min. of stress test**	**Baseline**	**Within 2 min. of stress test**	**Baseline**	**Within 2 min. of stress test**	**Baseline**	**Within 2 min. of stress test**
HR (bpm)		66.0±4.01	67.7±4.25	66.0±3.65	67.5±3.75#	68.1±2.93	69.7±3.28	68.5±3.11	70.2±2.92
AP (mm Hg)		3.9±1.97	6.6±2.15	3.9±1.86	4.6±2.02**§	3.5±2.10	5.8±2.48	4.2±2.12	6.3±2.71
AIx (%)		115.5±12.96	120.1±12.80	113.2±12.25	116.2±12.63*§	115.3±13.18	119.7±12.98	114.8±14.31	119.2±14.21
SEVR (%)		150.3±14.37	144.5±15.02	150.7±14.18	146.2±14.26#	144.8±15.33	139.0±15.00	143.5±14.77	138.2±15.19
Radial	SP	109.8±6.79	113.5±6.89	109.3±7.48	112.5±7.82#	112.8±4.18	116.5±4.93	113.4±3.73	116.9±4.03
	DP	72.8±5.15	75.5±5.73	73.4±6.17	75.6±6.09#	72.1±4.47	74.8±4.59	73.5±4.54	76.0±4.68
	MP	85.2±4.97	88.2±5.19	85.4±6.02	87.9±5.96#	85.7±4.09	88.7±4.40	86.8±4.00	89.6±3.96
	PP	37.0±6.12	38.0±6.95	36.0±5.92	36.9±6.59#	40.7±3.27	41.7±3.53	39.9±3.29	40.9±4.43
Aortic	SP	98.8±4.30	102.2±4.47	99.2±4.47	102.2±3.63#	98.5±4.10	101.8±3.80	100.6±5.63	103.8±4.86
	DP	66.8±4.22	71.2±4.86	67.2±4.39	70.3±5.03#	66.3±2.53	70.5±3.83	69.2±3.46	72.7±3.11
	MP	77.5±3.65	81.5±4.10	77.8±3.85	81.0±3.94#	77.1±2.63	80.9±3.23	79.7±3.76	83.1±3.49
	PP	32.0±4.59	31.0±5.01	32.0±4.59	31.9±5.10#	32.2±3.66	31.3±4.31	31.5±4.46	31.2±3.13

HR: Heart Rate; AP: Aortic Augmentation Pressure; AIx: Augmentation Index; SEVR: Sub Endocardial Viability Ratio; SP: Systolic Pressure; DP: Diastolic Pressure; MP: Mean Pressure; PP: Pulse Pressure. Data expressed as Mean ± SD. # Non-significant compared to baseline and placebo; *p<0.05 compared to Pre Treatment; **p<0.01 compared to Pre Treatment; § = p<0.05 compared to Placebo Post Treatment; SD: Standard Deviation

RESULTS: A total of twenty male subjects were screened, eight subjects were excluded because of abnormal laboratory investigations, and twelve subjects were enrolled in the study. The mean age, height and weight of the subjects were 24.75±2.01 yrs., 164.81±7.01cm, and 57.81±5.57 kg respectively. The data on the effects of *Emblica officinalis* on mental stress induced changes in waveform reflections is shown in **Table 1**. There was no significant difference in the baseline hemodynamic values between the two treatment groups. Excellent compliance was noted. Both the medications were well tolerated, no subject discontinued the study. All safety lab parameters were repeated after the test procedure and found to be within normal limits. There were no serious adverse events recorded in the study.

In the present study, post mental stress test, there is a sustained increase in Radial and Aortic Systolic and Diastolic Pressure, when compared to baseline in both the groups. However, there is slight to no change in the Heart Rate during the study. (**Fig. 2**)

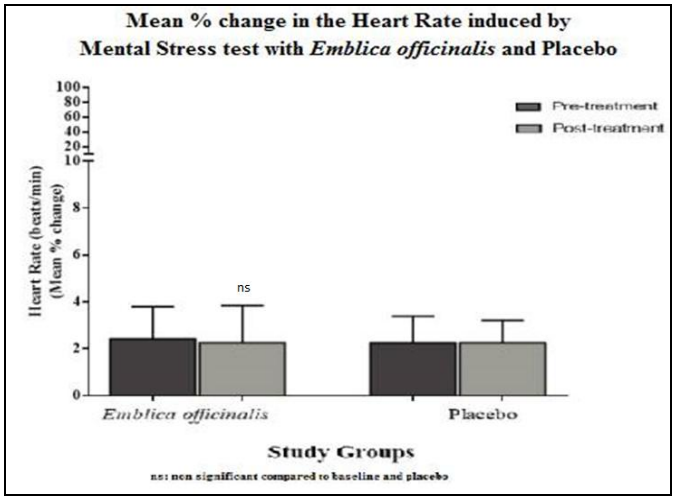

FIG. 2: MEAN % CHANGE IN THE HEART RATE INDUCED BY MENTAL STRESS TEST WITH *EMBLICA OFFICINALIS* AND PLACEBO

Augmentation Index and Aortic Augmentation Pressure showed a sustained increase with mental stress, denoting an increase in the wave reflections. The Sub-Endocardial Viability Ratio (SEVR) is reduced by mental stress compared to baseline.

Compared to pre-treatment, *Emblica officinalis* fruit extract produced a statistically highly significant decline ($p<0.01$) in Aortic Augmentation Pressure (from 6.6±2.15 to 4.6±2.02 mm Hg), whereas, it increased (from 5.8±2.48 to 6.3±2.71 mm Hg) with Placebo (**Fig. 3**).

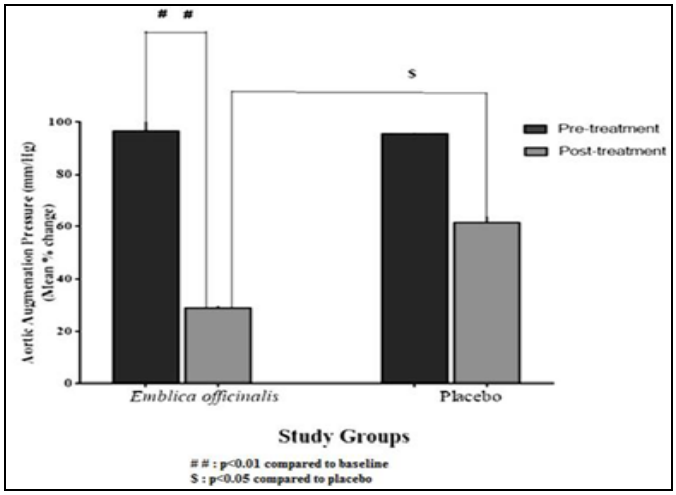

FIG. 3: MEAN % CHANGE IN AUGMENTATION PRESSURE INDUCED BY MENTAL STRESS TEST WITH *EMBLICA OFFICINALIS* AND PLACEBO

With respect to Augmentation Index, *Emblica officinalis* fruit extract produced a statistically significant decline ($p<0.05$) (from 120.1±12.80 to 116.2±12.63), whereas, it decreased (from 119.7±12.98 to 119.2±14.21) with Placebo (**Fig. 4**) (**Table 1**).

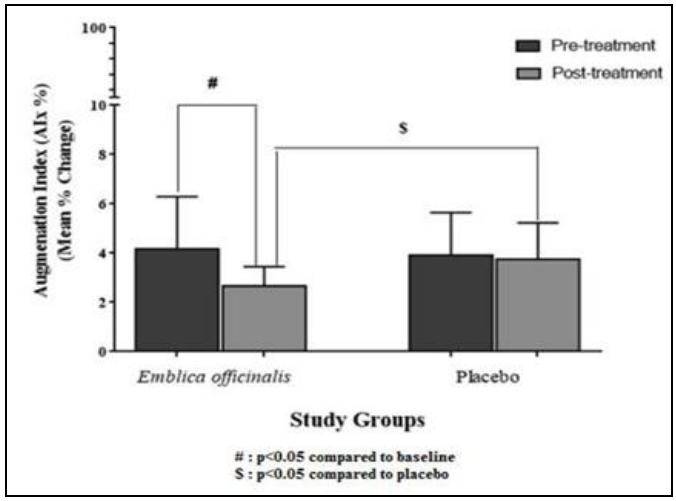

FIG. 4: MEAN % CHANGE IN AUGMENTATION INDEX INDUCED BY MENTAL STRESS TEST WITH *EMBLICA OFFICINALIS* AND PLACEBO

The group treated with *Emblica officinalis* fruit extract post stress test, showed a lesser decrease in mean % change of SEVR (-3.0±1.32 %), compared to the same in the pre-treatment (-3.9±2.37 %) and Placebo groups (-3.8±1.89 %). This was however not statistically significant. (**Fig. 5**).

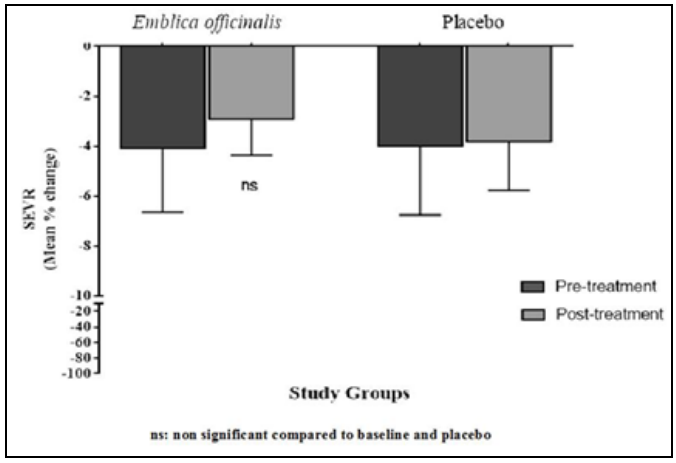

FIG. 5: MEAN % CHANGE IN SUB-ENDOCARDIAL VIABILITY RATIO (SEVR) INDUCED BY MENTAL STRESS TEST WITH *EMBLICA OFFICINALIS* AND PLACEBO

The group treated with *Emblica officinalis* fruit extract showed a decrease in mean % change of both the radial and aortic SBP and DBP pressure post stress test, compared to both the Pre-treatment

and placebo groups. This was however found to be statistically nonsignificant. (**Fig. 6)** (**Table 1**).

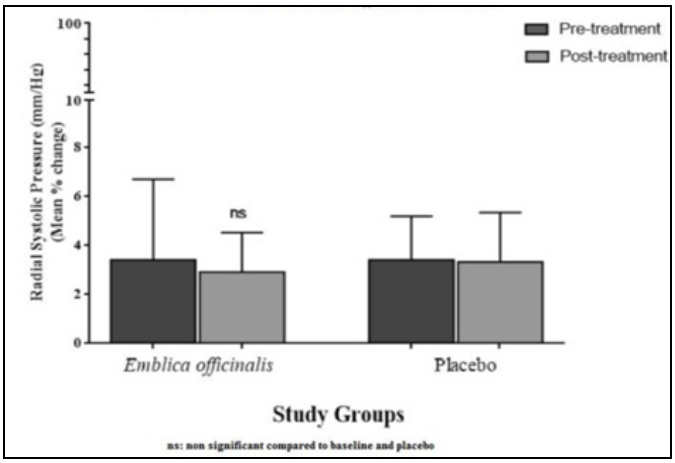

FIG. 6: MEAN % CHANGE IN RADICAL SYSTOLIC PRESSURE INDUCED BY MENTAL STRESS TEST WITH *EMBLICA OFFICINALIS* AND PLACEBO

These observations indicate that *Emblica officinalis,* by decreasing the Augmentation Index (as indicated by decreased wave reflections from the periphery and/or delayed return of the reflected wave) leads to decreased arterial stiffness. This in turn decreases cardiovascular morbidity and may improve general wellbeing.

DISCUSSION: Acute stress results in a substantial increase in circulating levels of catecholamines *i.e.* adrenaline, noradrenaline, and cortisol [22] causing an increase in cardiovascular reactivity. It leads to a hemodynamic pattern of increase in blood pressure, [23, 24] heart rate and cardiac output. The majority of studies investigating the effects of acute mental stress make use of various cognitive demands such as mental arithmetic, reading numbers backward, computer quiz, speech stress (public speaking), and reaction time stress tests.[25] These tests are known to induce circulatory reactions similar to those that evoked by the classical defense reaction.[26, 27] The stressors chosen in this study were more closely mimicking the stressors in real life, such as performance under time pressure with constant surveillance of the number of errors and lack of support from colleagues. In the present study, we found an increase in the above parameters after an episode of acute mental stress when compared to baseline, which were consistent with a number of other similar studies.[26, 28, 29]

Pulse wave analysis using applanation tonometry has been used as the technique for assessing central hemodynamics. As aortic and arterial stiffness increase, the transmission velocity of both forward wave of left ventricular ejection and reflected waves from periphery increase.[30] This causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole called augmentation of the central aortic pressure wave or augmented pressure (AP). Increased arterial stiffness and associated increased amplitudes of wave reflections are important independent prognostic indicators of cardiovascular disease risk because they affect left ventricular function, coronary blood flow and mechanical integrity of arteries.[22, 31, 32]

The main finding of the present study is that the *Emblica officinalis* treated group has produced a lesser increase in augmented pressure (AP) from baseline values ($p<0.01$) compared to the increase seen post stress in the subjects before the treatment was given, which reflects an improvement in the aortic stiffness, thus an improved status of cardiovascular health. Augmented pressure (AP) is often expressed as a percentage of total cPP (central PP). (AP/cPP x 100) called Augmentation Index (AIx). AIx is an independent predictor of cardiovascular disease as suggested by a recent meta-analysis.[33]

The Augmentation Index (AIx) is an indirect measure of arterial stiffness which increases with age. A decrease in the Augmentation Index (as indicated by decreased wave reflections from the periphery and/or delayed return of the reflected wave) indicates decreased arterial stiffness.[34] Arterial stiffness describes the reduced capability of an artery to expand and contract in response to pressure changes.[33]

It is measured by carotid-femoral pulse wave velocity, an independent predictor of cardiovascular morbidity and mortality in hypertensive patients, type 2 diabetes, end-stage renal disease and in elderly populations. Given the predictive power of pulse wave velocity, AIx, augmentation pressure, identifying strategies that prevent or reduce stiffening may be important in the prevention of cardiovascular events.[34] Further arterial stiffness increases at higher loading pressures without any structural change.[33]

Theoretically, this is because stress is transferred from elastin to collagen fibers.[32, 34] In the present study, the increase in AIx induced by mental stress was reduced ($p<0.05$) with *Emblica officinalis* fruit extract suggesting decreased arterial stiffness and hence may be beneficial in reducing cardiovascular morbidity.

Sub Endocardial Viability Ratio (SEVR), also known as "Buckberg Index" calculated through pulse wave analysis, is an index of myocardial oxygen supply and demand and has been identified as an independent predictor of coronary flow reserve.[35] It has been shown in the previous studies that SEVR decreases following exposure to stress, probably due to vasoconstriction leading to decreased myocardial perfusion.[36] The resulting low SEVR has been shown to be consistently associated with coronary artery disease.

In the present study, the SEVR has decreased post stress test which is in accordance to the studies previously done. The group treated with *Emblica officinalis* fruit extract has shown a lesser decline in SEVR value post stress test, compared to the decline before treatment indicating an improved myocardial perfusion. This was however not statistically significant.

The rise produced in radial and aortic SBP and DBP post-acute mental stress were decreased in the group treated with the *Emblica officinalis* fruit extract however the changes detected were not statistically significant, whereas the placebo group did not show any changes. Elevated brachial artery pressure (BP) is a classic major risk factor and a powerful predictor of cardiovascular organ damage; morbidity and mortality.[16] Studies have shown that increased arterial stiffness independent of brachial artery BP appears to be a novel and independent risk factor for cardiovascular disease and mortality in well-functioning older adults and hypertensive patients.[33]

In the present study *Emblica officinalis* fruit extract decreased arterial stiffness in healthy subjects during mental stress; thus may alleviate cardiovascular events and improve cardiovascular health.

Emblica officinalis is regarded as an important Ayurvedic herb, having a potent antioxidant activity. This ability of *Emblica officinalis* to act as an antioxidant may affect hemodynamic parameters and left ventricular contractile function and explain its potential as a cardio protective agent. [37, 38] Accordingly, in the present study it has been demonstrated that a continued administration of the fruit extract of *Emblica officinalis*, at a dose of 500 mg twice daily for 14 days has shown a beneficial anti stress activity without any side effects. The capacity to up-regulate the PI3K/Akt/GSK3β/β-catenin cardio protective pathway, and the ability to preserve cardiac tissue during ischemia-reperfusion injury could be an explanation for the possible mechanism of *Emblica officinalis* fruit extract in reducing cardiovascular changes produced by mental stress.[39]

CONCLUSION: In the present study, involving normal, healthy subjects, mental stress for a brief period has induced changes in wave reflections (indicating changes in aortic stiffness), and also has increased systolic pressure and pulse pressure. This study provides robust support to the view that mental stress reactivity can predict the patients prone to overt hypertension and its sequelae. *Emblica officinalis* fruit extract decreased these effects, thereby suggesting the beneficial role of this formulation in reducing the cardiovascular pharmacodynamic effects of mental stress and hence in decreasing the cardiovascular morbidity. Thus, it may be suggested that *Emblica officinalis* may be used as a safe and effective formulation in combating cardiovascular haemodynamic responses encountered during day to day stress.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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