



Research Article

EVALUATION OF CARDIOVASCULAR AND PHARMACODYNAMIC EFFECTS OF *TERMINALIA ARJUNA* SINGLE DOSE AND MULTIPLE DOSE IN HEALTHY HUMAN MALES

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ABSTRACT

Context: *Terminalia arjuna* is a medicinal plant used as a cardiogenic in Ayurveda. The presence of potent antioxidant constituents results in improvement in endothelial dysfunction seen in coronary artery disease.

Aim: To evaluate the cardiovascular and pharmacodynamic effects of single and multiple doses of *Terminalia arjuna* in healthy human male subjects.

Settings and Design: Randomized, double blind, placebo-controlled dose ranging study.

Methods and Material: After approval from the institutional ethics committee, written informed consent was taken from subjects. Eligible subjects were allocated to the single and multiple dose groups, with six subjects in each group. The active treatment (*Terminalia arjuna* crude powder capsules of 500 mg, 1000 mg, 1500 mg & 2000 mg single dose and 1500 mg multiple dose) and placebo capsules were administered in 2:1 ratio in all the study groups. Vital parameters and pharmacodynamic assessment of cardiac profiling were performed using cold pressor test (CPT), tilt table and platelet aggregation tests.

Statistical analysis used: The data was presented as mean \pm SD. No statistical tests were applied as the sample size was less (n=6 in each group).

Results: During CPT, *Terminalia arjuna* attenuated the rise in SBP, DBP and pulse rate in all the treatment groups compared to baseline. The CPT induced arterial stiffness was counteracted by treatment with 1500 mg & 2000 mg single dose and 1500 mg multiple doses of *Terminalia arjuna*. Cardiac output was increased with 1500 mg multiple dose at 60° tilt (Day 1) and at 45° & 60° phases of the tilt (Day 11). Platelet aggregation was markedly inhibited in 1500 mg multiple doses at Day 11.

Conclusions: Treatment with single (1500 mg & 2000 mg) and multiple doses (1500 mg for 10 days) of *Terminalia arjuna* produced remarkable changes in the cardiovascular profile. Further studies in larger number of subjects and in patients with cardiovascular diseases are needed to confirm these effects.

KEYWORDS: *Terminalia arjuna*, Cardiogenic, Cold pressor test.

INTRODUCTION

Terminalia arjuna (TA) is a medicinal plant used as a cardiogenic in Ayurveda. [1] Its stem bark possesses glycosides, large quantities of flavonoids, tannins and minerals. Flavonoids have been detected to exert antioxidant, anti-inflammatory and lipid lowering effects while glycosides are cardiogenic. The presence of potent antioxidant constituents results in improvement in endothelial dysfunction seen in coronary artery disease and thus making *Terminalia arjuna* unique amongst currently used medicinal plants. [2]

The stem bark of *Terminalia arjuna* possesses diuretic, inotropic, and chronotropic properties. [3]

Experimental studies of the aqueous extract of *Terminalia arjuna* have demonstrated dose-dependent decrease in blood pressure [3], an increase in the coronary flow [4], bradycardia [5], and an increase in the force of contraction of cardiac muscle. The inotropic effect is considered to be mediated through the high concentration of Ca⁺⁺ present in the plant. [6]

Further, studies have shown that the dried bark augments endogenous antioxidant compounds and thus prevent oxidative stress associated with ischemic-reperfusion injury of the heart [7] thereby protecting the myocardium against ischemic damage. [8]

Clinical studies involving stable angina patients evaluated the anti-ischemic effect of bark powder of *Terminalia arjuna* given as 500 mg three times a day. There was a significant fall in the mean anginal frequency, systolic blood pressure (SBP) and serum cholesterol levels with improvement in ECG changes.^[9]

However, there are no dose response studies evaluating the effects of *Terminalia arjuna* in healthy human subjects. Hence, this study was undertaken to evaluate the cardiovascular and pharmacodynamic effects of single and multiple doses of *Terminalia arjuna* in healthy human male subjects.

METHODOLOGY

The study was designed as a randomized, double blind, placebo-controlled dose ranging study to evaluate the effect of single dose (500 mg, 1000 mg, 1500 mg & 2000 mg) and multiple doses (500 mg three times a day for 10 days) of *Terminalia arjuna* (TA), conducted in the Department of Clinical Pharmacology and Therapeutics, NIMS, Hyderabad. The study was approved by the institutional ethics committee and all subjects gave written informed consent prior to participation in the study.

Healthy male subjects were screened according to the eligibility criteria of the study protocol and all vital parameters and lab safety parameters were performed one week prior to study initiation.

The eligible subjects were allocated to the single and multiple dose study groups, with six subjects in each group. The active treatment (*Terminalia arjuna* crude powder capsules of 500 mg, 1000 mg, 1500 mg & 2000 mg single dose and 1500 mg multiple dose) and placebo capsules were administered in 2:1 ratio in all the study groups, with 4 subjects receiving *Terminalia arjuna* and 2 subjects receiving placebo, as per prior randomization schedule. All the single doses were given on the day of study and multiple doses of 1500 mg were given as 1 capsule of 500 mg three times a day for 10 days.

The baseline measurements of vital parameters and pharmacodynamic assessment of cardiac profiling of subjects in all the groups were performed after an overnight fast, using non-invasive methods. The various cardiac profiling parameters that were assessed include - Brachial-Ankle Pulse Wave Velocity (baPWV) (cm/s) and Ankle-Brachial Index (ABI-Colin), Reflection Index (RI%) (Micromedical Pulse Tracer Gallingham, Kent, UK), Aortic Augmentation Pressure (AP) (mmHg), Pulse Pressure (PP) (mmHg), Aortic Augmentation Index (Aix) (%) and Sub Endocardial Viability Ratio (SEVR) (%) (Sphygmocor®) before and after cold pressor test (CPT). Blood pressure and pulse rate were taken before, during and after CPT. Then, tilt table test was performed and blood pressure, basal Impedance (ohms), cardiac output (L/min), cardiac index (L/min/m²), stroke volume (ml/beat), stroke volume index

(ml/beat/m²), systemic vascular resistance (dyne.sec/cm⁵), systemic vascular resistance index (dyne.sec/cm⁵/m²), left ventricular ejection time (ms), pulse rate (bpm), velocity index (/1000sec) and central velocity pressure (mmHg) were measured at 0°, 45°, 60° and again at baseline 0° tilt using L&T Nivomon monitor. Pretreatment blood samples were drawn for assessment of safety parameters.

Single Dose Group

In all the single dose groups, all procedures were repeated 3 hours post drug, as done at baseline and all the parameters were recorded. The subject's vital parameters were recorded before and at hourly intervals up to 6 hrs and then at 8, 12 and 24 hrs post treatment. The lab safety parameters were measured at 24 hours post administration of study medication. Any adverse drug reaction (ADR) reported was recorded in case report form. Subjects were discharged from the clinical research unit after all vital parameters were found to be normal 24 hours post treatment.

Multiple Dose Group

The dose of 1500 mg was chosen for multiple dose study as 1500 mg is the recommended dose for *Terminalia arjuna* and has been evaluated in clinical studies earlier.^[10] The dose was administered as one capsule of *Terminalia arjuna* 500 mg, three times a day. The initial dose was administered at the study site and all the procedures were conducted 3 hours post drug, as described above for single dose study. The subjects were asked to continue study medication for next 10 days. At day 11, after an overnight fast, baseline measurements of vital parameters were recorded and all the procedures done on day 1 were repeated. Any adverse drug reaction (ADR) reported was recorded in the case report form.



Figure: *Terminalia arjuna* and placebo capsules

RESULTS

Six volunteers each were enrolled and randomized in the study groups. All subjects completed the study uneventfully. The demographic characteristics of the study groups were homogenous in nature, as shown in Table 1.

Table1: Demographic Data

	Total No.	Age (yrs)	Weight (Kg)	BMI (Kg/m ²)
TA 500 mg Group				
TA Group	4	31.00 ± 2.16	63.53 ± 9.34	23.44 ± 2.58
Placebo	2	29.00 ± 4.24	66.30 ± 23.62	22.81 ± 6.50
TA 1000 mg Group				
TA Group	4	35.25 ± 8.77	61.05 ± 6.22	22.56 ± 3.38
Placebo	2	29.50 ± 0.71	62.25 ± 0.21	22.63 ± 0.81
TA 1500 mg Group				
TA Group	4	30.00 ± 1.83	63.50 ± 2.08	23.04 ± 0.65
Placebo	2	30.50 ± 3.53	74.00 ± 12.73	24.34 ± 2.62
TA 2000 mg Group				
TA Group	4	32.0 ± 2.16	64.50 ± 4.2	24.28 ± 1.24
Placebo	2	31.0 ± 0.01	65.15 ± 7.7	25.16 ± 3.41
TA 1500 mg Multiple Dose Group				
TA Group	4	33.75 ± 2.50	66.75 ± 1.70	24.20 ± 1.37
Placebo	2	31.50 ± 0.70	63.50 ± 0.70	23.55 ± 0.63

Effect of treatments on vital parameters with Cold Pressor test

In all the study groups, cold pressor test (CPT) increased systolic, diastolic blood pressure (SBP, DBP) and pulse rate (PR) at 30 sec during the test from baseline, whereas after 1 min and 10 min of CPT, SBP, DBP & PR were within normal limits. At 3hrs post treatment with *Terminalia arjuna* 500 mg single dose, there were increases in SBP, DBP & PR at 30 sec during CPT which were however much lower than that compared to pre-treatment values. Similar effects were seen with 1000 mg, 1500 mg & 2000 mg single dose and 1500 mg multiple dose treatments. In the placebo group, after 3hrs of treatment, cold pressor test did not produce any remarkable changes in the vital parameters from baseline to during 30sec, after 1min and 10min of CPT.

Table 2A - Effect of CPT on pharmacodynamic parameters at baseline - Single dose group

	baPWV (cm/s)	ABI	Reflection Index (RI%)	AP(mmHg)	PP(mmHg)	AIX (%)	SEVR (%)
TA 500 mg Group							
TA Before CPT	1153 ± 69.1	1.03 ± 0.02	79.48 ± 6.73	8.00 ± 1.15	33.25 ± 4.92	131.8 ± 2.06	183.8 ± 4.03
TA After CPT	1158 ± 55.45	1.06 ± 0.02	78.23 ± 6.81	9.75 ± 2.75	34.50 ± 9.25	140.5 ± 3.69	197.3 ± 2.21
Placebo Before CPT	1173 ± 3.53	1.09 ± 0.05	76.65 ± 4.73	5.00 ± 1.41	31.00 ± 2.82	121.0 ± 9.89	177.0 ± 7.07
Placebo After CPT	1185 ± 21.21	1.09 ± 0.00	72.65 ± 0.91	11.00 ± 2.82	35.00 ± 11.31	145.0 ± 5.65	191.0 ± 5.65
TA 1000 mg Group							
TA Before CPT	1186 ± 31.46	1.08 ± 0.05	83.90 ± 2.81	5.75 ± 0.95	27.25 ± 0.95	126.0 ± 1.41	165.0 ± 9.55
TA After CPT	1218 ± 20.21	1.09 ± 0.06	80.95 ± 2.89	7.75 ± 0.95	29.50 ± 1.29	138.3 ± 3.59	182.0 ± 10.30
Placebo Before CPT	1163 ± 53.03	1.09 ± 0.003	78.95 ± 1.90	7.50 ± 2.12	35.00 ± 1.41	131.0 ± 4.24	167.5 ± 4.95
Placebo After CPT	1175 ± 0.0	1.04 ± 0.017	74.30 ± 5.23	8.5 ± 2.12	33.50 ± 2.12	143.0 ± 4.24	184.5 ± 3.53
TA 1500 mg Group							
TA Before CPT	1125 ± 45.64	0.975 ± 0.02	79.65 ± 2.63	7.00 ± 2.94	33.00 ± 2.944	21 ± 6.97	180.3 ± 22.97
TA After CPT	1223 ± 117	1.074 ± 0.04	82.05 ± 3.21	11.50 ± 2.38	30.75 ± 0.9574	37 ± 7.39	173.8 ± 31.45
Placebo Before CPT	1213 ± 17.68	1.04 ± 0.046	79.80 ± 2.121	2.00 ± 1.414	29.50 ± 2.121	7 ± 4.243	117.0 ± 21.21
Placebo After CPT	1350 ± 35.36	1.00 ± 0.042	81.15 ± 1.63	6.00 ± 2.828	33.50 ± 2.121	17 ± 7.071	136.5 ± 12.02
TA 2000 mg Group							
TA Before CPT	1169 ± 8.48	1.08 ± 0.03	65.98 ± 4.62	8.00 ± 0.81	23.25 ± 0.95	131.5 ± 3.69	155.5 ± 7.93
TA After CPT	1225 ± 0.01	1.11 ± 0.03	71.80 ± 4.58	12.50 ± 1.29	30.25 ± 2.21	144.0 ± 3.74	148.3 ± 7.50
Placebo Before CPT	1188.0 ± 53.03	1.09 ± 0.91	68.45 ± 1.62	8.0 ± 0.01	25.00 ± 1.41	136.5 ± 6.36	171.0 ± 9.89
Placebo After CPT	1288.0 ± 17.68	1.12 ± 0.00	73.50 ± 2.12	11.50 ± 0.70	33.50 ± 0.70	141.5 ± 3.53	163.5 ± 3.53

Table 2B - Effect of CPT on pharmacodynamic parameters at baseline - Multiple dose group

	baPWV (cm/s)	ABI	Reflection Index (RI%)	AP(mmHg)	PP(mmHg)	AIX (%)	SEVR (%)
TA 1500 mg Multiple Dose Group: Day 1							
TA Before CPT	1119.0±79.2	1.09±0.02	71.73±1.17	9.50±3.10	23.25±2.63	133.8±6.55	153.0±10.86
TA After CPT	1238.0±0.01	1.12±0.01	75.05±1.60	13.75±1.70	28.50±2.08	146.0±1.82	149.5±9.88
Placebo Before CPT	1138±17.68	1.13±0.0	73.15±4.03	9.50±3.53	22.0±1.41	132.5±4.95	151.5±3.53
Placebo After CPT	1300±35.36	1.09±0.0	78.65±1.90	11.50±3.53	26.0±2.82	143.0±1.41	148.0±5.65
TA 1500 mg Multiple Dose Group: Day 11							
TA Before CPT	1113±17.68	1.13±0.0	70.55±4.47	7.50±1.73	22.25±0.95	130.8±4.99	142.8±4.11
TA After CPT	1057±26.16	1.14±0.20	68.23±5.51	5.00±0.81	19.50±1.29	121.3±2.5	151.3±9.5
Placebo Before CPT	1150 ±106.1	1.13±0.0	68.50±0.70	7.50±0.70	23.0±1.41	130.5±2.12	137.5±2.12
Placebo After CPT	1238 ±123.7	1.15±0.0	73.00± 1.41	12.50±0.70	30.00±2.82	140.0±1.41	133.5±6.36

The cold pressor test produced arterial stiffness at baseline and the same is evidenced by an increase in baPWV, RI, AP, PP and AIX and in all groups also as a decrease in values of SEVR in 1500 mg, 2000 mg single dose and 1500 mg multiple dose and placebo groups.

Effect of Treatments on Pharmacodynamic parameters during Cold Pressor test

Table 3A - Effect of treatments on pharmacodynamic parameters during CPT - Single dose group

	baPWV (cm/s)	ABI	Reflection Index (RI%)	AP(mmHg)	PP(mmHg)	AIX (%)	SEVR (%)
TA 500 mg Group							
TA Before CPT	1178±35.24	1.06±0.02	80.00±3.74	6.75±1.25	33.50±3.78	125.8±3.50	177.5±6.80
TA After CPT	1159±88.73	1.06±0.04	79.13±5.15	8.25±1.70	31.75±2.63	136.0±6.92	195.3±10.81
Placebo Before CPT	1175±0.00	1.07±0.00	78.3±6.08	6.50±0.71	30.5±3.54	124±12.0	175±7.78
Placebo After CPT	1203±3.53	1.11±0.00	75.7±3.32	9.00±0.00	31.0±1.41	141±0.70	194±22.6
TA 1000 mg Group							
TA Before CPT	1216±30.92	1.15±0.08	85.08±2.46	7.00±0.81	27.0±0.81	132.5±4.04	174.8±8.34
TA After CPT	1188±30.69	1.13±0.02	80.98±4.61	9.75±1.89	31.75±3.40	144.5±5.44	201.3±12.45
Placebo Before CPT	1178±53.03	1.093±0.01	80.60±2.82	6.50±0.70	30.0±1.41	114.5±4.95	151.0±9.89
Placebo After CPT	1208±24.75	1.098±0.01	78.80±0.70	7.50±0.70	35.0±1.41	128.0±1.41	176.5±2.12
TA 1500 mg Group							
TA Before CPT	1263±59.51	1.11±0.03	80.15±6.16	6.50±3.87	34.00±6.976	18.25±7.455	152.8±31.60
TA After CPT	1204±48.88	0.97±0.02	78.15±6.03	5.75±2.87	27.75±5.188	20.00±5.416	167.3±45.01
Placebo Before CPT	1225±0.01	1.05±0.03	80.50±2.121	1.5±0.7	6.0±2.828	28.0±0.0	121.0±29.7
Placebo After CPT	1338±53.03	1.07±0.06	80.80±0.28	3.50±2.121	12.0±8.485	28.50±0.71	144.0±22.63
TA 2000 mg Group							
TA Before CPT	1200±35.36	1.13±0.02	67.40±2.96	7.75±0.95	23.25±1.89	136.0±11.78	155.8±6.60
TA After CPT	1144±43.84	1.10±0.02	62.50±2.38	6 ±0.81	19 ±1.15	130.8±12.63	162.5±10.75
Placebo Before CPT	1163±53.03	1.06±0.01	70.10±4.95	7.50±0.70	24.50±2.12	132.5±0.7	161.5±17.68
Placebo After CPT	1250±35.36	1.11±0.01	73.45±4.03	12 ±1.41	30.50±0.7	140.5±2.12	148.0±0.01

Table 3B - Effect of treatments on pharmacodynamic parameters during CPT - Multiple dose group

	baPWV (cm/s)	ABI	Reflection Index (RI%)	AP(mmHg)	PP(mmHg)	AIX (%)	SEVR (%)
TA 1500 mg Multiple Dose Group Day 1							
TA Before CPT	1207±9.92	1.13±0.01	72.55±1.18	6.75±0.95	24.25±2.63	124.5±5.68	144.3±0.86
TA After CPT	1150±35.36	1.15±0.03	69.80±2.46	5.25±1.78	21.50±3.41	120.5±2.08	161.0±6.68
Placebo Before CPT	1113±17.68	1.11±0.03	71.50±0.70	7.0±0.0	22.50±0.70	129.5±2.12	143.5±0.70
Placebo After CPT	1225±70.71	1.08±0.01	79.0±1.41	11.50±2.12	27.50±3.53	140.0±2.82	134.5±17.68
TA 1500 mg Multiple Dose Group Day 11							
TA Before CPT	1107±61.52	1.13±0.0	71.65±1.98	7.75±1.70	20.25±1.50	127.5±8.22	133.3±10.69
TA After CPT	1032±44.55	1.15±0.0	67.9±2.45	5.50±1.29	18.25±1.25	119.5±7.55	146.3±4.03
Placebo Before CPT	1150±35.36	1.19±0.00	70.8±2.54	8.50±0.70	20.50±2.12	131.0±4.24	150.0±2.82
Placebo After CPT	1213±88.39	1.14±0.01	74.95±0.91	12.50±0.70	28.50±0.70	145.5±4.95	147.5±0.70

Treatment with *Terminalia arjuna* decreased baPWV in all the treatment groups. However the changes in other pharmacodynamic parameters recorded during cold pressor test were not found to be remarkable. The CPT induced arterial stiffness was counteracted by treatment with *Terminalia arjuna* and there was decrease in baPWV, RI, AP, PP, AIX and increase in SEVR in 1500 mg, 2000 mg single dose and 1500 mg multiple dose groups both at Day 1 & Day 11. There were no remarkable changes in the placebo group.

Effect of Treatments on Tilt Table Test on Various Pharmacodynamic parameters

Tilt table test per se did not produce any remarkable change in SBP, DBP, PR and cardiac output at different degrees of tilt in any of the study groups. Treatment with *Terminalia arjuna* 1500 mg & 2000 mg single doses produced a mild increase in cardiac output during 45° & 60° phases of the tilt. *Terminalia arjuna* 1500 mg multiple dose increased cardiac output at 60° tilt (Day 1) and at 45° & 60° phases of the tilt (Day 11).

Table 4: Effect of Treatments on Platelet aggregation test

	% Platelet Aggregation (ADP)		
	Pretreatment	Post Treatment	% Inhibition
TA 500 mg Group			
<i>T.arjuna</i>	75.00±2.85	78.88±2.89	Nil
Placebo	76.8±0.35	78.0±0.1	Nil
TA 1000 mg Group			
<i>T.arjuna</i>	75.75±2.53	78.38±2.05	Nil
Placebo	76.50±1.14	78.75±1.77	Nil
TA 1500 mg Group			
<i>T.arjuna</i>	74.0±3.65	78.75±2.63	Nil
Placebo	77.25±3.889	80.75±2.475	Nil
TA 2000 mg Group			
<i>T.arjuna</i>	65.63±7.01	63.38±9.12	4.81±3.95
Placebo	69.25±8.13	71.65±9.40	Nil
TA 1500 mg Multiple Dose Group Day 1			
<i>T.arjuna</i>	70.50±2.12	73.38±2.13	Nil
Placebo	67.75±1.76	69.75±2.47	Nil
TA 1500 mg Multiple Dose Group Day 11			
<i>T.arjuna</i>	69.25±2.90	58.0±3.24	16.28±1.60
Placebo	70.25±3.18	69.75±7.42	1.80±2.54

Significant inhibition in platelet aggregation was seen with *Terminalia arjuna* 2000 mg single dose and *Terminalia arjuna* 1500 mg multiple dose at day 11. Placebo treatment did not produce any change in the platelet aggregation test.

Adverse Events - All subjects tolerated both treatments and procedures well. No subjects developed any adverse drug reaction. Study was completed

uneventful. There were no remarkable changes in any of the hematological, biochemical safety lab parameters with either treatment.

DISCUSSION

This was a placebo-controlled, phase I dose ranging study evaluating the safety and efficacy of single doses of *Terminalia arjuna* 500 mg, 1000 mg, 1500 mg & 2000 mg single dose and multiple dose of

Terminalia arjuna 1500 mg (500 mg three times a day for 10 days) on cardiovascular profile in healthy human male volunteers.

The stem bark of *Terminalia arjuna* has been used for the treatment of various cardiovascular diseases in preclinical studies to demonstrate cardioprotective properties including positive inotropic, hypolipdemic, coronary vasodilatory and antioxidant effects. The biologically active compounds in the stem bark include triterpenoids, tannins, flavonoids and minerals. [11]

In our study, cold pressor test (CPT) was performed to induce arterial stiffness which manifested as an increase in systolic and diastolic blood pressure and pulse rate. Treatment with *Terminalia arjuna* resulted in lower increments in SBP, DBP & PR, at 30 sec during CPT compared to pretreatment CPT increments of the same parameters, thus attenuating the cardiovascular effect of CPT & protecting against arterial stiffness. Within the treatments, *Terminalia arjuna* 1500 mg multiple dose produced lower increments at Day 11 compared to any of the single doses of *Terminalia arjuna*. This effect of *Terminalia arjuna* may be ascribed to its cardioprotective properties of vasodilation and anti-oxidant effects. Also few experimental studies have demonstrated its anti-hypertensive activity. [12] This has been attributed to certain tannins and glycosides that strengthen heart muscles, relieve stress and have specific antioxidant properties congenial for the cardiovascular system. [13,14]

Further, CPT-induced arterial stiffness was also evaluated with changes in pharmacodynamic parameters before and after CPT. Treatment with *Terminalia arjuna* 1500 mg for 10 days counteracted the CPT induced arterial stiffness by decreasing baPWV, RI, AP, PP, AIX and increase in SEVR compared to baseline. This effect was seen with both single and multiple doses of *Terminalia arjuna*, with the effect being more prominent in multiple dose group. This indicates that multiple dose administration of *Terminalia arjuna* protects against the cardiovascular effects induced by cold pressor test.

The role of vascular endothelium has been studied in relation to arterial stiffness and it was demonstrated that an intact and functional vascular endothelium is essential to maintain vascular tone thus countering any arterial stiffness. [15] By virtue of its anti-oxidant activity, *Terminalia arjuna* promotes the function of intact vascular endothelium.

The cardiac function was also assessed with tilt table test. Treatment with both single and multiple doses of *Terminalia arjuna* did not alter the vital parameters except for a mild increase in cardiac output at 45 and 60 degree tilt, which was comparable in both the groups. This effect may be due to the cardiotonic activity of *Terminalia arjuna* manifesting as positive inotropy and positive lusitropy secondary to

enhancement in calcium handling of myocardial sarcoplasmic reticulum. [16]

The effect of *Terminalia arjuna* on platelet aggregation was evaluated using agonists- ADP & Collagen. Inhibition of platelet aggregation was seen with *Terminalia arjuna* 2000 mg single dose and 1500 mg multiple dose at Day 11. However, this effect was much higher with the multiple dose treatment suggesting a dose-dependent inhibition of platelet aggregation by *Terminalia arjuna*. The anti-platelet aggregatory effect of *Terminalia arjuna* may be due to its property of desensitizing platelets to the agonist by competing with platelet receptor or by interfering with signal transduction. [17]

Both the treatments were safe and well tolerated and no adverse effects were reported in either of the treatment groups.

CONCLUSION

There were no significant changes in any of the pharmacodynamic parameters tested with single dose of 500 mg & 1000 mg *Terminalia arjuna*. However, treatment with single doses of 1500 mg & 2000 mg and multiple doses of 1500 mg for 10 days of *Terminalia arjuna* produced remarkable changes in the cardiovascular profile. The active treatments showed mild decrease in pharmacodynamic parameters such as baPWV, AIX, AP, PP, ABI and reflection index on cold pressor test & a mild increase in cardiac output at 45° and 60° of tilt compared to baseline. Marked reduction in platelet aggregation was recorded in the 1500 mg multiple dose treatment group. All the treatments were safe, well tolerated and no adverse events were reported. Further studies in larger number of subjects and in patients with cardiovascular diseases are needed to confirm these effects of *Terminalia arjuna* on cardiovascular profile.

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