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Therapeutic validation of *Ipomoea digitata* tuber (*Ksheervidari*) for its effect on cardio-vascular risk parameters

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Ipomoea digitata Linn. (*Ksheervidari*) is a well known medicinal plant used in Ayurveda for its health promoting effects in human beings. Its tuber powder was evaluated first time in a single blinded, placebo controlled study for its antihypertensive potential and its effect on lipid profile, fibrinolytic activity and total antioxidant status in individuals with stage 1 hypertension. Administration of 3 gm tuber powder significantly ($p<0.001$) decreased systolic, diastolic and mean blood pressure, increased fibrinolytic activity and total antioxidant status with a significant reduction ($p<0.05$) in serum total cholesterol, LDL cholesterol and atherogenic index at the end of 12 weeks. It was tolerated well without any significant side effect. In the placebo group, there were no significant alterations in any of the parameters at the end of study.

Keywords: Hypertension, *Bhumi-kushmanda*, Fibrinolysis, Antioxidant

IPC Int. Cl.[8]: A01D 14/01, A01D 14/02, A01D 14/03, A01D 14/04, A01D 14/05, A01D 14/06, A01D 14/07, A01D 14/08, A01D 14/09, A01D 14/10

Abbreviations: Atherogenic index, AI, Blood pressure, BP; Ischemic heart disease, IHD; Body mass index, BMI; Joint national committee, JNC; Gram, gm; High density lipoprotein cholesterol; HDL-C; Low density lipoprotein cholesterol, LDL-C; Total antioxidant status, TAS; Very low density lipoprotein cholesterol, VLDL-C.

Ipomoea digitata Linn. syn. *Ipomoea paniculata* (L.) R.Br. (Fig.1) is a member of family Convolvulaceae and called as *Bilai-kand*, *Bhui-khola*, *Ksheervidari*, *Payasvinee*, *Bhumi-kumra*, *Bhumi-kushmanda* in various languages[1]. Plant and its medicinal properties has been well mentioned in the ancient literature[2] as follows:

अन्या क्षीरविदारी स्यादिक्षुगन्धेक्षुवल्लरी ।
इक्षुवल्ली क्षीरकन्दः क्षीरवल्ली पयस्विनी । ।
क्षीरशुक्ला क्षीरलता पयःकन्दा पयोलता ।
पयोविदारीका चेति विज्ञेया द्वादशाह्वया । । (राजनिघण्टु)

रसायनी च वल्या च शीता मूत्रकफप्रदा ।
स्निग्धा वर्ण्या गुरूः स्वर्याः पित्तरूग्रक्तदोषहा ।।
पित्तशूलहरा वातदाहजिन्मूत्रमेहजितृ ।
ज्ञेया कन्दगुणा ह्यस्याः सदृशा वल्लिवद्गुणैः ।। (निघण्टुरत्नाकरम्)

Its tubers are eaten raw in Midnapore district of West Bengal, India[3]. Raw tuber is also taken to treat blood dysentery and used as an astringent. Juice of its tubers with one glass of cow milk is given for 7 days to increase lactation by *Kandha* tribe of Orissa[4]. Sun-dried root powder, boiled in sugar and butter is administered to promote weight gain and to moderate menstrual discharge. Tubers have also been used for treatment of debility, spermatorrhoea, fever, bronchitis, scorpion stings and menorrhagia[5].

Yaogika cikitsa and *Dravya guna* has mentioned its usefulness in patients with hypertension and heart disease. Their recommendations are based on ethnomedicinal observations in Rarh region. A teaspoonful of powdered tuber if given twice a day with honey is beneficial for the patients of high blood pressure and heart disease[6,7].

There are many drugs available for management of hypertension which is a common cardiovascular risk factor for IHD. However, drug treatment of mild hypertension has been associated with metabolic alterations that increase the risk of cardiovascular diseases, resulting in stand off or even a negative overall effect. In this regard dietary spices and various plant products have been evaluated from time to

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time[8]. *Ksheervidari* is one such medicinal plant which has shown some promise against hypertension as shown in animal models[9], yet it has not been scientifically validated in human studies. In this regard, this study is an attempt to evaluate the tubers of *Ipomoea digitata* on various cardiovascular risk parameters in hypertensive individuals.

Methodology

Tubers of *Ipomoea digitata* were procured from the forests of West Midnapore, Bengal and cultivated under the vigilance of Society for Microvita research and Integrated Medicine (SMRIM) at Udaipur (Figs.1 a & b). After noting whole taxonomic characters and identification[10], voucher specimen of the plant was deposited in the Herbarium at Laboratory of Ethnobotany and Agrostology, Department of Botany, ML Sukhadia University, Udaipur, Rajasthan (India) for authentication of information and future reference. Herbarium number to voucher specimen was also provided (EA-540*) (EA—Ethnobotany and Agrostology Herbarium number)

Tubers were thoroughly washed under running tap water, and cut into small pieces (Fig. 1c). They were airdried in shade at an ambient temperature. The dried material was ground in an electrical grinder to make a fine homogenous powder which was filled in gelatin capsules. Each capsule contained 750 mg of the dried powder. Placebo contained lactose powder filled in similar gelatin capsules. It was selected because it doesn't alter the biochemical parameters.

After approval from institutional ethical committee (No.RNT/State/2008/F.comn/597), 60 newly diagnosed male individuals having essential hypertension (Primary hypertension), between the ages of 40-50 yrs (BMI<25), who attended medical out patient department of Maharana Bhopal General Hospital attached to RNT Medical College, Udaipur during January 2008 to March 2009 were enrolled for the study.

All the patients selected were of stage 1 (≥140/90 to 159/99 mm Hg) hypertension of JNC VII[11]. The patients with stage 2 (≥160/100 mm Hg) hypertension of JNC VII, secondary hypertension, diabetes, ischemic heart disease, renal and endocrine diseases were not included in the study. Similarly, the patients who were smokers, alcoholics, on lipid lowering drugs, dietary restrictions or weight reduction program were excluded from this study.

After informed consent, the selected individuals were randomly categorized to the following two groups. The study subjects, however, were unaware of this categorization.

Group I (n=30) Treated group: They were administered *I. digitata* tuber powder filled in capsules, in a dose of 1.5 gm twice daily for a period of 12 weeks.

Group II (n=30) Placebo group: They received matched placebo capsules in the same doses for 12 weeks. However, 10 individuals dropped out during the study period. Therefore, final results are based on 20 individuals.

The placebo and tuber powder filled capsules were similar in size, shape and weight; hence the patients were blinded for that matter. During the study period, the patients were advised not to alter their dietary and exercise habits. They were also instructed not to take any medication without prior consultation.

Blood pressure was measured by a mercury sphygmomanometer (Pagoda Delux) with a standard

Fig. 1 (a)—Twining plant; (b) *Ipomoea digitata* Linn. Tuber; (c) *Ipomoea digitata* Linn. sliced tuber

size cuff as per recommendations of JNC VII. Average of two or more readings with the gap of 5 minutes was taken at each time of blood pressure recording. Blood pressure was recorded in sitting position initially and at every 4th week for 12 weeks. Mean BP and Pulse pressure was calculated from the following formula[12]:

Mean blood pressure = Diastolic blood pressure + 1/3rd of pulse pressure.

Pulse pressure = Systolic blood pressure - Diastolic blood pressure

Blood samples were collected in a fasting state, initially and at the end of 4th, 8th and 12th week for analysis of plasma fibrinolytic activity, serum lipid profile and total antioxidant status. Fibrinolytic activity[13] was assessed as euglobulin lysis time as described by Buckell and Elliot. It is based on the principle that euglobulin fraction clotted with thrombin and the time taken for clot lysis is estimated and expressed in units by multiplying the reciprocal of lysis time in minutes by 10000.

Blood cholesterol[14], Triglycerides[15] and HDL-C[16] were estimated colorimetrically by enzymatic methods employing standard diagnostic kits (Reckon Diagnostics P. Ltd., Baroda). VLDL-cholesterol (VLDL – C) and LDL-cholesterol (LDL – C) were calculated by Friedwald formula[17] as follows:

VLDL – C = Triglycerides / 5

LDL – C = Total Cholesterol - (HDL-C + VLDL-C)

Total antioxidant status was assessed using standard kit supplied by Randox, UK where the color produced by ABTS (2,2'-Azino-di-[3-ethylbenz thiazoline sulphonate]) radicals is measured at 600 nm in a spectrophotometer (Milton Roy Co.) which is proportional to concentration of antioxidants present in the sample[18].

All the values were expressed as mean ± standard error (SE). Results were statistically analyzed with student's t-test for paired data and a 'p' value of less than 0.05 was considered as significant.

Results and discussion

Administration of *Ipomoea digitata* tuber powder in a dose of 1.5 gm twice daily significantly decreased systolic ($p<0.001$), diastolic ($p<0.01$) and mean ($p<0.001$) blood pressure at the end of 4 weeks. Although the reduction in blood pressure was statistically significant at the end of fourth week yet the levels of systolic blood pressure did not reach up to the normal values of less than 120 mm Hg. At the end of 8 weeks there was further decrease observed in systolic, diastolic and mean blood pressure and systolic blood pressure lowered to 126.4 ± 1.83 from 157.6 ± 1.16 mm Hg. At the end of the study, the systolic (118.8 ± 0.34 mm Hg) and diastolic (76 ± 2.45 mm Hg) blood pressure reached within the range of normal level (≤ 120/80 mm Hg) as defined by JNC VII criteria (Table 1). The placebo controlled group did not show any significant alteration in systolic, diastolic and mean blood pressure at any stage of the study (Fig. 2).

On an average, there was a fall of 38.8 mm Hg in systolic and 19.2 mm Hg in diastolic blood pressure at the end of 12 weeks in treated group (Fig. 3). This statistically significant decrease in blood pressure is important in terms of its long term morbidity and mortality from cardiovascular diseases. Randomized controlled trials have shown that in patients with mild hypertension, lowering of 5-6 mm Hg in diastolic and 10 mm Hg in systolic blood pressure reduces stroke risk by about one third and risk of coronary events by about one sixth[19].

Table 1—Effect of *Ipomoea digitata* tuber powder (3 gm) on blood pressure in stage 1 hypertensive individuals (n=30)

BLOOD PRESSURE (mm Hg)	INITIAL (I)	4 WEEKS (II)	8 WEEKS (III)	12 WEEKS (IV)
SYSTOLIC	157.60 ± 1.16	129.2 ± 2.58 [a]	126.4 ± 1.83 [b]	118.80 ± 0.34 [c,d]
DIASTOLIC	95.20 ± 1.49	85.2 ± 2.33 [e]	78.00 ± 2.00 [b]	76.00 ± 2.45 [c,d]
MEAN	115.99 ± 1.34	97.19 ± 1.65 [a]	93.73 ± 1.12 [b]	90.26 ± 1.48 [c,d]

Values are expressed as Mean ± SE
Mean Blood Pressure = Diastolic blood pressure + 1/3rd of pulse pressure.
p Value –
<0.001- a II v/s I, b III v/s I, c IV v/s I,
<0.01 – e II v/s I,
NS –d IV v/s III

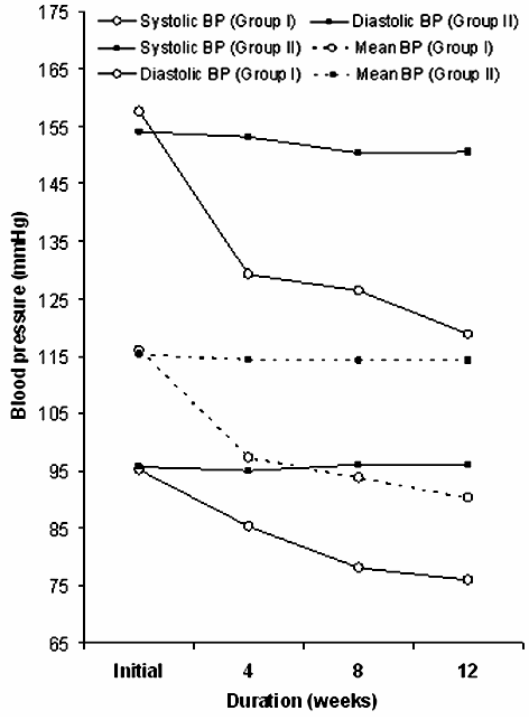

Fig. 2—Pattern of blood pressure change after administration of *Ipomoea digitata* (Group I) and matched placebo (Group II) in hypertensive individuals

There were 80 % of individuals who attained the optimum level of diastolic blood pressure (≤ 80 mm Hg) at the end of 4 weeks and all the individuals achieved the optimum level at the end of 8 weeks. However, in systolic blood pressure, initially there were 20 % of individuals who attained the optimum level of systolic blood pressure of ≤ 120 mmHg at the end of 4 weeks. The percentage reached to 100 % at the end of 12 weeks.

Mean BP is the product of cardiac output and peripheral vascular resistance. Administration of 3 gm *Ipomoea digitata* tuber powder also significantly reduced mean blood pressure (22.18 %) at the end of the study (Table 1). Pulsatile pressure is also dependent on large and small artery compliance, a reduction of which contributes to a progressive increase in systolic pressure with aging. The pressure difference between systolic and diastolic provides a crude guide to stiffness of the large conduit arteries[20,21].

Hypertension and atherosclerosis often co-exist in individual patients. Hypertension and its complications, its modifications seem to be an attractive means to favorably affect the development of cardiovascular events in hypertensive patients.

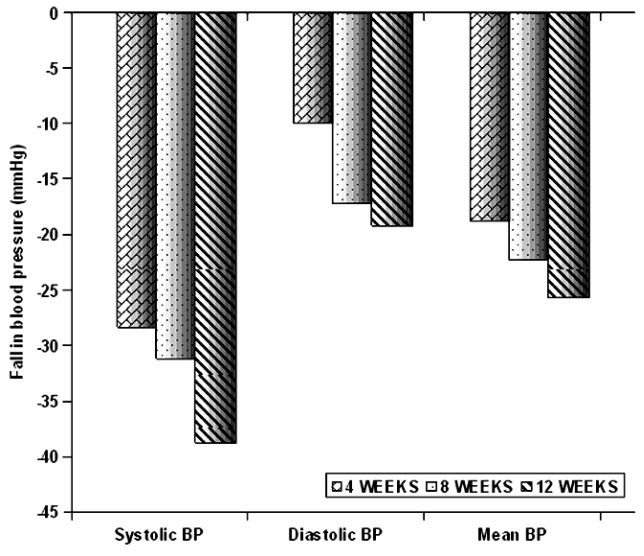

Fig. 3—Reduction in blood pressure (mm Hg) at the end of 4th, 8th and 12th weeks after daily administration of 3 gm *Ipomoea digitata* tuber powder in stage 1 hypertensive individuals (n=30)

However, recent large clinical trials still emphasize that the main drives of clinical benefit from blood pressure lowering therapy is the magnitude of blood pressure reduction[22].

Hypertension is usually associated with an abnormal level of antioxidant status and reduced fibrinolysis[23]. Increased blood lipids further add to its risk in producing coronary atherosclerosis. In this regard, various dietary compounds and some plant materials are important as they have effect on blood pressure as well as other risk factors of endothelial dysfunction[24-26]. *Ipomoea digitata* not only lowers blood pressure; but also affects other parameters inductive to atherogenesis with a wide safety profile.

In the present study, administration of *Ipomoea digitata* tuber powder has led to significant ($p<0.001$) rise in fibrinolytic activity which is an important factor responsible for maintaining a perfect haemorrheological state (Table 2). The fibrinolytic activity is considered to be a major physiological means of disposing fibrin after its haemostatic function has been fulfilled. The process is of great importance in wound healing and re-canalization of the thrombosed vessels. If the fibrin is not removed properly then its organization and fatty deposition on the artery involved, result in atheroma formation[27].

The antioxidant status in humans reflect the dynamic balance between antioxidant defense and prooxidant conditions and have been suggested as a

useful tool in estimating the risk of oxidative damage[28,29]. *Ipomoea digitata*; besides its blood pressure lowering and fibrinolysis enhancement properties, has also demonstrated significant ($p<0.001$) improvement in serum total antioxidant status (TAS) after 12 weeks of its administration in stage 1 hypertensive individuals (Table 2). TAS was progressively increased by 39, 90 and 103 % at the end of 4, 8 and 12 weeks respectively after administration of 3 gm tuber powder in two divided doses (Fig. 4).

Favorable reductions were also observed in serum total cholesterol (26.11 %), triglycerides (16.06 %), VLDL-C (16.06 %) and LDL-C (32.54 %) levels at the end of 12 weeks in treated (group I) hypertensive individuals (Table 3). The levels of reduction attained statistical significance with total cholesterol and LDL-C while the changes in triglycerides, HDL-C and VLDL-C were statistically not significant. However, the ratio of HDL-C and LDL-C was significantly ($p<0.05$) increased at the end of 12 weeks. Impressively, atherogenic index, the marker of atherogenesis was also found to be continuously decreasing by 10.15, 14 and 25.15 % at the end of 4, 8 and 12 weeks of the study, respectively (Fig. 5) but the statistically significant ($p<0.05$) reduction was observed only at the end of the study. In the placebo treated hypertensive individuals, the lipid fractions, fibrinolysis and total antioxidant status were significantly unaltered throughout the study (Tables 2 & 3).

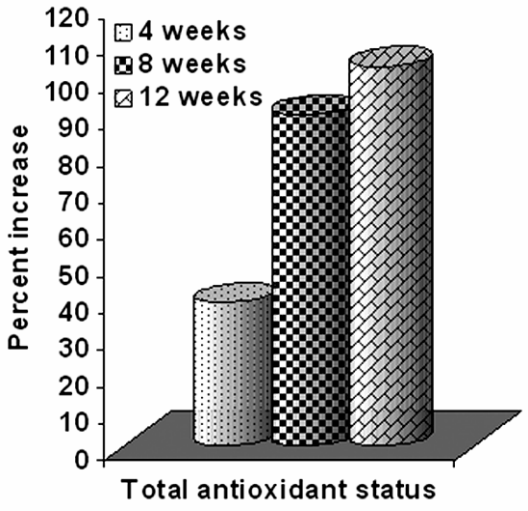

Fig. 4—Percent increase in total antioxidant status after daily administration of *Ipomoea digitata* tuber powder (3 gm) in stage 1 hypertensive individuals

Looking at the temporal profile of the effects of *Ksheervidari* on various cardiovascular risk parameters, its therapeutic potential has become more apparent. In the present study, administration of *I. digitata* in hypertensive individuals has enhanced fibrinolysis, decreased systolic and diastolic pressure significantly even at the end of fourth week, whereas the significant reduction of atherogenic lipids was not observed. To counteract the lipid factor in inflicting injury to endothelium in the process of atherosclerosis, the TAS has started increasing significantly even at the end of 4 weeks; possibly preventing oxidation of LDL-C. The plant therefore counteracts the risk parameters and interacts with the situations of endothelial dysfunction, thereby improving its functions which are important for cardiovascular health.

Tubers of *Ipomoea digitata* has been reported to yield compounds as taraxerol, taraxerol acetate, umbelliferone, scopoletin, scoparone, β-sitosterol and its 3-0-β-D-glucoside, 1-o-ethyl-β-D glucopyranoside[9,30]. Many of these chemical compounds possess pharmacological activities, involved in protection against endothelial dysfunction. Scopoletin, a coumarin present in the tubers of *I. digitata* has been shown to cause hypotension in animal study[31]. It relaxes the smooth muscles by dilating blood vessels and also acts as a non-specific spasmolytic

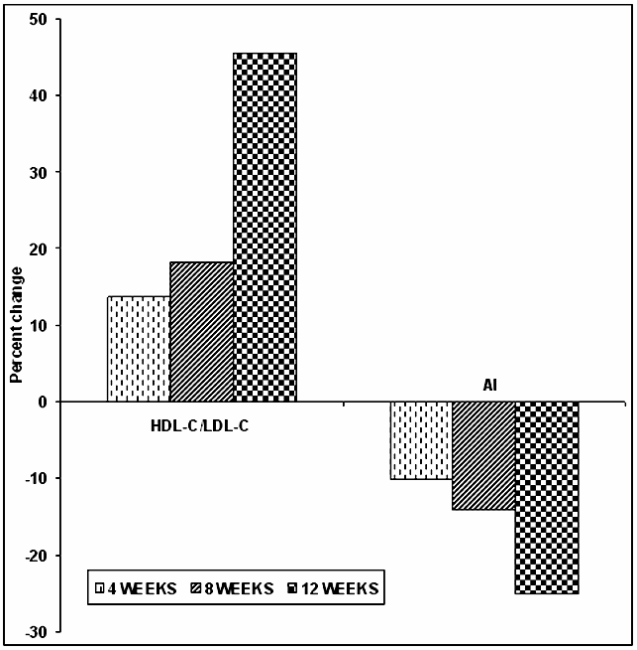

Fig. 5—Percent change in HDL-C/LDL-C ratio and atherogenic index (AI) after daily administration of 3 gm *Ipomoea digitata* tuber powder in stage 1hypertensive individuals (n=30)

Table 2—Effect of *Ipomoea digitata* tuber powder and placebo (3 gm) on fibrinolytic activity (FA) and total antioxidant status (TAS) in stage 1 hypertensive individuals

PARAMETER	GROUP	INITIAL(I)	4 WEEKS(II)	8 WEEKS(III)	12 WEEKS(IV)
FA	TREATED	85.71 ± 7.35	101.08 ± 8.70 [a]	101.86 ± 6.45 [b]	125.25 ± 11.02 [c,d]
(Units)	PLACEBO	78.96 ± 4.56	80.50 ± 7.46 [*]	82.69 ± 5.65 [*]	80.97 ± 10.46 [*]
TAS(mM/L)	TREATED	0.59 ± 0.05	0.82 ± 0.08 [a]	1.12 ± 0.06 [e]	1.20 ± 0.11 [c,f]
	PLACEBO	0.61 ± 0.07	0.75 ± 0.07 [*]	0.70 ± 0.08 [*]	0.70 ± 0.05 [*]

Values are expressed as Mean ± SE NS-Not significant
p Value –
<0.05 - a II v/s I, d IV v/s III
<0.02 - b III v/s I
<0.001 – c IV v/s I
<0.01 - e III v/s I
NS – f IV v/s III, *As compared to initial.

Table 3—Effect of *Ipomoea digitata* tuber powder and placebo (3 gm) on lipid profile in stage 1 hypertensive individuals

PARAMETERS	GROUP	INITIAL(I)	4 WEEKS(II)	8 WEEKS(III)	12 WEEKS(IV)
Cholesterol(mg/dl)	Treated	262.21 ± 34.26	219.05 ± 28.22 [a]	225.03 ± 24.65 [b]	193.74 ± 22.30 [c, d]
	Placebo	255.46 ± 15.88	245.26 ± 18.67 [a]	250.14 ± 13.99 [b]	240.91 ± 16.03 [e]
Triglycerides(mg/dl)	Treated	169.40 ± 17.31	156.82 ± 15.53 [a]	139.35 ± 11.51 [b]	142.19 ± 17.38 [d, e]
	Placebo	174.70 ± 19.56	166.64 ± 3.50 [a]	170.45 ± 16.06 [b]	164.50 ± 15.45 [e]
HDL-C(mg/dl)	Treated	40.91 ± 3.63	38.04 ± 2.97 [a]	40.90 ± 2.60 [b]	40.40 ± 4.04 [d, e]
	Placebo	45.57 ± 3.95	48.57 ± 3.40 [a]	48.69 ± 2.26 [b]	46.92 ± 3.14 [e]
VLDL-C(mg/dl)	Treated	33.87 ± 3.58	31.36 ± 3.10 [a]	27.96 ± 2.23 [b]	28.43 ± 3.47 [d, e]
	Placebo	34.94 ± 2.91	33.32 ± 2.67 [a]	34.09 ± 3.16 [b]	32.9 ± 2.85 [e]
LDL-C(mg/dl)	Treated	185.16 ± 31.66	149.65 ± 27.88 [a]	156.02 ± 26.73 [b]	124.90 ± 22.86 [c, f]
	Placebo	174.95 ± 17.55	163.37 ± 15.67 [a]	167.36 ± 19.57 [b]	170.09 ± 18.45 [e]
HDL-C/ LDL-C	Treated	0.22 ± 0.11	0.25 ± 0.10 [a]	0.26 ± 0.09 [b]	0.32 ± 0.17 [c, d]
	Placebo	0.26 ± 0.04	0.29 ± 0.08 [a]	0.29 ± 0.07 [b]	0.27 ± 0.09 [e]
Atherogenic index (AI)	Treated	6.40 ± 0.43	5.75 ± 0.54 [a]	5.50 ± 0.98 [b]	4.79 ± 0.62 [c, d]
	Placebo	5.60 ± 0.46	5.04 ± 0.57 [a]	5.13 ± 0.58 [b]	5.32 ± 0.96 [e]

Values are expressed as Mean ± SE, NS - Not significant, AI=Total cholesterol/HDL-C
p Values-
NS – a II v/s I, b III v/s I, d IV v/s III, e IV v/s I
<0.05 - c IV v/s I, f IV v/s III.

agent like papaverine. Moreover, it also possesses *in vitro* antioxidant activity as shown by Shaw and associates [32].

An ether soluble fraction from the tubers of *I. digitata* has also been reported to possess hypotensive, myocardium depressant and muscle relaxant activities. Administration of 5 and 10 mg/kg ether soluble drug intravenously in normotensive anesthetized dogs reduced blood pressure by 20 and 32 mm Hg, respectively. Moreover, this hypotensive effect was not modified by ganglionic, adrenergic, cholinergic blockade, antihistaminic drugs or bilateral cervical vagotomy[9].

Umbelliferone, a benzopyrone present in the tubers of *Ipomoea digitata* is a well known natural antioxidant[33]. β-sitosterol is another important sterol present in this plant which has been shown to possess antioxidant[34], antimicrobial[35], anti-cancer[36], angiogenic[37], antihyperglycemic[38] and hypocholesterolemic[39] properties. However, the specific bioactive molecule from *Ksheervidari* responsible for its hypotensive and antioxidant properties should be isolated for its maximum therapeutic benefit.

The present single blinded placebo controlled study therefore, suggests that *Ksheervidari* possesses components due to which its long term administration significantly lowers blood pressure and blood lipids, and enhances fibrinolysis and antioxidant status in stage 1 hypertensive individuals. Looking to its beneficial effects with a wide safety profile, it can be developed as a safe and economical plant derived hypotensive agent with its multifaceted benefits.

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