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Effect of *Pueraria tuberosa* DC. (Indian Kudzu) on Blood Pressure, Fibrinolysis and Oxidative Stress in Patients with Stage 1 Hypertension

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Abstract: The Indian Kudzu (*Pueraria tuberosa* DC.) is an important medicinal plant widely used in Indian and Chinese traditional systems of medicine. The present study is an attempt to evaluate effect of its tubers on blood pressure, coagulation parameters and antioxidant status in patients with stage 1 (primary) hypertension. In a long term, single blinded, placebo controlled study; 15 patients with stage 1 hypertension (group I), were administered 3 g *P. tuberosa* in two divided doses while another 15 patients (group II) were administered matched placebo for a period of twelve weeks. A significant fall of 25, 11 and 16 mmHg was observed in systolic ($p<0.001$), diastolic ($p<0.05$) and mean ($p<0.001$) blood pressure, respectively at the end of the study. Along with blood pressure reduction, there was a significant ($p<0.01$) reduction in plasma fibrinogen and significant enhancement of plasma fibrinolytic activity ($p<0.001$) and serum total antioxidant status ($p<0.05$). It was tolerated well without any untoward side effects.

Key words: Vidarikand, fibrinogen, antioxidant, puerarin, isoflavones

INTRODUCTION

Pueraria tuberosa (Roxb. ex. Willd.) DC.; is a perennial woody climber with large tuberous roots and member of family Fabaceae. It is a rapidly growing plant and therefore, has acquired the name as 'Mile a minute vine' or 'Foot a night vine'. It is distributed throughout the India up to the height of 1200 m. It is commonly known as Bilaikanda, Vidarikanda, Ghora-bel, Indian Kudzu in different languages (NISCAIR, 2003).

P. tuberosa is an important medicinal plant in traditional systems of medicine. In Ayurveda, the tubers of *P. tuberosa* are described as sweet, refrigerant, emollient, laxative, aphrodisiac, galactogogue, diuretic, emetic, cardiotonic, expectorant, febrifuge and used for the treatment of hepatosplenomegaly, leprosy, dyspepsia, spermatorrhoea, tuberculosis and cough (Warrier *et al*., 1997). In ethnomedicine, tubers are used as an edible and to treat various ailments such as diarrhea, fever, chest pain, rheumatism, abdominal pain etcetera (Jain, 1991).

Plants are the potential sources for the development of effective and safe therapeutic agents. Many of the plants have shown to modify the risk factors involved in endothelial dysfunction, such as blood lipids, blood sugar, coagulation, fibrinolysis, blood pressure, oxidative stress etc. (Jain *et al*., 2012; Dey and De, 2010; Burta *et al*., 2008). *P. tuberosa* is one such important plant which has shown to possess antioxidant (Pandey *et al*., 2007), hypoglycemic (Raghuwanshi and Jain, 2012), hypolipidemic (Tanwar *et al*., 2008), antimicrobial (Ratnam and Raju, 2009), fibrinolysis enhancing (Verma *et al*., 2009a) and cardioprotective (Verma *et al*., 2009b) activities. Its phytochemical constituents have shown to possess vasodilator, antihypertensive and antioxidant (Dong *et al*., 2004; Vera *et al*., 2007; Foti *et al*., 2005; Pandey and Tripathi, 2010) properties in various experimental studies. Few clinical studies have also shown beneficial effect of Indian Kudzu in various cardiovascular risk parameters in patients of ischemic heart disease (Verma *et al*., 2009a, b). In view of its traditional use and important pharmacological properties, the present study was envisaged to observe the effect of long term administration of tubers of *P. tuberosa* on blood pressure, fibrinolysis, fibrinogen and total antioxidant status in patients with stage 1 hypertensive individuals.

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MATERIALS AND METHODS

Collection of plant material: Tubers of *P. tuberosa* were collected from forests of Aravalli hills near Udaipur district. A voucher specimen of the plant (EA-264) was deposited at the Herbarium in Laboratory of Ethnobotany and Agrostology, Department of Botany, Mohanlal Sukhadia University, Udaipur for future reference.

Preparation of plant material: Tubers were cut in small pieces and air-dried in shade at ambient temperature. After complete drying these were grinded in an electrical grinder to make fine homogenous powder and filled in gelatin capsules. Each capsule contained 0.75 g powder. Matched placebo was also prepared by filling the capsules with lactose powder.

Study protocol: The study was approved by Institutional ethical committee. It was a single blinded, placebo controlled study. The study was in accordance with the guidelines of the Declaration of Helsinki and Tokyo (2004). After informed consent, study subjects were selected from the out patient department of Maharana Bhopal General Hospital attached to RNT Medical College, Udaipur, Rajasthan, India.

Subject distribution and drug administration: Thirty, non obese (BMI<25), newly diagnosed patients of primary hypertension stage 1 (≥140/90 to 159/99 mmHg) of JNC VII (Chobanian *et al*., 2003), between the ages of 35 to 50 years were selected and randomly divided into two groups of 15 each. Group I (Treated group) was administered 1.5 g *P. tuberosa* twice a day for 12 weeks. Group II (Placebo group) received matched placebo for similar duration.

The patients with stage 2 (≥160/100 mmHg) 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 oral contraceptives, lipid lowering drugs, dietary restrictions or weight reduction program were excluded from this study. During the entire study period, they were not allowed to alter their dietary and exercise schedule which they were following for last three months.

Blood pressure measurement: The blood pressure was measured with a mercury sphygmomanometer with a standard size cuff in accordance with recommendations of JNC VII. Average of two or more readings with the gap of five minutes was taken at each time of blood pressure recording. Blood pressure was recorded in sitting position, initially weekly up to 4 weeks and then at an interval of 4 weeks till the end of the study. Mean blood pressure was determined by the formula: Diastolic blood pressure + 1/3rd of pulse pressure.

Blood chemistry: All the blood samples were collected in fasting state initially and at an interval of four weeks, till the end of the study for the analysis of plasma fibrinolytic activity (Buckell, 1958), fibrinogen (Nath and Debnath, 1970) and serum total antioxidant status (Miller *et al*., 1993).

Statistical analysis: Data were expressed as mean±SE. Results were statistically analyzed with student's t-test for paired data and a 'p' value less than or equal to 0.05 was considered as significant.

RESULTS AND DISCUSSION

There was a significant fall in systolic ($p<0.01$) and mean ($p<0.05$) blood pressure at the end of 4 weeks after administration of 3 g *P. tuberosa* while diastolic blood pressure was not reduced significantly. After eight weeks, a significant decrease in systolic ($p<0.001$) and mean ($p<0.02$) blood pressure was observed and at the end of the study, systolic ($p<0.001$), diastolic ($p<0.05$) and mean ($p<0.001$) blood pressure were reduced significantly (Table 1, Fig. 1-3). There was a progressive enhancement in plasma fibrinolytic activity and highest level of significance was achieved at the end of 12 weeks ($p<0.001$). Total antioxidant status was also increased progressively but the level of significance ($p<0.05$) was achieved only at the end of 12 weeks. Plasma fibrinogen levels were decreased significantly ($p<0.01$) at the end of the study (Table 2). However, administration of placebo did not significantly alter any of the parameters during the study.

Administration of 3 g *P. tuberosa* in two divided doses led to progressive fall in systolic, diastolic and mean blood pressure (Table 1). It was statistically significant at 4, 8 and 12 weeks except diastolic blood pressure which achieved statistical significance only at the end of 12 weeks. At the end of study, there was 25 mmHg decrease in systolic ($p<0.001$), 11 mmHg decrease in diastolic ($p<0.05$) and 16 mmHg fall in mean ($p<0.001$) blood pressure (Fig. 4). This fall in blood pressure is important because randomized controlled trials have shown that in patients with mild hypertension, lowering of blood pressure decreases morbidity and

Table 1: Effect of *Pueraria tuberosa* (3 g) on blood pressure in stage 1 hypertensive individuals (N = 15 in each group)

Blood pressure (mmHg)	Initial (I)	4 Weeks (II)	8 Weeks (III)	12 Weeks (IV)
Systolic				
Group I	151.66±7.95	136±7.77[a]	131.66±5.66[b]	126.66±6.68[c,d]
Group II	153.20±1.29	154.13±1.49[e]	157.2±1.02[f]	157.10±1.49***
Diastolic				
Group I	91±6.10	86±3.66[g]	86±3.84[f]	80±3.66[g,d]
Group II	95.73±0.87	96.93±0.86[g]	95.2±1.49[f]	95.2±1.49***
Mean				
Group I	111.22±5.39	102.66±3.69[h]	101.21±3.68[*]	95.55±4.11[c,**]
Group II	114.88±0.79	115.98±0.68[e]	115.86±1.18[f]	115.83±1.15***

Values are Mean±SE, p<0.01: [a] II vs. I, *III vs. I, p<0.001: [b]III vs. I, [c] IV vs. I, p<0.05: [d]IV vs. III, [g]IV vs. I, [h]II vs. I, p<0.02: **IV vs. III, ns: [e] II vs. I, [f]III vs. I, ***IV vs. I, Group I: Treated group, Group II: Placebo group

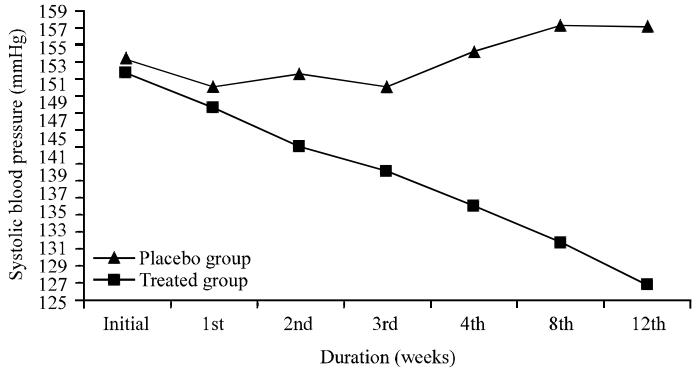

Fig. 1: Response in systolic blood pressure after administration of 3 g *P. tuberosa* in stage 1 hypertensive individuals

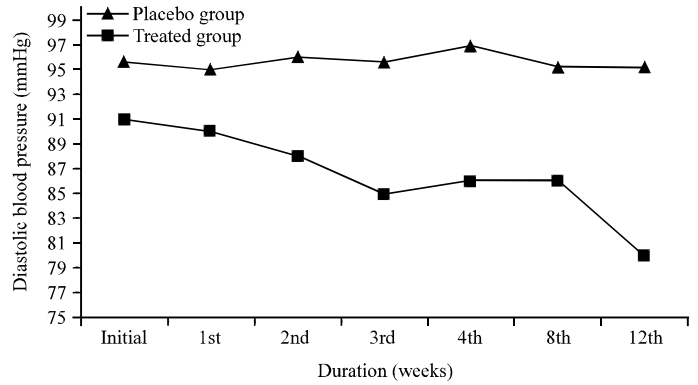

Fig. 2: Response in diastolic blood pressure after administration of 3 g *P. tuberosa* in stage 1 hypertensive individuals

mortality from cardiovascular diseases. On an average 5-6 mmHg reduction in diastolic and 10 mmHg in systolic blood pressure reduces stroke risk by about one third and risk of coronary events by about one sixth (Collins and MacMohan, 1994; Guyton and Hall, 2006). In view of this, it is expected that anti-hypertensive effect of *P. tuberosa* would lead to significant decrease in cardiovascular morbidity and mortality.

Along with the fall in blood pressure, there was also progressive reduction in fibrinogen and enhancement of fibrinolytic activity (Table 2). The effect started even at the end of 4 weeks. Reduced fibrinolytic activity and increased fibrinogen levels have been reported in Ischemic Heart Disease (IHD), hypertension and diabetes in many of the scientific studies (Gupta, 1969; Rani *et al*., 1981). Clot formation and fibrinolysis is a balance of plasmin activation/inhibition and thrombin-thrombomodulin activity that regulates fibrin polymer formation and degradation. In health, there exists a dynamic equilibrium between fibrin deposition and its cleaning by fibrinolytic process. If the fibrin is not removed properly then its organization and fatty

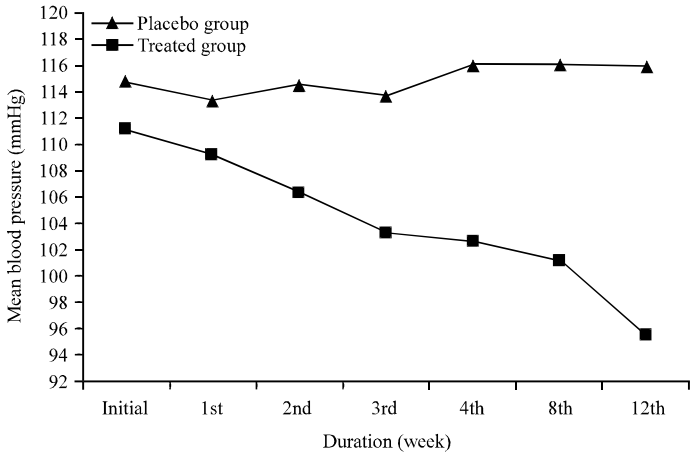

Fig. 3: Response in mean blood pressure after administration of 3 g *P. tuberosa* in stage 1 hypertensive individuals

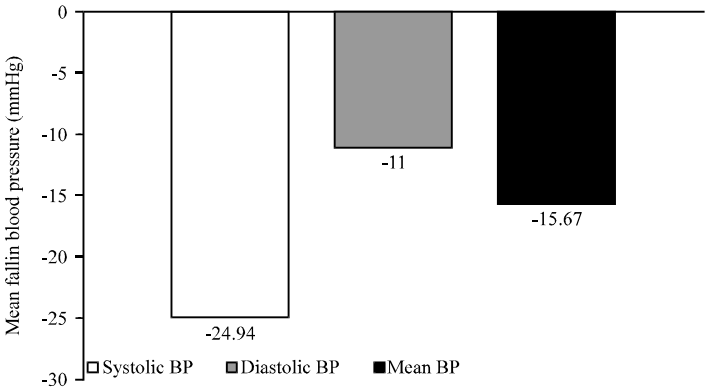

Fig. 4: Mean fall in blood pressure at the end of 12 weeks

Table 2: Effect of *P. tuberosa* (3 g) on fibrinolytic activity, fibrinogen and total antioxidant status in stage 1 hypertensive individuals (N = 15)

Parameters	Initial (I)	4 Weeks (II)	8 Weeks (III)	12 Weeks (IV)
Fibrinolytic activity (IU)				
Group I	67.52±3.92	102.44±9.93[a]	125.39±11.54[b]	134.74±9.61[d,e]
Group II	70.67±3.22	77.59±3.94*	75.43±7.09**	76.74±4.10***
Fibrinogen (mg %)				
Group I	293.42±10.43	250.52±11.89[a]	209±14.17[b]	212.85±9.64[c,e]
Group II	242.82±21.39	236.77±17.6*	237.32±17.08**	245.48±19.46***
TAS (mmol L^{-1})				
Group I	0.82±0.17	0.89±0.18*	0.96±0.19**	1.266±0.21[f]
Group II	0.81±0.23	0.87±0.24*	0.88±0.20**	0.9±0.19***

Group I: Treated group, Group II: Placebo group, p<0.02: [a]II vs. I, p<0.01: [b]III vs. I, [c]IV vs. I, p<0.05: [f]IV vs. I, p<0.001: [d]IV vs. I, NS: [f]IV vs. III, *II vs. I, **III vs. I, ***IV vs. I

deposition on the artery involved, result in atheroma formation (Kannel *et al*., 1987). The process is of great importance in wound healing and recanalization of thrombosed vessels (Fearnley, 1963). In this regard, *P. tuberosa* has shown to be an excellent fibrinolytic agent. Fibrinogen is an independent risk factor for coronary artery disease and stroke and its reduction by Indian Kudzu is also worth noting (Table 2).

Hypertension is a multifactorial disease prevalent in developed and developing countries. It is a common cardiovascular risk factor for IHD and cerebrovascular accidents. It is usually associated with an abnormal level of antioxidant status and reduced fibrinolysis (Kashyap *et al*., 2005). The free radical scavenging property or antioxidant capacity has been well studied in the pathogenesis of diabetes, cardiovascular diseases, diabetes mellitus, neurological and psychiatric disorders,

renal and lung diseases (Kusano and Ferrari, 2008). In view of this, significant ($p<0.05$) enhancement in total antioxidant status (54%) is commendable property of Indian Kudzu (Table 2).

Tubers of *P. tuberosa* are found to be rich in flavone compounds and isoflavones such as puerarin, daidzein, genistein, genistin, tuberosin besides other phytochemicals such as pterocarpenes and coumestans, hydroxytuberosone, 3-O-methylanhydrotuberosin, anhydrotuberosin, tuberostan, tuberosin, puerarone, puerarostan, beta sitosterol, stigmasterol etc. (Verma *et al*., 2009a; Bhutani *et al*., 1969; Pandey and Tripathi, 2010). Many of these compounds have shown beneficial effect on cardiovascular, cerebrovascular and endocrine systems, including diabetes and its complications (Wong *et al*., 2011).

Plants have diverse pharmacological activities due to presence of variety of phytochemicals and therefore, they act synergistically on various metabolic activities and oxidative s tress. Puerarin, isolated from tubers of Kudzu has shown to induce endothelium independent relaxation in rat aortic rings and augment coronary collateral circulation in experimental acute myocardial infarction (Dong *et al*., 2004; Liu *et al*., 1999). It also protects the myocardium against ischemia and reperfusion injury via opening the calcium-activated potassium channel and activating protein kinase C (Gao *et al*., 2007) while Genistein, an isoflavones reduces systolic blood pressure and enhances endothelium-dependent aortic relaxation to acetylcholine (Vera *et al*., 2007).

Many experimental studies have shown hypolipidemic (Tanwar *et al*., 2008), hypoglycemic (Raghuwanshi and Jain, 2012) and antioxidant (Pandey *et al*., 2007) properties of Indian Kudzu. Clinical studies have also demonstrated its favorable effect in angina, biochemical parameters (Verma *et al*., 2009b) and fibrinolytic activity (Verma *et al*., 2009a) in patients with ischemic heart disease.

In the present study, the crude drug has been used which has shown beneficial effect on blood pressure, fibrinolysis and antioxidant status. We have earlier shown that even with the crude drug, the fibrinolysis enhancement corresponds with the puerarin pharmacokinetics (Verma *et al*., 2009a).

The exact mechanism of antihypertensive effect of *P. tuberosa* is not very clear. However, it contains many bioactive compounds such as puerarin, daidzein, genistein, tuberosin etc. which have shown to induce vasodilation, affect K^+ channels (Sun *et al*., 2007; Deng *et al*., 2012), rennin angiotensin system (Cai *et al*., 2011) and attenuating hypertension induced by dietary NaCl (Cho *et al*., 2007) which might be responsible for its beneficial effect on blood pressure.

In conclusion, Indian Kudzu has shown to possess significant antihypertensive, antioxidant and fibrinolysis enhancing properties in patients with stage 1 hypertension. It is safe to administer, well tolerated and did not produce any side effects. However, it needs further evaluation with increasing doses and longer duration of administration to a larger subset of patients.

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