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Antihypertensive, ACE Inhibitory and Antioxidant Activity of Whole Plant of *Rhynchosia beddomei*

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ABSTRACT

Pharmacological investigation of methanolic extract of *Rhynchosia beddomei* whole plant (MERB) for its antihypertensive activity, ACE inhibition, antioxidant activity via radical scavenging activity. Albino Wistar rats were treated with dexamethasone (30 µg/kg/day s.c) or saline for 14 days. MERB (300 mg/kg b.w., p.o.) was administered from day 8 to 14 day of study. Chronic fructose treatment in rats has repeatedly been shown to elevate blood pressure in association with insulin resistance. MERB (300 mg/kg b.w, p.o) was able to prevent the establishment of hypertension by decreasing the elevated blood pressure levels. The reduction in blood pressure is attributed to the inhibition of ACE by 49.6%. The preliminary phytochemical investigation suggests that the MERB possesses flavonoids, phenolics and steroids. MERB exhibited 1, 1-diphenyl-2-picrylhydrazyl radical-scavenging activity with IC_{50} value of 7.4 µg/ml as well as superoxide ion extinguishing ability with IC_{50} value of 12.5 µg/ml. MERB exhibits antihypertensive activity by inhibiting angiotensin converting enzyme and antioxidant activity by radical scavenging property. These findings reveal the presence of potential active constituents of MERB.

Keywords: Serum *Rhynchosia beddomei,* Dexamethasone, Hypertension, Fructose, Fabaceae .

Introduction

Hypertension is a cardiovascular disease where elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. Hypertension is considered a state of oxidative stress that can contribute to the development of atherosclerosis [1] and other hypertension-induced organ damage [2]. Assessment of antioxidant activities and lipid peroxidation by-products in hypertensive's indicates an excessive amount of Reactive Oxygen Species (ROS) and a reduction of antioxidant mechanism activity in blood as well as in several other cellular systems, [3]including not only vascular wall cells, [4]but also those found in circulating blood [5, 6]. Chronic intake of glucocorticoids, especially at supraphysiological doses, leads to elevated systolic blood pressure[7]. Increased vascular sensitivity to glucocorticoids has been also demonstrated in patients with essential hypertension[8].

Angiotensin converting enzyme, is a zinc metallopeptidases that converts the angiotensin I (inactive decapeptide) to angiotensin II (a potent vaso-constrictor), and bradykinin (a hypotensive peptide) to inactive components. High ACE activity leads to increased concentration of angiotensin II and hypertension. Therefore, development of agents that hinder the conversion of angiotensin I to angiotensin II, and brady-kinin to inactive components began as a therapeutic strategy to treat hypertension. ACE inhibitors such as captopril and lisinopril play key roles in treating hypertension and maintaining the electrolyte balance. But captopril [9] has been reported to have side effects on prolonged use. The oxidative stress in cardiac and vascular myocytes caused by ROS has been noted to induce cardiovascular tissue injury and to sustain homeostasis of the vascular wall, a balance between the endogenous transmitter's angiotensin II, nitric oxide, and ROS is of great value. It has been clearly noted that hypertension caused by chronically increased levels of angiotensin II is mediated in part by superoxide anions [10].

The cardiovascular diseases caused by increased levels of angiotensin II are found to be mediated by vasoconstriction and thus decreased concentration of vascular nitric oxide seems to promote the angiotensin II dependent cardiovascular diseases [11]. It is claimed that phenolic compounds are powerful chain breaking antioxidants [12]. The scavenging activity of phenolic group is due to its hydroxyl group [13]. Superoxide radicals can react with water to form hydrogen peroxide. Hydrogen peroxide is scavenged by

flavonoids. Flavonoids are a group of polyphenolics compounds, which have been reported to possess ACE inhibitory activity [14]. The activity of flavonoids and other polyphenols may be due to the formation of chelate complexes with the zinc atom within the active centre of zinc-dependent metallopeptidases [15].

The genus Rhynchosia belongs to the family Fabaceae (Leguminosae). *Rhynchosia beddomei* is an endemic medicinal plant from the Eastern Ghats of India. The plant was used in various human ailments by the tribal people of the Eastern Ghats. *Rhynchosia beddomei* was found to have abortifacient, antibacterial, antifungal, diabetic and hepatoprotective properties [16, 17]. The leaves are also used for wounds, cuts, boils and rheumatic pains by tribal people in India [18, 19]. It is also observed that MERB has a variety of anticancer effects such as cell growth and kinase activity inhibition, apoptosis induction, suppression of the secretion of matrix metalloproteinases and tumor invasive behavior [20]. The objectives of the present study were to explore the effects of the methanolic extract of *Rhynchosia beddomei* for anti-hypertensive action and pharmacological effects on hypertensive related abnormalities induced by dexamethasone and high fructose diet in normal rats and also to investigate probable antioxidant activity of MERB.

Materials and Methods

Animals: Healthy male rats (Albino wistar strain) weighing 200-250gm was selected for the study. The rats were kept in a laboratory animal unit with a 12-h light/dark cycle. Throughout the experiment, room temperature was maintained at 25 °C. The rats were maintained on a standard chow diet and water ad libitum prior to dietary manipulation. They were trained for the first week to become acclimated to the procedure of indirect blood pressure measurement.

Preparation of plant extract: Whole plant of *Rhynchosia beddomei* Baker was collected from seshachalam hills in tirupathi, chittoor district of Andhra Pradesh. The plant was identified and authenticated by Dr. K. Madhava Chetty. The coarse powdered whole plant (1Kg) was extracted using reflux with methanol for 1h to obtain methanol extract.

Acute toxicity: Acute toxicity of *Rhynchosia beddomei* was determined using female albino mice. The animals were fasted 3 h prior to the experiment according to the procedure (OECD guideline no. 423) and were observed for 48 h following oral administration of different doses of *Rhynchosia beddomei*, as per the guidelines.

In-Vitro Antioxidant Assays

DPPH radical scavenging activity: The hydrogen donating ability of extracts was examined in the presence of DPPH stable radical. One milliliter of 0.3 mM DPPH methanolic solution was added to 2.5 mL of test solution of different concentrations and allowed to react at room temperature. After 30 minutes the absorbance values were measured at 517 nm. Methanol (1.0 mL) and plant extract solution (2.5 mL) was used as blank, DPPH solution (1.0 mL, 0.3 mM) and methanol (2.5 mL) served as negative control. Ascorbic acid was used as standard.

NBT reduction assay: A reaction mixture (3mL) per tube was prepared with 1.4 mL of 50 mM KH_2PO_4-KOH pH 7.4 containing 1mM EDTA, 0.5 mL of 100 µM hypoxanthine, 0.5mL of 100µM NBT. The reaction was started by adding 0.066 units per tube of xanthine oxidase freshly diluted in 100µL of phosphate buffer and 0.5 mL of test extract in saline. The subsequent rate of NBT reduction was determined by spectrophotometric method at 560nm. Ascorbic acid was used as standard. The results were expressed as the percentage inhibition of NBT.

***In vitro* ACE-inhibitory activity:** ACE-inhibitory activity was measured *in vitro* using the spectrophotometric assay [21, 22]. The substrate, hippuryl histidil-leucine (HHL) and angiotensin converting enzyme (ACE) from rabbit lung (EC 3.4.15.1). Testing solutions (40 µl) were incubated with 100 µl of 0.1 M borate buffer (pH 8.3) containing 5 mM HHL and 0.3 M NaCl and with 20 µl of ACE (2 mU) at 37^{0}C for 30 min. The reaction was stopped with 150 µl of 1 M HCl.

The hippuric acid formed was extracted with ethyl-acetate (1000 µl), centrifuged at 1500 rpm for 10 min and 750 µl of the organic phase were evaporated. The residue was dissolved in 800 µl of distilled water and the absorbance was measured at 228 nm. Triplicate tests were performed for each sample. Inhibitory activity was expressed as the protein concentration-determined by the bicinchoninic acid assay (Pierce, Rockford, IL, USA) using bovine serum albumin as standard- needed to inhibit 50% of ACE activity (IC_{50}).

Dexamethasone induced Hypertension: The Wistar albino rats were fed with pellet feed and water ad libitum. The behavior of rats was examined daily. On the day 1 the animals were weighed individually and the weights were noted down [23,]. Administration of positive control (dexamethasone) and vehicle was done for 13 days consecutively in such a way that the rats would be in hypertensive stage. From 8th day the treatment was done with the *Rhynchosia beddomei* extracts (300 mg/kg) and standard amlodipine (3 mg/kg b.w, p.o.). Blood Pressure (BP), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Beats per minute (BPM), was measured by the tail–cuff method.

Fructose-induced hypertension and effect of *Rhynchosia beddomei*: At age of 6 weeks, the experimental rats were randomly assigned to two groups. The Group-I of rats received the control diet containing 60% vegetable starch, 11% fat, and 29% protein throughout the experiment [24]. The second group received a diet containing 60% fructose, 11% fat, and 29% protein for three weeks. From week 4, this Group-II rat's was further divided into four groups of 6 animals each and assigned the following treatment regimens: fructose-fed, fructose plus amlodipine (3 mg/kg b.w.), fructose plus MERB (300 mg/kg/day).

Pulse rate and systolic blood pressure were measured every 3 days. At the end of the experiment, the animals were sacrificed by decapitation and blood samples were collected for biochemical determinations. Plasma glucose and triglycerides levels were determined using a Hitachi 704 automatic plasma analyzer. Plasma insulin was determined by the radio immunological method with rat insulin as standard.

Results and Discussion:

In acute toxicity study of *Rhynchosia beddomei* the maximum accepted dose was found to be 3000 mg/kg b.w. (p.o). The MERB was subjected for *in vivo* antihypertensive activity with dexamethasone induced hypertension model. Dexamethasone induced hypertension group showed a significant increase in BP, SBP, DBP and moderate decrease in BPM when results were compared to control group (Table 1). Further rats treated with MERB (300 mg/kg b.w, p.o) and standard amlodipine (3 mg/kg b.w, p.o) showed a significant decrease in the BP, SBP, DBP & BPM when compared with dexamethasone induced group (Table 1). The increased BP by the administration of dexamethasone may be due to salt retention and glucocorticoid actions of dexamethasone. MERB lowers the elevated blood pressure levels. This is followed by multifaceted metabolic changes ensuing in decline in food consumption; reduction in body weight, profound obesity often accompanied by diabetes and development of insulin resistance with enhanced blood glucose and triglyceride levels. MERB prevented the rise in triglyceride, glucose in blood and also prevented the progressive reduction in body weight caused by dexamethasone (Table 2.1).

Fructose induced hypertension group showed a highly significant increase in BP, SBP DBP; Also the present study revealed that the rats treated with MERB (300 mg/kg b.w, p.o) and standard Amlodipine (3 mg/kg b.w, p.o) showed a significant decrease in the BP, SBP, DBP, Mean BP and Heart rate when compared with fructose induced hypertension group in table 2. Fructose induced hypertension group showed a significant increase in the triglyceride, insulin levels and no change in the glucose level respectively when results were compared to control group. Rats were treated with MERB (300 mg/kg b.w, p.o) and standard amlodipine showed significant decrease in the triglyceride, insulin and no change in the glucose levels was observed when results were compared with fructose induced hypertension group shown in table 2.1.

In Fructose induced hypertension model, rats treated with MERB (300 mg/kg b.w, p.o) and standard Amlodipine (3 mg/kg b.w, p.o) showed a significant decrease in the body weight at week 2 and 6 respectively when compared with fructose induced group (Table 2.2). Animals also showed a significant reduction in the feed intake at week 6 when compared with the control group, which resulted in significant decrease in body weight with MERB and amlodipine treated (table 2.2 and 2.3-supplementary information). In addition, Fructose induced hypertension group showed a significant reduction in the fluid intake at week 1 & 2 followed by the significant increase the fluid intake at week 5 & 6 when compared with control group. Whereas, MERB and amlodipine treated groups showed significant decrease in the fluid intake on the week 1, week 5 week 6 respectively. There is no significant change in the fluid intake found in the remaining weeks which were shown in table no 2.4 of supplementary information).

DPPH radical scavenging activity and NBT reduction assay showed that MERB possess antioxidant activity. DPPH radical scavenging activity IC_{50} value for Vitamin C and MERB were 8.4 µg/ml and 7.4 µg/mL respectively. In NBT inhibition assay, IC_{50} value for MERB was 12.5 µg/ml against the standard Vitamin C (8.4 µg/ml). The whole plant of *Rhynchosia beddomei* demonstrated ACE inhibitory activity at a concentration of 800 µg/ml, showing an inhibition of 72.52 %. The IC_{50} value of MERB extract was 385 µg/ml and standard captopril, was 0.3 ng/ml (Table 3). MERB inhibited ACE in a concentration dependent manner. The antihypertensive, ACE inhibition and antioxidant properties are possibly due to the presence of phenolic and flavonoid content in the MERB.

From the Histopathological studies of myocardium shows intact arrangement of the cardiac muscle fibers where as the in the induced group, myocardium shows partially haphazard arrangement of the cardiac muscle fibers. MERB and standard treated shows its restoration to normal.

GROUPS	Dexamethasone induced hypertension.			
	BP	SBP	DBP	BPM
Control	110.0 ± 0.705	114.9 ± 1.679	92.48 ± 1.709	329.9 ± 3.794
Dexamethasone (0.2 ml s.c)	121.1 ± 0.965	126.0 ± 1.641^{***a}	117.9 ± 1.231^{***a}	321.8 ± 1.265^{*b}
Dexamethasone + MERB(300 mg/kg, b.w.)	90.92 ± 2.302	98.73 ± 3.405^{***b}	79.33 ± 1.929^{***b}	289.5 ± 5.607^{***b}
Dexamethasone + Amlodipine (3mg/kg, b.w.)	86.92 ± 0.830	86.88 ± 0.861^{***b}	85.88 ± 0.511^{***b}	280.1 ± 5.464^{***b}

Table 1: Effect of MERB on Dexamethasone induced hypertension in rats

Values are expressed as Mean ±SEM, n=6, analysed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's multiple comparision test. Where * represents significant at P ≤ 0.05, ** represents highly significant at P≤0.01, ***represents very significant at P≤0.001.[a] control vs Dexamethasone induced [b] dexamethsone induced group vs MERB and amlodipine treated groups.

Parameters	Control	Fructose	Fructose+MERB (300 mg/kg, b.w.)	Fructose + Amlodipine (3 mg/kg, b.w.)
BP	103.3 ± 3.34	157.0 ± 2.29***a	107.4 ± 3.5***b	101.0 ± 1.34***b
SBP	105.0 ± 2.5	144.2 ± 3.54***a	116.2 ± 4.04***b	116.1 ± 1.42***b
DBP	72.8 ±1.78	126.0 ± 1.43**a	105.2 ± 3.25**b	92.3 ± 2.5**b
Mean BP	101 ± 1.31	122.5 ± 2.20***a	100.7 ± 3.00***b	96.3 ± 2.00***b
Heart rate	294.8 ± 4.3	337.4 ± 7.75***a	292 ± 4.27**b	304.3 ± 1.79**b

Table 2: Antihypertensive effect of MERB on fructose fed albino wistar rats[a]

[a]Values are expressed as Mean ±SEM, n=6, analysed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's comparision test Where * represents significant at P ≤ 0.05, ** represents highly significant at P≤0.01, ***represents very significant at P≤0.001.[a] control vs fructose induced group, [b] fructose induced group vs drug treatment groups.

GROUPS	**Glucose (gm/dL)**	**Triglycerides (gm/dL)**	**Insulin (IU/ml)**
Control	86.69 ± 0.068	1.352 ± 0.135	2.843 ± 0.218
Fructose	167.54 ± 0.327	3.277 ± 0.415**a	4.452 ± 0.196***a
Fructose + MERB (300 mg/kg, b.w.)	89.46 ± 0.369	1.725 ± 0.386**b	3.423 ± 0.382**b
Fructose + Amlodipine (3 mg/kg, b.w.)	82.32 ± 0.542	1.665 ± 0.289**b	3.235 ± 0.208**b

Table 2.1: antihypertensive effect of MERB on biochemical changes[a]

[a]Values are expressed as Mean ±SEM, n=6, analysed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's comparision test. Where * represents significant at P ≤ 0.05,** represents highly significant at P≤0.01, ***represents very significant at P≤0.001.[a] control vs fructose induced group, [b] fructose induced group vs. drug treatment groups**.**

Groups	Weekly body weight changes (gms)						
	0 day	1st week	2nd week	3rd week	4th week	5th week	6th week
Control	157.2 ± 5.45	166.9 ± 4.1	195.4 ± 6.5	205.8 ± 7.1	2	224.8 ± 9.2	236.6 ± 9.2
Fructose	192.5 ± 6.26	217.4 ± 5.1**a	228.9 ± 8.4*a	236.3 ± 9.1*a	240.3 ± 10*a	245.5 ± 10.9*a	256.3 ± 10.8*a
Fructose + MERB (300mg/kg b.w.)	218.0 ± 8.08	229.3 ± 6.7	215.8 ± 8.3**b	246.5 ± 12.2	249.5 ± 12.4	225.9 ± 13.6*b	233.1 ± 12.1**b
Fructose + Amlodipine (3 mg/kg, b.w.)	213.1 ± 5.06	220.3 ± 5.1	229.1 ± 5.7	237.31 ± 6.2	232.1 ± 6.2	231.13 ± 6.2*b	224.11 ± 6.9**b

Table 2.2: Effect of drug treatment on body weight changes[a]

[a]Values are expressed as Mean ±SEM, n=6, analysed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's comparision test. Where * represents significant at P ≤ 0.05, ** represents highly significant at P≤0.01, ***represents very significant at P≤0.001. [a] control vs fructose induced group, [b] fructose induced vs MERB and amlodipine treated groups.

Groups	Weekly Feed Intake(gms)					
	1st week	2nd week	3rd week	4th week	5th week	6th week
Control	60.83 ± 1.352	58.97 ± 1.349	52.07 ± 2.063	52.67 ± 1.169	49.78 ± 1.169	55.20 ± 0.735
Fructose alone	54.00 ± 1.732*a	45.38 ± 1.411*a	43.20 ± 1.652	40.17 ± 1.338	41.97 ± 1.228	38.88 ± 0.749**a
Fructose +MERB	35.67 ± 1.626**a	39.58 ± 1.42*b	32.08 ± 1.154*b	35.47 ± 0.914	35.10 ± 2.173	33.37 ± 1.265*b
Fructose + Amlodipine	30.17 ± 1.27**a	37.56 ± 1.45*b	28.77 ± 1.672*b	27.52 ± 1.146**b	23.03 ± 1.320**b	25.58 ± 0.479**b

Table 2.3: Effect of drug on weekly feed intake.

Values are expressed as Mean ±SEM, n=6, analysed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's comparision test, Where * represents significant at P ≤ 0.05, ** represents highly significant at P≤0.01, ***represents very significant at P≤0.001. [a] control vs fructose induced group, [b] fructose induced vs MERB and amlodipine treated groups.

Groups	Weekly Fluid Intake(ml)					
	1st week	2nd week	3rd week	4th week	5th week	6th week
Control	269.3 ± 6.37	285.2 ± 6.03	253.2 ± 7.92	277.8 ± 8.0	274.8 ± 8.32	261.7 ± 7.01
Fructose alone	256.7 ± 6.23**a	182.3 ± 5.90**a	265.0 ± 14.2*a	308.3 ± 9.17	316.2 ± 7.2**a	311.8 ± 8.17**a
Fructose + merb (300mg/kg, b.w.)	172.3 ± 5.80**b	197.3 ± 9.99	226.5 ± 7.12	256.2 ± 7.11	275.7 ± 8.73**b	228.3 ± 9.1**b
Fructose +Amlodipine (3mg/kg, b.w.)	216.7 ± 5.20**b	193.5 ± 5.32	255.7 ± 6.70	247.8 ± 6.9	274.5 ± 4.99**b	204.5 ± 9.9***b

Table 2.4: Effect of drug treatment on weekly fluid intake**.**

Values are expressed as Mean ±SEM, n=6, analysed in graph pad prism version 5.04 by one way ANOVA followed by Tukey's comparision test, Where * represents significant at P ≤ 0.05, ** represents highly significant at P≤0.01, ***represents very significant at P≤0.001. **[a]** control vs fructose induced group, **[b]** fructose induced vs MERB and Amlodipine treated groups.

Extract / Standard	Concentration	% Inhibition	IC_{50}
MERB	100	21.10 ± 0.38	385 ± 1.32 (µg/ml)
	200	34.90 ± 0.33	
	400	56.04 ± 0.49	
	800	72.52 ± 0.54	
Captopril	0.1	35.12 ± 0.23	0.3 ± 0.02 (ng/ml)
	0.2	45.38 ± 0.32	
	0.4	68.20 ± 0.45	
	0.8	78.01 ± 0.56	

Table 3. *In vitro* ACE inhibitory activity of MERB and Captopril MERB- *Rhynchosia beddomei* bark methanolic extract
Values are expressed as mean ± SEM of three parallel measurements. *P < 0.01 when compared with standard.

Test extract	DPPH radical scavenging activity IC_{50} (µg/mL)	NBT inhibition assay IC_{50} (µg/mL)
MERB	7.4	12.5
Vitamin C	8.4	8.4

Table 4. NBT and DPPH radical scavenging activity of *Rhynchosia beddomei* extracts
Values are expressed as mean ± SEM of three parallel measurements. *P < 0.01 when compared with standard.

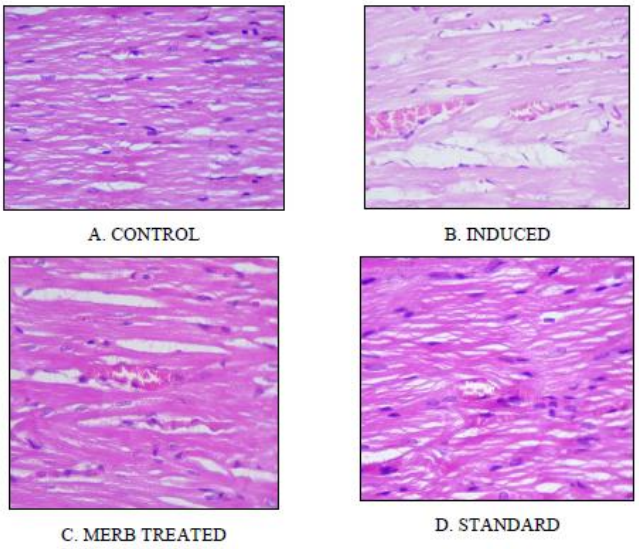

Figure 1: Histopathology report of Myocardium: In the histological report for the myocardium A. Control the myocardium shows intact arrangement of the cardiac muscle fibers, B. Induced group the myocardium shows partially haphazard arrangement of the cardiac muscle fibers, C. MERB treated, the myocardium shows intact arrangement of the cardiac muscle fibers, which shows its restoration to normal. D. Standard the myocardium shows intact arrangement of the cardiac muscle fibers.

Conclusion

Hypertension is a risk factor for apoplectic stroke. ACE regulates blood pressure and ACE inhibition will help reduce hypertension, cardiovascular disease and other related ailments. Antihypertensive activity of MERB in dexamethasone and fructose treated rats was confirmed by decreased BP, ACE inhibition; and antioxidant activity by radical scavenging property. At firstly the phytochemical constituents of MERB extract were found to be triterpenoids, steroids, flavonoids and saponins. These results may lend further support to mount up evidence that the MERB extract containing compounds which, if taken in sufficient quantities, could conceivably be beneficial in the attenuation and prevention hypertension and hyperinsulinemia. The current study has demonstrated that the whole plant extract of *Rhynchosia beddomei* is capable of inhibiting angiotensin converting enzyme, quenching free radicals and acting as reducing and chelating agents. Further studies are required to investigate the antihypertensive properties of individual components of extract of *R. beddomei*.

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