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EVALUATION OF ANTIHYPERTENSIVE ACTIVITY OF *CUCURBITA MAXIMA*

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ABSTRACT

Cucurbita maxima, belongs to family Cucurbitaceae, is commonly known as pumpkin. Several literature reports suggest it to be antidiabetic, antihypertensive, anticancer, immunomodulators, antibacterial and antihyperlipidaemic. The present study was conducted to investigate the effect of the methanolic extract *Cucurbita maxima* of on blood pressure of both normotensive and hypertensive (egg- feed and glucose- induced) rats. The effect of the extract on systolic, diastolic, mean blood pressures and heart rate were evaluated by using non-invasive blood pressure measurement apparatus (NIBP). The extract at doses of 200 and 400 mg/kg (p.o) exhibited a significant decrease in blood pressure and heart rate of normotensive rats. While at the dose of 200mg/kg (p.o) it produces less significant effect than 400 mg/kg (p.o). The 400mg/kg of the extract produces a highly significant effect was selected for antihypertensive effect in egg feed and glucose treated hypertensive rats. A significant antihypertensive was observed at 400 mg/kg (p.o) in both hypertensive models. In addition, a non-significant decrease in ALT, AST, and ALP but significant decrease in total cholesterol, triglycerides, LDL and increase in HDL levels were observed in the serum of the extract treated animals. The methanolic extract of *Cucurbita maxima* possesses safer active principles which exert both hypotensive and antihypertensive effects in normal and hypertensive animal models respectively.

KEYWORDS: *Cucurbita maxima*, Immunomodulatory, Hypertensive, Glucose.

INTRODUCTION

Hypertension is the most common cardiovascular illness and is a major public health issue in developed as well as in developing countries. World Health Organization (WHO) has carried out epidemiological studies in India in between 1995 to 2006. According to this, prevalence of hypertension is 29.3% in men and 25.2% women has been found at the end of 2006.[1] High blood pressure has been found to be associated with many chronic conditions such as insulin resistance, obesity, concomitance, atherosclerosis and cardiovascular diseases. Most of these hypertension associated disorders are prevalent in developing countries because of poor lifestyle and insufficient health care system. Hypertension has become a common problem in the developing countries.[2]

Hypertension involves mainly essential and secondary types. The pathogenesis of hypertension is multi factorial and highly complex which will be caused by increase in sympathetic nervous system activity, increase in production of sodium-retaining hormones and vasoconstrictors, deficiencies of vasodilators such as prostacycline and nitric oxide, inappropriate or increased rennin secretion and genetic predisposition while pathogenesis of secondary hypertension will be caused by chronic kidney disease, renovascular disease, Cushing's syndrome, pheochromocytoma, drugs such as non-steroidal anti-inflammatory drugs and oral contraceptives.

Symptoms associated with high blood pressure can include, shortness of breath (dyspnea), fatigue, dizziness or fainting spells (syncope), chest pressure or pain, bluish color to lips and skin (cyanosis), racing pulse or heart palpitations, headache and nose bleeds. Generally, hypertension is diagnosed by physical history, laboratory tests, sphygmomanometer and digital blood pressure monitoring.

Many antihypertensive synthetic remedies are available to prevent and manage the hypertension, but many of this drugs cause serious and life threatening side effects. Synthetic antihypertensive like diuretics cause muscle cramps, extreme tiredness, skin rash, dehydration, blurred vision and abnormal heart rate, ACE inhibitors cause kidney failure, cough, skin rash and fever, calcium channel blockers cause fatigue, skin rash, constipation

and edema, β-blockers cause bronchospasm, Reynaud's syndrome, heart failure and postural hypotension, as β-blockers cause bronchospasm so contraindicated in asthma, others like centrally acting drugs cause sexual dysfunction. In addition, all antihypertensive drugs are contraindicated during pregnancy accept methyldopa. [3] Other major drawback of synthetic anti-hypertensive drugs is high cost.

Herbal medicines have been used for a number of diseases throught the world. Traditional medicines importance is rapidly growing in the modern world; a very little attention has been given to determine their mechanism of action, side effects, toxicities and interactions. Hence biological evaluation of most of these herbal medicines remains yet to be determined.[4] Furthermore, there is a need to determine the safety and efficacy of traditional herbal medicines.

Cucurbita maxima, belongs to family Cucurbitaceae, is commonly known as pumpkin.*C. maxima* reported to have antidiabetic,[5] hepatoprotective.[6] anthelmintic,[7] immunomodulatory, anticancer, antibacteria, antihypercholesterolemic and anti-inflammatory [8] activities. It is rich in polysaccharides, contains high amounts of amino acids, fatty acids, carotenoids, minerals and vitamin E. The plant is reported to have triglyceride fatty acid mixture, tetrahydro-thiophene, linoleic acid, calotropoleanyl ester, cholesterol and 13(18)- oleanen-3-ol.[9] The present study was designed to evaluate the hypotensive and antihypertensive effects of methonolic extract of *Cucurbita maxima*.

MATERIALS AND METHODS

PLANT MATERIAL:

Cucurbita maxima, belongs to family Cucurbitaceae procured from medicinal garden,jagan's college of pharmacy, Jangalakandriga, Nellore, India. And these were authenticated by prof. P.Jayaraman, Director, National institute of herbal science,W.Tambaram, chennai.

PREPARATION OF PLANT EXTRACTS

The collected whole plant of *Cucurbita maxima*, belongs to family Cucurbitaceae was subjected to dry to brittle material at 60°C in hot air oven to remove moisture. This dried herb was subjected for size reduction using mixer grinder and comminuted to very fine powder. Methanolic extracts of *Cucurbita maxima*, were prepared using methanol as a solvent in soxhlet apparatus.

SELECTION OF ANIMALS

Either sex Wistar albino rats (n=5) of weighing 220-300 g were used for the present study. The animals were procured from animal house, Department of Pharmacology, Jagan' College of Pharmacy, Jangalakandriga, Nellore, India. The animals were placed at random and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of 24±20˚C and relative humidity of 30 – 70 %. A light and dark cycle was followed. All animals were fed on standard balance diet and provided with water *ad libitum*. All the experimental procedures and protocols used in study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of Jagan' College of Pharmacy, and care of laboratory animals was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

BIOCHEMICAL PARAMETERS

For the estimation of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total cholesterol, triglycerides, low-density lipoprotein (LDL) and high density lipoprotein (HDL) blood sample was collected in clot activator gel tubes. The serum was separated by centrifuging the blood samples at 2000 rpm for 10 minutes. The separated serum was then used for the measurement of these biochemical parameters by using commercially available reagent kits (Abbott Laboratories,USA)[10]

Determination of hypotensive effect of aqueousmethanolic extract of *Cucurbita maxima* innormotensive rats

Normotensive rats of either sex were randomly assigned into three groups (n = 5). Group 1 received 100 mg/kg of the aqueous methanolic extract of *Cucurbita maxima* while animals in group 2 and group 3 received 200 mg/kg and 400 mg/kg of the extract respectively. After intra-peritoneal administration of various doses of the extracts, blood pressure and heart rate of each of these groups was determined from the tails of rats at 0 hour, 2 hour, 4 hour and 6 hours by using noninvasive blood pressure (NIBP) measuring apparatus (ML125, AD instruments). Briefly, the animal was placed in the NIBP restrainer and an appropriate cuff with sensor was then mounted on its tail and warmed to about 33– 35°C. The tail cuff was inflated to a pressure well above the expected systolic blood pressure i.e. 250 mm Hg and slowly released during which the pulse was recorded by using Power Lab data acquisition system and computer running Lab chart 5.0 software. Systolic blood pressure (SBP), Mean blood pressure (MBP) and heart rate were measured directly using pulse tracing while the diastolic blood pressure (DBP) was calculated from SBP and MBP using the equation: DBP= (3MBP-SBP) /2[11]

Determination of the antihypertensive effect of the aqueous - methanolic extract of *Cucurbita maxima* in hypertensive rats

Egg feed-induced hypertensive rats: Sprague Dawley rats of either sex were divided into two groups (n = 5). Group 1 was treated with a specially prepared egg feed diet (p.o) for 21 consecutive days in order to produce cholesterol-induced hypertension. Animals in group 2 were treated with (p.o) egg feed diet and an aqueous methanolic extract of *Cucurbita maxima* (400 mg/kg) for the same period. Animals in both groups were given

normal saline instead of tap water ad libitum. Blood pressure and heart rate of each of these groups were measured at week 0, week 1, week 2, week 3 using NIBP .

Glucose-induced hypertensive rats

Rats of either sex were randomly divided into two groups (n = 5). Group 1 received 10 % glucose solution (p.o) instead of tap water for 21 consecutive days. Animals in group 2 were given orally 10 % glucose solution and methanolic extract of *Cucurbita maxima* (400 mg/kg) for the same time period. Animals were fed on standard diet ad libitum. Blood pressure and heart rate of these groups were measured at week 0, week 1, week 2, and week 3 using NIBP.[12]

STATISTICAL ANALYSIS

The results were expressed as means ± standard error of mean (SEM) and statistical analysis was carried out as one way ANOVA followed by posthoc Dunnett test for all the experiments of the present investigation except sub chronic studies test for which two way ANOVA followed by post-hoc Bonferroni's test has been applied. $P < 0.05$ was considered as significant.

RESULT AND DISCUSSION

Hypotensive activity in normotensive rats: The methanolic extract of *Cucurbita maxima*, showed a significant decrease in the SBP, MBP and DBP and heart rate of normotensive rats at the doses of 200 mg/kg and 400 mg/kg. However, there was no significant reduction in heart rate and blood pressure at 100 mg/kg. The maximum effect in all the parameters was observed at 400 mg/kg (Table1).

Hypertensive rats

Egg-feed induced hypertensive rats: The extract at the dose of 400 mg/kg significantly prevented the increase in blood pressure and heart rate of treated animals as compared to control. Similarly, a reduction in heart rate was observed after the 1st week of treatment. At week 2 and week 3, the extract exhibited a more significant decrease in heart rate (Table 2).

Glucose induced hypertensive rats:

The methanolic extract of *Cucurbita maxima*, significantly prevented the increase in SBP, MBP, DBP and heart rate of glucose induced hypertensive rats (Table3).

Table 1. Effect of *Cucurbita maxima* on blood pressure and heart rate of normotensive rats

Time In Hours	Doses											
	100 mg/kg				200 mg/kg				400 mg/kg			
	SBP	MBP	DBP	HR	SBP	MBP	DBP	HR	SBP	MBP	DBP	HR
0h	128± 1.61	105± 1.41	94.2± 1.36	395 ± 11.0	129.0± 2.05	106.0 ± 0.74	95.0± 2.09	363.± 12.5	125.0 ± 1.28	105.1 ± 0.91	95.1 ± 1.88	389.2 ± 18.3
2h	126± 1.71	104± 1.11	96.2± 1.71	384 ± 12.5	119.3± 2.5b	97.0± 2.13a	85.9± 3.0c	345.± 7.16	114.3 ± 3.23c	98.56 ± 1.77d	88.5 ± 3.23	364.4 ± 6.37
4h	129± 1.61	103± 1.19	95.4± 1.96	383 ± 17.4	118.0± 2.05	93.0± 2.13a	95.0± 2.09	363.± 12.5	104.3 ± 3.23c	93.56 ± 1.77d	84.5 ± 3.23	351.4 ± 6.37
6h	128± 1.01	104± 1.85	95.3± 1.01	389 ± 1.30	111.3± 2.5b	94.0± 2.13a	85.9± 3.0c	345.± 7.16	102.4 ± 3.08a	82.6 ± 2.05a	71.7 ± 2.86a	323.4 ± 15.3b

Values are expressed in means ± SEM (n=6). One way ANOVA followed by post-hoc Dennett Where a = ($P < 0.0001$), b = ($P < 0.001$), c = ($P < 0.01$) and d = ($P < 0.05$) vs. control (0 hour).

Table 2. Effect of *Cucurbita maxima* on blood pressure and heart rate of egg feed induced hypertensive rats.

weeks	SBP (mmHg)		DBP (mmHg)		MBP (mmHg)		Heart rate (beats/min)	
	control	Treated 400mg/kg	control	Treated 400mg/kg	control	Treated 400mg/kg	control	Treated 400mg/kg
Week0	121.6± 0.96	123.5± 1.47	103.7± 1.21	105.2± 0.54	94.7± 1.78	96.0± 1.00	380.8± 6.24	384.2 ± 6.19
Week1	131.0± 1.67b	115.6± 2.16	109.2± 2.25c	102.3± 0.98	98.3± 1.63	95.7± 1.26	391.0± 4.61	372.8± 5.43
Week2	141.8± 2.54a	107.5± 5.75b	111.3± 1.78b	100.6± 0.48	103.3± 2.45b	90.8± 2.40	429.6± 12.1	357.2± 10.51c
Week3	163.5± 2.24a	96.5± 6.00a	124.0± 1.39a	83.3± 4.63a	105.6± 1.69a	76.8± 4.42a	469.8± 29.6a	350.0 ± 6.55a

Values are expressed in means ± SEM (n=6). One way ANOVA followed by post-hoc Dennett Where a = ($P < 0.0001$), b = ($P < 0.001$) and c = ($P < 0.01$) vs. control (Week 0).

Table 3. Effect of *Cucurbita maxima* on blood pressure and heart rate of glucose induced hypertensive rats

weeks	SBP (mmHg)		DBP (mmHg)		MBP (mmHg)		Heart rate (beats/min)	
	control	Treated 400mg/kg	control	Treated 400mg/kg	control	Treated 400mg/kg	control	Treated 400mg/kg
Week0	123.3± 0.68	123.6± 0.95	103.3± 0.43	104.0± 0.80	93.3± 0.81	94.3± 0.89	381.6± 10.6	383.1± 6.92
Week1	134.5± 4.71	102.4± 4.36a	113.9± 2.04a	97.3± 2.44c	104.7± 5.00c	94.5± 2.85	398.4± 7.85	380.4± 12.0
Week2	138.8± 4.76c	98.0± 367a	121.1± 0.84a	94.0± 2.72b	111.3± 2.13a	86.5± 3.65c	402.6± 8.50c	354.4± 8.90a
Week3	143.5± 3.41a	93.0± 3.65a	128.1± 1.40a	92.2± 1.83a	117.7± 2.10a	84.2± 2.78b	449.0± 17.9a	349.2± 3.96a

Values are expressed in means ± SEM (n=6). One way ANOVA followed by post-hoc Dennett Where a = (P < 0.0001), b = (P <0.001) and c = (P < 0.01) vs. control (Week 0).

This decrease in blood pressure and heart rate by methanolic extract of *Cucurbita maxima* in both normotensive and hypertensive rats could be linked to a number of mechanisms. Experimental studies demonstrated that glucose and fructose contributes to the rise in blood pressure.[13-14]There is also evidence that especially prepared egg feed which is rich in cholesterol also induced hypertension in rats.[15] It is well reputed that one of the reason for glucose-induced hypertension is increase in sympathetic activity. Increase in sympathetic activity by any mean usually contributes to increase in heart rate and blood pressure**.** In the present investigation, the extract tested was found to significantly decrease the heart rate could be a strong reason of its antihypertensive effect in both normotensive and hypertensive rats. Previously it has been documented that one of the factors of hypertension is dyslipidemia which is associated with high glucose intake.[16] High cholesterol diet such as egg-feed diet is also associated with dyslipidemia as well as hypertension.[17] In the present study the extract significantly reduced cholesterol level in rats which further justifies its antihypertensive effect. Endothelial dysfunction and oxidative stress are the important factors which lead to hypertension.[18] It is also well-established that high sugar consumption is associated to increased tissue production of reactive forms of oxygen. Moreover, in hypertensive patients, lower concentrations of antioxidants have been documented.[19] Furthermore, an increased glucose level has also been involved in a reduction in nitric oxide levels ultimately resulting in an increased blood pressure.

It has been reported that plants rich carotenoids, minerals and vitamin E having an antioxidant effect which improves endothelial dysfunction through increase NO formation, Decrease LDL formation, increase prostacyclin formation, increase EDHF mediated vasorelaxation and decrease Endothelin-1 production [20]. It has also been reported that *Cucurbita maxima.*

CONCLUSION

It is concluded that the methanolic extract of *Cucurbita maxima* contains some active principles which exert antihypertensive effect in experiment models of rats. Moreover, the present study shows that *Cucurbita maxima* are safe for use and these findings justify the folkloric claim. However, detailed studies are required to isolate the active constituent(s) and evaluate its exact mechanism of antihypertensive effect.

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