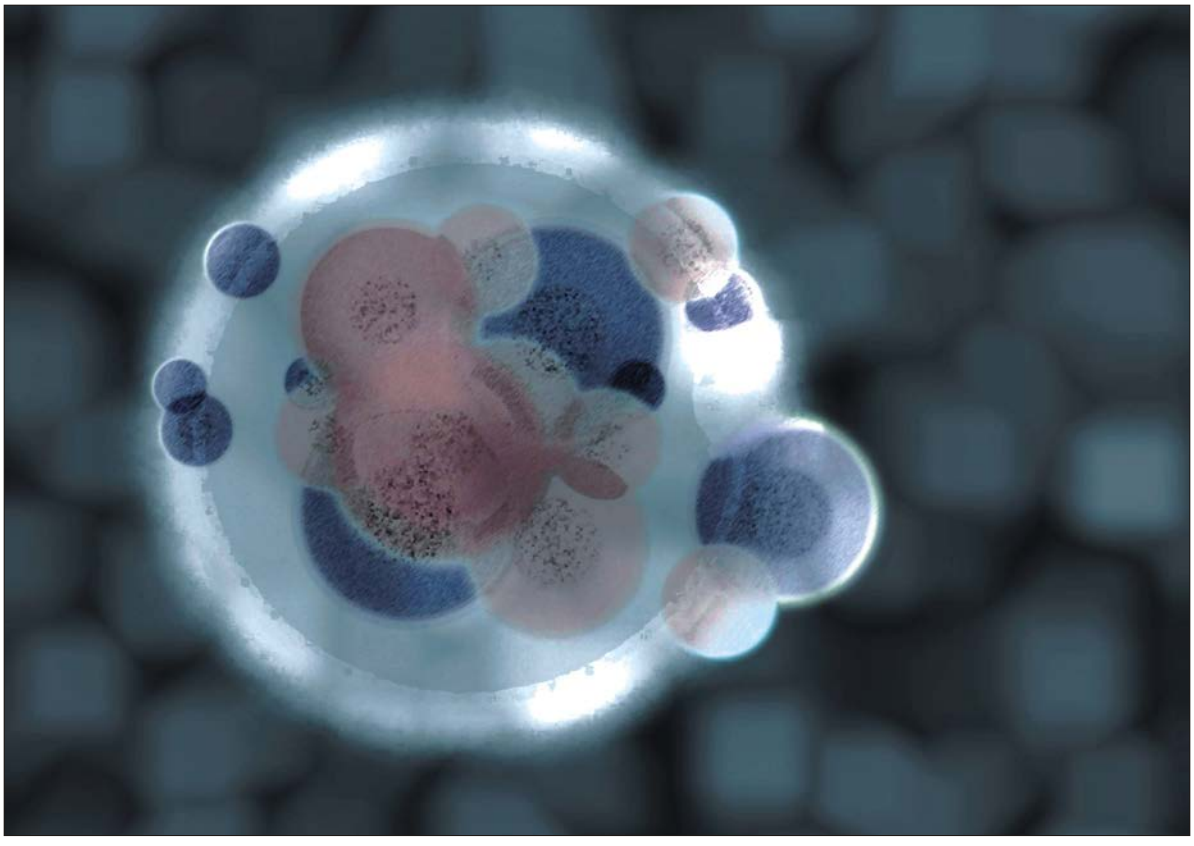

Journal of Biological Sciences

ISSN 1727-3048

science alert

ANSInet
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Journal of Biological Sciences 8 (6): 1082-1086, 2008
ISSN 1727-3048

Comparison of Hypotensive and Hypolipidemic Effects of *Catharanthus roseus* Leaves Extract with Nifedipine on Adrenaline Induced Hypertensive Rats

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Abstract: The leaves extract of *Catharanthus roseus* was investigated for hypotensive and hypolipidemic effects in Adrenaline-Induced Hypertensive Rats (AIHR) and compared with those of nifedipine in a crossover design. The pharmacologically Active components responsible for hypotensive activities were isolated from plant using bioassay guided purification approach and the structure of the compounds were proposed by spectroscopic methods. *Catharanthus roseus* leaves extract and commercial drug nifedipine were administered through intraperitoneal (i.p) route for one week. Different biochemical parameters such as heart weight, blood glucose level, serum cholesterol level, serum triglyceride level, body weight and the relationships between them were measured. *Catharanthus roseus* leaves extract at a dose of 30 mg/155±15 g of body weight was injected in rat at every morning during the treatment period. Clinically effective plasma concentration as a hypotensive drug was obtained after the injection of 0.1 mg/155±15 g of body weight of the drug. The *Catharanthus roseus* leaves extract made significant changes in each cardiovascular parameter after investigation. *Catharanthus roseus* leaves extract treated animals have shown the hypotensive effects. Hypotensive effects were also shown by nifedipine.

Key words: Hypertension, antihypertensive, *Catharanthus roseus*, nifedipine, adrenaline

INTRODUCTION

Hypertension is a medical word for high Blood Pressure (BP). Blood carries nutrients and oxygen to our body and picks up waste like carbon dioxide (Amran *et al*., 2004; Nammi *et al*., 2003; Dupuis *et al*., 2005). The heart pumps blood through arteries and blood returns to the heart through veins. Blood pressure is the push of blood against the walls of the arteries. But if the blood is being pushed too hard against the walls of the vessels, they might be damaged (Gillman *et al*., 1990). High blood pressure is the long term and persistent increase in blood pressure above the normal range, defined as a systolic blood pressure at or above 140 mmHg or a diastolic blood pressure at or above 90 mm Hg. The condition of high blood pressure is also known as hypertensive disease (Antia and Okokon, 2005). Hypertension may be divided into two groups (a) Primary or essential hypertension, where the definite cause for the rise in blood pressure is not known. Although the cause of essential hypertension is mainly three types-genetic factor, stress condition and intake of excess Na^+ salt; (b) Secondary hypertension that are usually considered as drug induced and disease induced. Nifedipine belongs to the group of drugs that are termed calcium channel blocking agents. These drugs affect the movement of calcium into heart and blood vessel cells and cause a relaxing effect of the muscles to allow an increased amount of blood flow into the heart. Many of these calcium channel blockers are used to treat angina pectoris and they are used to help reduce blood pressure (Gillman *et al*., 1990).

Catharanthus is the dried whole plant of *Catharanthus roseus* (G. Don (syn. *Vinca rosea* Linn.)), locally known as nayantara, belongs to the family Apocynaceae. The plant is indigenous to Madagascar but now found in tropical regions and cultivated as an ornamental plant in Southern Florida, Africa, India, Thailand, Taiwan, Eastern Europe and Australia. *Catharanthus roseus* is an erect ever blooming pubescent herb or sub herb, 40-80 cm high, woody at the bases. Madagascar periwinkle's most potent constituent is the reserpine. Reserpine is recommended for the treatment of hypertension, mild anxiety states and chronic psychoses (Singh *et al*., 2001). It works by decreasing heart rate and relaxing the blood vessels so that blood can flow more

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easily through the vessels. In severe hypertension, reserpine may be used together with more potent hypertensive drugs where reserpine enhances the reaction to bring about the desired relief within a short time. Reserpine has a calming effect in chronic psychoses involving anxiety, psychomotor hyperactivity or aggressive behavior. Leaves of *Catharanthus roseus* possess hypotensive properties. *Catharanthus roseus* also used as a cerebral vasodilator.

MATERIALS AND METHODS

Plant materials: Fresh leaves of *Catharanthus roseus* were collected in November 2004 from the botanical garden of our University and authenticated by the herbarium of Department of Botany, University of Rajshahi, Rajshahi, Bangladesh.

Preparation of the plant sample: The fresh leaves were collected, dried in the sun for 7 days and finally in an oven below 60°C. The dried plant material was ground into fine coarse powder and extracted with ethanol in cold condition (Nikkon *et al*., 2003) and the extract was given to the animals following the works of other investigators (Nikkon *et al*., 2003; Nammi *et al*., 2003).

Preparation of dose of the plant extract: *Catharanthus roseus* leaves extract was given as 200 mg kg^{-1} body weight of rats. The average body weight of hypertensive rats was measured 155±15 g. Thus the daily single dose of *Catharanthus roseus* leaves extract was 30 mg/155±15 g body weight of rats dissolved in 0.1 mL dimethylsulfoxide (DMSO) and then diluted with saline.

Dose preparation of antihypertensive drug: The daily dose of nifedipine for human is 50 mg/70 kg body weight. According to the body weight the dose of nifedipine required for rats were 0.1 mg/155±15 g body weight of rats dissolved in 0.1 mL dimethylsulfoxide (DMSO) and then diluted with saline.

Animal model: Albino rats were purchased from International Center for Diarrheal Disease Research, Bangladesh (ICDDR, B), Dhaka, Bangladesh. Rats were allowed free access to distilled water. A cycle of light and dark (12 h light and 12 h dark) and a temperature of 24±2°C were maintained in the room. At first rats were anesthetized with diethyl ether and 100 μL of adrenaline was injected into rats by intraperitoneal (i.p.) injection using a 1 mL disposable syringe for consecutive 5 days to induce hypertension. To confirm the induction of hypertension, the serum cholesterol, serum triglyceride and blood glucose levels were measured and compared with that of control rats that received only normal saline (Gillman *et al*., 1990). The animals used in this study were cared for in accordance with the guidelines for the animal experiment.

Experimental treatment of rats: The animals were randomly divided into four groups. Group 1 was consisted of control rats which received normal saline, Group 2 was consisted of Adrenaline Induced Hypertensive Rats (AIHR), Group 3 was consisted *Catharanthus roseus* leaves extract treated adrenaline induced hypertensive rats and Group 4 was consisted of nifedipine treated adrenaline induced hypertensive rats to compare pharmacological activities. *Catharanthus roseus* leaves extract and commercial drug nifedipine were administered through intraperitoneal (i.p) route for one week at their respective doses in every morning till the completion of investigation. Treatment was done six times for obtaining accurate result.

Description and measurement of different parameters: Before treatment different biochemical parameters such as heart weight, Serum Triglyceride Level (STL), Serum Cholesterol Level (SCL), Blood Glucose Level (BGL) and body weight of Group 1 and Group 2 rats were measured. The rats were sacrificed to collect blood sample and heart from each rat and investigated. Collected blood samples were analyzed for the determination blood glucose level by using BioLand G-423 glucose test meter (BioLand, Germany). Then the data were compared with the standard value. Collected blood samples about 1-2 mL was centrifuged at 4000 rpm for 10 min to separate the serum to determine STL, SCL by measuring absorbance using UV spectrophotometer (Shimidzu UV-1200, Tokyo, Japan), using wet reagent diagnostic kits (Boehringer Mannheim, GmbH) according to manufacturer's protocol.

Drugs and chemicals: Phosphate buffer, Sodium buffer, Potassium dihydrogen phosphate, Ether (Diethyl either), 0.1N HCl, Acetone, Ethanol were of analytical grade and purchased from the local agent (A.Q. Choudhury and Co., Dhaka). Active nifedipine was a kind gift from the Square Pharmaceuticals Ltd., Bangladesh.

Statistical analysis: In the whole animal study each group consisted of six animals. Data were expressed as Mean±SEM. Differences in mean values between experimental groups were analyzed by unpaired t test. A probability value of 0.05 ($p<0.05$) was considered to be significant.

RESULTS

The effects of leaves extract of *Catharanthus roseus* with nifedipine on heart weight, STL, SCL, BGL and body weight were investigated in control and Adrenaline Induced Hypertensive Rats (AIHR).

Effect of *Catharanthus roseus* leaves extract and nifedipine on heart weight in adrenaline-induced hypertensive rats: The mean heart weight of control, adrenaline induced hypertensive and leaves extract of *Catharanthus roseus* and nifedipine treated animals are shown in Fig. 1. Hypotensive and hypolipidemic effect were observed in animals treated with *Catharanthus roseus* leaves *extract* and nifedipine. To determine whether or not there was a statistically significant difference achieved by the *Catharanthus roseus* leaves extract and nifedipine during treatment one-way ANOVA followed by DMCT was applied and compared with the AIHR. A significant reduction in heart weight of Cath-treated and nife-treated animals were observed.

Effect of *Catharanthus roseus* leaves extract and nifedipine on blood-glucose level in adrenaline-induced hypertensive rats: The mean blood glucose level of control, adrenaline induced hypertensive and leaves extract of *Catharanthus roseus* and nifedipine treated animals are shown in Fig. 2. A significant decrease in blood glucose level was observed in animals treated with *Catharanthus roseus* leaves extract and nifedipine. To determine whether or not there was a statistically significant difference achieved by the leaves extract of *Catharanthus roseus* and nifedipine during treatment one-way ANOVA followed by DMCT was applied and compared with the AIHR. A significant reduction in blood glucose level of Cath-treated and Nife-treated animals were observed.

Effect of *Catharanthus roseus* leaves extract and nifedipine on total serum triglyceride and serum cholesterol in adrenaline-induced hypertensive rats: The mean serum total cholesterol and triglyceride levels of control, adrenaline induced hypertensive and leaves extract of *Catharanthus roseus* and nifedipine treated animals are shown in Fig. 3. Hypotensive and hypolipidemic effects were observed in animals treated with *Catharanthus roseus* leaves extract and nifedipine. Significant decreases in serum triglyceride and serum cholesterol level were observed in animals treated with leaves extract of *Catharanthus roseus* and nifedipine. To determine whether or not there was a statistically significant difference achieved by the leaves extract of

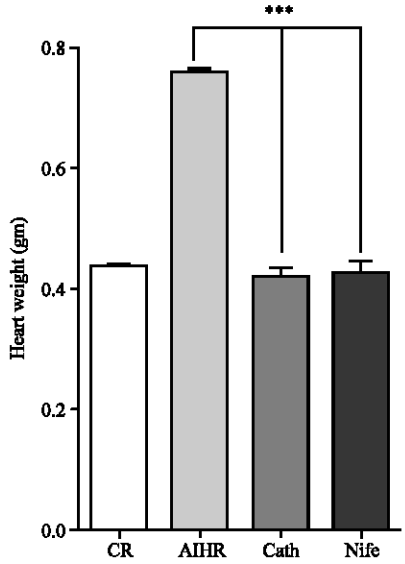

Fig. 1: Effect of *Catharanthus roseus* leaves extract and nifedipine on heart weight in adrenaline-induced hypertensive rats. The data are shown as Mean±SEM (n = 6 in each case). *** Indicates significant change in heart weight between AIHR and Cath-treated, Nife-treated animals. Cath-*Catharanthus roseus* leaves extract and Nife-nifedipine

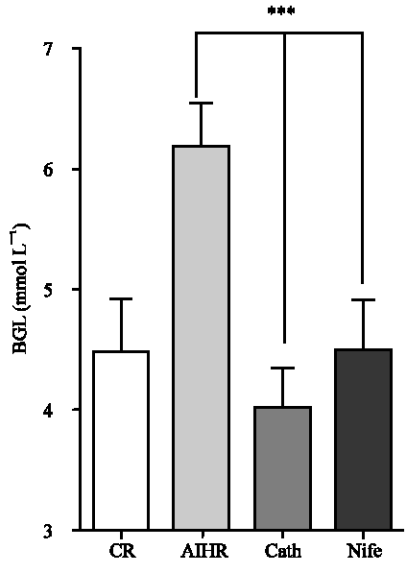

Fig. 2: Effect of *Catharanthus roseus* leaves extract and nifedipine on blood-glucose level in adrenaline-induced hypertensive rats. The data are shown as Mean±SEM (n = 6 in each case). *** Indicates significant change in heart weight between AIHR and Cath-treated, Nife-treated animals. Cath-*Catharanthus roseus* leaves extract and Nife-nifedipine

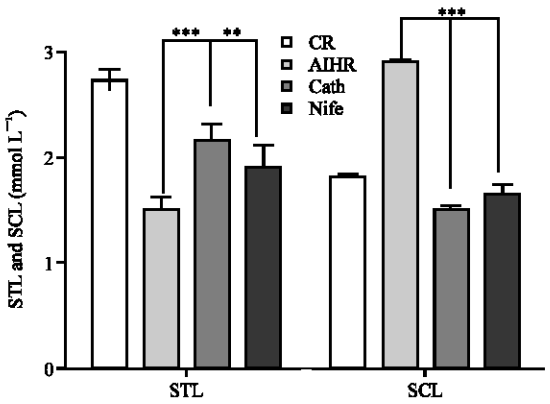

Fig. 3: Effect *Catharanthus roseus* leaves extract and nifedipine on total serum triglyceride and serum cholesterol level in adrenaline-induced hypertensive rats. The data are shown as Mean±SEM (n = 6 in each case). *** Indicates significant change in serum triglyceride level between AIHR and leaves extract of Cath-treated animals, ** Indicates significant change in STL between AIHR and Nife-treated animals, *** indicates significant change in serum cholesterol level between AIHR and leaves extract of Cath-treated animals, Nife-treated ($p<0.0001$) animals. Cath-*Catharanthus roseus* leaves extract and Nife-nifedipine

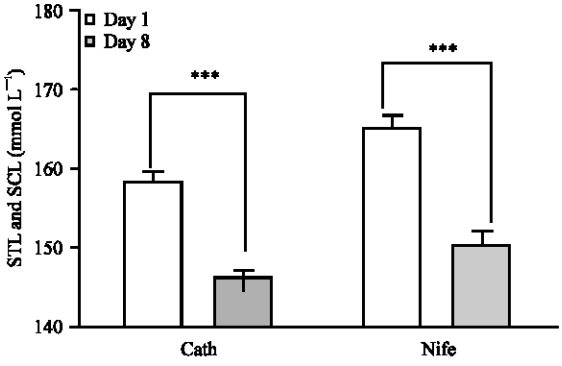

Fig. 4: Effect of *Catharanthus roseus* and nifedipine on body weight in adrenaline-induced hypertensive rats. The data are shown as Mean±SEM (n = 6 in each case). *** Indicates significant change in body weight between AIHR and Cath-treated animals, *** Indicates significant change in body weight between AIHR and Nife-treated animals. Cath-*Catharanthus roseus* leaves extract and Nife-nifedipine

Catharanthus roseus and nifedipine during treatment one-way ANOVA followed by DMCT was applied and compared with the AIHR. A significant reduction in serum triglyceride level of the extracts of Cath-treated and Nife-treated animals were observed.

Effect of *Catharanthus roseus* leaves extract and nifedipine on body weight in adrenaline-induced hypertensive rats: The mean body weight of *Catharanthus roseus* leaves extract and nifedipine treated animals (after intraperitoneal administration of a single dose) are shown in Fig. 4. Hypotensive and hypolipidemic effect were observed in animals treated with *Catharanthus roseus* leaves extract and nifedipine. A significant decrease in body weight was observed in animals treated with leaves extract of *Catharanthus roseus* and nifedipine. To determine whether or not there was a statistically significant difference achieved by the extract and drug during treatment one-way ANOVA followed by DMCT was applied and compared with the AIHR. A significant reduction in body weight (Day 1 and 8) of leaves extract of Cath-treated and Nife-treated animals were observed.

DISCUSSION

Hypertension is a common debilitating illness among peoples in both developed and developing countries. Community surveys in industrialized countries have shown a prevalence of 15-33% in people aged 30 years. The disease continues to be a leading cause of morbidity and mortality from the coronary artery disease and stroke. Fortunately, antihypertensive drug therapy is available to reduce blood pressure to a normal level, which is necessary to manage cardiovascular disease, coronary heart disease and other cardiovascular related complications. In this respect, herbal drugs are helpful and render encouraging results in comparison to synthetic drugs due to their fewer side effects and easy availability (Miyata, 2007). In the present study hypertension was induced in rats by intraperitoneal injection of adrenaline in accordance to earlier observation (Boesen *et al*., 2005). Standard value of body weight, heart weight, blood glucose level, serum triglyceride level and serum cholesterol level were determined. Except serum triglyceride level, the standard values of body weight, heart weight, blood glucose level and serum cholesterol level were high in adrenaline induced hypertensive rats when compared to control rats. Because of metabolic effects of adrenaline, serum triglyceride level was low in hypertensive rats (Gillman *et al*., 1990; Boesen *et al*., 2005). This study was

performed to analyze the differential effects of plant extract and nifedipine on body weight, heart weight, blood glucose level, serum triglyceride level and serum cholesterol level of hypertensive rats and compared with those of control rats.

CONCLUSION

The present study revealed that *Catharanthus roseus* leaves extract has got profound hypotensive and lipid lowering activity and this study has similarity with previous investigation (Nikkon *et al*., 2003; Setoguchi *et al*., 2002; Boesen *et al*., 2005). The mechanism by which *Catharanthus roseus* leaves extract lowers blood pressure is not yet fully established. However, the hypotensive action may be due to the stimulation of the muscarinic receptors of the parasympathetic nerve by the compounds or to their action as an antagonist of β-adrenergic receptors but it may act as a Ca^{++} channel blocker (Amran *et al*., 2004). From these overall results, we can conclude that the *Catharanthus roseus* leaves extract possess hypotensive and lipid lowering effects. The intake of *Catharanthus roseus* leaves extract as medicine or as supplement to diet might have potential benefit in the treatment of hypertension.

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