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Original Article

Investigation of the Effect and Possible Mechanism of Antihypertensive Activity of Lycopene-rich Extract of *Solanum lycopersicon* in Wistar Rats

Ani Celestine Okafor[1,*], Maduka Nweke Luke[1], Okeke Pearl Adaobi[1], Okolo Kenneth Obinna[2], Ndubuisi Richard Nonso[3], Okorie Pamela Onyinye[1], Chukwuaja Brien John[4], Agu Francis Uchenna[4], Anyaeji Pamela Somke[1], Eghosa Iyare Edorisiagbon[1], Okechukwu Omire-Oluedo[1], Nwachukwu Daniel Chukwu[1]

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[1]Department of Physiology, Faculty of Basic Medical Sciences, University of Nigeria, Enugu Campus NIGERIA.
[2]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Enugu State University of Science and Technology, Enugu, NIGERIA.
[3]Department of Science Laboratory Technology, Faculty of Physical Sciences, University of Nigeria, Nsukka, Enugu State Nigeria, NIGERIA.
[4]Department of Physiology, Faculty of Basic medical Sciences, Gregory University Uturu

***Correspondence**

Dr. Ani Celestine Okafor
Department of Physiology, College of Medicine, University of Nigeria, Enugu, Campus, NIGERIA.

Email: celestine.ani@esut.edu.ng

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ABSTRACT

Background and Aim: Hypertension is a common debilitating illness among people in both developed and developing countries. This study investigated the effect and possible mechanism of the antihypertensive activity of lycopene-rich extract of *Solanum lycopersicon* (LRESL) on Wistar rats. **Methods:** Sixty hypertensive Wistar rats were divided into seven experimental groups viz: Group A served as a normotensive group and received food and clean distilled water *ad libitum*. Group B was the hypertensive untreated group; Groups C-E served as hypertensive group administered with 100, 200, and 400 mg/kg LRESL, respectively. While group F was hypertensive and received 10 mg/kg amlodipine and group G received 200 mg/kg of LRESL+0.5 mg/kg Lisinopril respectively. **Results:** There was a statistical significant decrease (P<0.05) in the systolic and diastolic blood pressure and the decrease was in a dose-dependent manner. The heart rate showed no statistical significant difference among the groups. The total cholesterol (TC) increased in the positive and normal control compared to other groups. There was a significant decrease in the triglyceride (TG), low density lipoprotein cholesterol (LDL-C) in all hypertensive treated groups. The decrease in the LRESL treated groups was in a dose-dependent manner and there was no significant difference between the groups compared to the normotensive and positive control. Moreover, the high density lipoprotein cholesterol (HDL-C) had a significant reverse effect of the LDL-C as there was a significant increase (P<0.05) in HDL-C and the increase was more significant in group E and G respectively. The serum cardiac arginase (SCAr) activity also decreased significantly (P<0.05) in all groups except group B compared to the normotensive and positive control groups and in a dose-dependent manner. The serum nitric oxide (SNO) concentration also increased in all test groups in a dose-dependent pattern except the positive control group. **Conclusion:** This study suggests that LRESL has an antihypertensive property and elicited this through multiple mechanisms involving a decrease in SCAr, LDL-C, body weight and marked elevation of SNO and could be used as a novel compound channeled into the production of antihypertensive drugs.

Key words: Lycopene, Cardiac arginase, Nitric oxide, Lipid profile, Body weight.

INTRODUCTION

Hypertension is a silent killer disease. It is one of the leading causes of disability, mortality, and morbidity along the population. It is the most common chronic disease in the world.[1] Hypertension is a cardiovascular disease that causes many cardiovascular pathologies including coronary artery disease, heart failure, atherosclerosis, renal insufficiency and myocardium infarction.[2] Most of the antihypertensive drugs have efficacy but have side effects that are hostile to health. Recently, attention has been focused on herbal medicine, which is traditionally used as potential therapeutic agents in the prevention and management of hypertension.

Hypertension is defined as a persistent increase in blood pressure of >140 mmHg (systolic) and or ≥ 90 mmHg (diastolic).[3] Not less than 46.4% Nigerian over 15 years of age has hypertension[4] and it is positively and independently associated with high morbidity and mortality rates in Africa. Hypertension and overweight places an excessive financial burden on the population and health systems consuming a scarce resource and thus places a lot of economic burden on the individual loss of productivity and premature death at a younger age.[5] Hypertension remains a global challenge even in the 21st century with attendant increased mortality rates. Considering the uncomfortable side effects of

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antihypertensive drugs and the fact that many hypertensive patients need more than two kinds of drugs per day. Alternative and supplementary treatment for blood pressure control has been suggested such as lifestyle modification, especially dietary intervention. Thus, the quest for alternative management medications suffixed our investigation of the lycopene-rich extract of *Solanum lycopersicon* (tomatoes) commonly consumed within Nigeria. Tomatoes out of its juiciness and rich flavor, holds a place in the prevention and management of hypertension. This attribute is suggestive of the presence of lycopene, potassium, beta-carotene and antioxidants in tomatoes.[6] Tomatoes play an active role in the management of hypertension, coronary heart disease, ischemic stroke, type II diabetes, and certain diseases. Worldwide, about 58% of diabetic mellitus and 21% of Ischemic heart diseases are attributed to high blood pressure.[7-8]

Blood pressure (BP) is the pressure exerted by circulating blood upon the walls of blood vessels and is one of the principal vital signs. During each heartbeat, blood pressure varies between maximum (systolic) and minimum (diastolic) pressure. The mean blood pressure (BP), due to pumping of the heart and resistance to flow in the blood vessels decreases as the circulating blood moves away from the heart. Although that of a healthy adult human is 120 (systolic) and 80 mmHg (diastolic), systolic and diastolic arterial BPs are not static but undergo natural variations from one heart beat to another and throughout the day in a circadian rhythm. They also change in response to stress, nutritional factors, drugs, diseases, exercise and momentarily from standing up. Persistently raised blood pressure exceeding about 120 (systolic) and 90 mmHg (diastolic) at rest is called hypertension.

Lycopene, a carotenoid found in tomatoes, is an antioxidant with protective effects on lipid peroxidation and anti-atherosclerotic capacity.[9] A meta-analysis suggested that lycopene taken in a dosage ≥ 25 mg daily is effective in reducing LDL cholesterol by about 10%, which is comparable to the effect of low dose of statins in patients with slightly elevated cholesterol levels. Some plant-derived pharmaceuticals have scientifically been proven to elicit antihypertensive activity via multiple mechanisms. These mechanisms are elicited to counteract the effect of hypertension and associated risk factors such as hypercholesterolemia, hypertriglyceridaemia, and oxidative stress on blood vessel walls. They include direct vasodilatation of the blood vessel, blocking of calcium channels, inhibition of α-adrenoreceptor response, induction of negative ionotropic response of smooth muscle, inhibition of platelet aggregation, reduction of vascular resistance, and improvement of pulmonary oxygen utilization.[7] Enhanced activity of nitric oxide and improved handling of intracellular calcium has also been found to play a critical role in the reduction of vascular resistance and blood pressure that are elevated in hypertensive rats and humans.[10-11]

In the last 2 decades, plants have remained historically important as sources of novel compounds with the potentials of being channeled into drug pipelines for the development of safe, efficacious, and cost-effective antihypertensive drugs. In sub-Saharan Africa, initial ethnopharmacological surveys have identified over 100 species of plants with antihypertensive activity in animals and humans.[12-13] *Solanum Lycopersicon* from *Solanaecea* family. Tomatoes contain lycopene, a nutrient that could be beneficial for lowering your cholesterol, preventing skin damage, and decreasing your blood pressure. A study published in the Journal of Nutrients suggests that adding lycopene to your diet could help significantly reduce blood pressure. Tomato products or extracts are used as the lycopene source in most studies. The extracts contain lycopene, β-carotene, and the colorless carotenoids phytoene and phytofluene, in addition to a myriad of other active nutrients such as tocopherols and polyphenols. Many of these are strong antioxidants and are known inducers of the antioxidant defense pathway, which is one of the mechanisms for the cardiovascular protective effect.[14] In our recent work, we found the aqueous fresh tomato extract of *Solanum Lycopersicon* to elicit a dose-dependent inhibition of blood pressure elevation in sodium chloride-induced hypertensive rats.[15] Therefore, we hypothesize that mechanisms exist to mediate the hypotensive action of *Solanum lycopersicon,* which remain largely unknown. Meanwhile, the use of *Solanum lycopersicon* in animals has been found to be safe with an LD_{50} > 5000 mg/kg[15] and without adverse biochemical effects in rats. Moreover tannins, terpenoid, flavonoids, and alkaloids phytoconstituents, have been implicated in the various pharmacological activities of the plant including antibacterial and antidiabetic properties. Interestingly, these phytoconstituents were also found in other *Solanum lycopersicon* plants in association with antihypertensive activity.[14] Given the long-term use of *Solanum lycopersicon* as an antihypertensive plant, it is undoubtedly important to understand its mechanisms of action to advance its potential as a source of novel compounds for future development of antihypertensive drugs.

MATERIALS AND METHODS

Ethical Approval

Ethical approval was obtained from the Institutional Animal Ethics and Care Committee of the University of Nigeria, Enugu Campus with reference number (NHREC/21/07/2508BFWA00002458-1RB)

Drugs

The following drugs were used in the research, viz –Adrenaline, Dobutamine (Sigma- Aldrich Ltd US) were purchased from a controlled drug dealer and supplier of Pharmacology and Therapeutics laboratory, Faculty of Basic Clinical Sciences, Enugu State University College of Medicine, Parklane Enugu and were authenticated by Pharmacist Ezugwu Chigozie.

Solvents and Chemicals

These were used mainly for the preliminary extraction and subsequent fractionation of extracts. They include methanol (100%), ethanol (98%), Ethyl acetate (97%), and n-hexane (98%) purity. Other reagents used such as potassium chloride, calcium chloride, sodium hydroxide, magnesium sulphate, etc were of analytical grade and were purchased from local chemical and reagent dealers, Ogbete Main market Enugu Nigeria.

Plant Collection, Identification and Authentication

A freshly harvested sample *of Solanum lycopersicon* (Fresh tomatoes) was purchased from Riyom Market Women Tomato farmers in Bukuru Local Government Area of Jos, Plateau State, Nigeria. The fruits were thoroughly washed with tap water to ensure the microbes adhering to their surface are removed and transported to Pharmacognosy Laboratory, Faculty of Pharmaceutical Sciences, Enugu State University of Science and Technology, Agbani where it was identified by a Botanist/ Pharmacognosist (Mr. Patrick Ebele Obi). The fresh sample was later dried and kept in their herbarium for future reference.

Sample Preparation/Aqueous Extraction

Plant extracts were prepared by the method of Tomoki *et al*., with minor modifications.[16] The seeds of the ripe and thoroughly washed *Solanum lycopersicon* fruits were removed. The fruits were then chopped into cubes, which were freeze-dried for 3 days until a moisture content of approximately 0.9% was obtained. The freeze-dried *Solanum lycopersicon* was ground in a mill (Binatone grinder: Model No: HFB-3489) and passed through a 500mm mesh sieve and later transferred to a rotary evaporator for the evaporation of the water that was used.[16] The dried

extract was collected and weighed in varying concentrations and kept in airtight containers at 4°C.

Extraction of Lycopene From Aqueous *Solanum Lycopersicon* Extract

A simple and efficient method of extraction using a conventional solvent and anti-solvent precipitation for the isolation of lycopene from *Solanum Lycopersicon* was used. A total of 1000 grams of lyophilized *Solanum lycopersicon* paste was weighed into a glass tube with a glass filter at the bottom. The material was extracted for one hour with one liter of ethyl acetate. The extraction yield was 272 g, ethyl acetate has been documented as the most efficient of the extraction solvents studied for lycopene because of its high affinity to tomato paste. All carotenoids were separated from the crude extract using an anti-solvent salification method (methanol).[15] The isolated and precipitated lycopene was 272.50 mg / 500g, which is a 77.43% recovery rate. The lycopene isolation method developed in this study was more effective than the methods already available for large-scale isolation of the lycopene preparation.

Recovery Procedure

The recovery procedure of natural lycopene from *Solanum lycopersicon* was composed of two steps. First, all carotenoids were extracted from *Solanum lycopersicon* by conventional solvent extraction using organic solvents that possess different polarities. A 100 g sample was weighed into a 3 liter glass tube with a glass filter bottom (50 mm × 1500 mm), and crude lycopene was extracted for 1 hr with 1 liter of different organic solvents: n-hexane, ethanol, and ethyl acetate. In the ratio (1:1:2) v/v. The resulting crude lycopene extract was evaporated at reduced pressure to approximately 1% of the initial volume. The extraction solvent showed the highest extraction efficiency for the next isolation procedure.[15]

The recovery yield was calculated thus:

$$\text{Extraction yields (y) were calculated as : } Y = 100 \times \frac{Ce \times V}{Ct \times m}$$

where *ce* is the concentration of extracted lycopene in the solvent, *V* is the volume of the solvent, *ct* is the total lycopene content of the peels, and *m* is the dry weight of the peel.

Thin-Layer Chromatography (TLC)

To confirm the purity of the precipitated lycopene, TLC was conducted according to the method of Santiago *et al.* with slight modification.[17] Briefly, Silica Gel 60 F_{254} (0.25mm, Merck, Darmstadt, Germany) activated at 110°C for 10 min was used for the TLC plates. The crude carotenoids and the precipitated lycopene and supernatant were developed with n-hexane: acetone (1:9, v/v) on the TLC plates. Authentic lycopene was also developed and identified with methyl orange coloration.

Quantitative Analysis of Lycopene Extracted

Extracted lycopene from fresh samples of *Solanum lycopersicon* was also analyzed using the HPLC system under the same conditions. To avoid exposure to light and oxygen, all experiments were conducted using dark amber glassware or transparent glassware wrapped with aluminum foil and filled with nitrogen gas. The nitrogen gas was obtained from a N2 generator (G4010E, Domnick, Hunter, England; less than 100 ppm oxygen content). All isolation procedures were performed at least three times independently.[18]

Experimental Animals

One hundred male Wistar rats (180-250 g) obtained from Animal House Colony of the Department of Pharmacology and Therapeutics, College of Health Sciences, Benue State University Makurdi were used. They were well sorted out and the sorting was based on the influence of blood pressure values.[19] Males were preferred to females because they were bigger and usually had fewer hormonal interferences. The rats were acclimatized in a room 27°C at 12 hr dark/light cycle. They were not restrained in cages during the acclimatization period and had access to food and clean water *ad libitum.*

Acute Toxicity (LD_{50}) Test for Lycopene-Rich Extract

The acute toxicity test was done according to the method of Chinedu *et al.*[20] This method is divided into stages, with the outcome from each stage determining the next step to take (i.e., whether to terminate or proceed to the next stage).

Stage 1: This is the initial stage and it requires four animals. These animals were divided into four groups of one animal each. Then different doses of the test substance were administered to the different animals. The animals were observed for 1-hr post-administration and then 10 min every 2 hr intervals for 24 hr. The behavioral signs of toxicity and mortality were recorded. Where no mortality was recorded at this stage, the testing proceeded to stage 2.

Stage 2: This stage involved three animals, which were divided into three groups of one animal each. Different doses of the test substance (higher than those used in stage 1) were administered to the different animals and then observed for 10 min every 1 hr after administration and periodically for 24 hr. Behavioral signs of toxicity and mortality were noted as well. As no mortality occurred, testing proceeded to stage 3.

Stage 3: This stage also required three animals which were distributed into three groups of one animal each. Various high doses of the test substances (with 5000 mg/kg as the highest) were administered to the different animals. Observation was done for 1 hr after administration and no mortality was confirmed. Then the acute toxicity test was calculated, thus

$$LD_{50} = \frac{M_0 + M_1}{2}$$

where M_0 = highest dose of test substance that gave no mortality, M1 = lowest dose of test substance that gave mortality

Method of Induction of Hypertension in Wistar Rat

Hypertension was induced in the rats after their initial baseline physical and cardiovascular parameters were assessed according to the method of Ani *et al.* with little modification.[15] For a rough estimation, typical young male adult rat weighing between 300 and 350 g consumes around 20 g of normal rat chow per day, that is, about 48 g/kg body weight per day and this is equivalent to 1.6 g NaCl per 325 g of body weight per day or about 5 g of NaCl per kilogram weight for day. Based on this, 8 g of NaCl (Uncle Palm Iodized salt with Batch No; FT 256) was weighed using a digital weighing balance by Ohaus, USA, and transferred to a 500 ml beaker and made up to 100 ml with clean water using a delivery pipette to prepare sodium chloride solution and was mixed with 92 g of normal rats chow and 2% NaCl in drinking water and was kept for them *ad libitum*.[15] They were allowed to feed on the diet (Pelletinized diet) for six weeks (32 days). Blood pressure was measured on the final day (Day 28) of the 4th week and those with confirmed hypertension were divided as designed in the experiment. This was followed by treatment with the extracted lycopene-rich extract from the fresh sample of *Solanum lycopersicon*. The post-treatment blood pressures were measured and recorded every two weeks for one month.

Experimental Design

The selected sixty hypertensive and ten non-hypertensive Wistar rats were divided into six experimental groups of 10 rats each and group thus:

Group A = normal control group and received normal saline as placebo

Group B= Hypertensive untreated group (positive control)

Group C= Hypertensive + 100 mg/kg lycopene extract (orally)

Group D= Hypertensive + 200 mg/kg lycopene (orally)

Group E= Hypertensive + 400 mg/kg lycopene (orally)

Group F= Hypertensive + 10 mg/kg Amlodipine as standard drug

Group G =Hypertensive + 200 mg/kg Lycopene-rich extract + 5mg/kg Lisinopril

Determination of the Systolic, Diastolic and the Heart Rate

Non-invasive blood pressure meter (NIBP) (LE 5001) by PANLAB Equipment was used for the determination of the cardiovascular parameters (systolic, diastolic, and pulse rate). The sensitive blood pressure meter was switched ON and allowed to acclimatize for about 20 min; the selector switch located at the back of the equipment was switched to the area marked for rats. The rats' tail was briefly immersed in water at temperature of 45°C with a thermostat and allowed for about 30 s for the dilatation of the tail veins to increase blood flow to the tail region. Before this, the rats were introduced into the transparent glass restrainer before the immersion of the tails into hot water. The animals were covered with pieces of dark clothes for reduction of anxiety. The tail cuff/transducer were introduced into the base of the tail region and the selector switch turned ON immediately, and the pulse waves indicated "ready", the readings were displayed on the screen of the apparatus. The foot control switch was matched to save the reading and then recorded.[15]

Lipid Profile Assessment

The total cholesterol level (TC), high density lipoprotein (HDL-C), and triglycerides (TG) for all experimental animals were determined using the hand-held cardiocheck self-test meter (Mission cholesterol Meter) by ACON Lab Ltd Shanghai China according to the method of Ani *et al.*[15] and was used for the determination of the lipid profiles in the experimental animals using whole blood collected from the tail vein using insulin syringe. The equipment has already been calibrated prior to its use after purchase. The MEMO clip was inserted and the device switched ON, the test strip for each sample was inserted, after which two drops (0.2 ml) of blood samples were placed on the strips, and within a few seconds that the blood samples were dropped, a pink coloration was observed respectively and the automatic button was pressed which led to the instant display of the result (TC, TG, HDLC, etc) and were recorded in milligram per deciliter (mg/dl). The LDL- Cholesterol was calculated using Friedewald equation; Thus

$$\text{LDL} - \text{C} = \left(\frac{\text{Total cholesterol} - \text{High density Lipoprotein cholesterol} - (\text{Triglyceride}/5)}{1} \right)$$

Analysis of Enzyme (Cardiac Arginase) Activity

The enzyme (cardiac arginase) activity was analyzed using the method of Hanedan *et al.*[21] Five Wistar rats from each group were selected at random and sacrificed using 25% urethane anesthesia and an incision was made on the thorax using a sharp surgical blade and blood was bled out. Then a piece of cardiac (right ventricle) from the diseased (hypertensive) and healthy (hypertensive treated) were excised, rinsed with normal saline (0.9% NaCl) and immediately desiccated with filter paper, and kept frozen at –20°C until analysis.

Then 1g of tissue samples was homogenized with distilled water (1/10, w/v) in a glass Potter-Elvehjem homogenizer in an ice bath. The mixture that was homogenized was centrifuged at 14,000 rev per minute for 10 min in a cooled centrifuge. The supernatants were used as the enzyme source. Cardiac arginase activity was determined by the measurement of urea produced by hydrolysis of L-arginine through arginase enzyme by the thiosemicarbazide diacetyl monoxime urea method.[22] In this analysis, the enzyme source was diluted with $MnCl_2$ at the ratio of 1:5 for cardiac tissue was used as a new enzyme source with pre-incubation at 55°C for 5 min using a water-bath. Tubes that contained 0.2 mL of the enzyme source, 0.4 mL of L-arginine, and 0.4 mL of carbonate buffer were incubated at 37°C for 10 min. The reaction was ceased by adding 3 mL of acid reagent to the tubes after the incubation period. Thereafter, 2 mL of color reagent was added to the tubes, which were kept in a boiling water bath for 10 min. The tubes were then removed from the boiling water bath and cooled, and the absorbance was recorded at 520 nm using a digital spectrophotometer. One unit of arginase activity is an expression in mg protein of enzyme activity, producing 1 μmol of urea from L-arginine for 1 hr at 37°C.

Measurement of Serum Nitric Oxide (SNO) Concentration

Serum Nitric oxide concentration was determined by Griess reagent method (Promega Corp, Madison, USA) using available reagents.[23] Briefly, sera were added into the wells (96-well enzymatic assay plate). A sulfanilamide solution was added to all experimental samples, and after incubation, N-1-naphtylethylenediamine dihydrochloride solution was added. Then, the absorbance was measured by a microreader in 520 nm wavelength. The samples NO concentration was determined by comparison with the nitrite standard reference curve.[23]

Statistical Analysis of Data

All data were expressed as mean ± standard deviation. The differences among treatment groups were analyzed by one-way analysis of variance (ANOVA) followed by Tukey *post hoc* test for multiple comparisons using SPSS Version 21. $P \leq 0.05$ considered as statistically significant.

RESULTS

Results of the antihypertensive effect of lycopene rich extract of *Solanum lycopersicon* showed a significant increase ($P<0.05$) in the systolic blood pressure of all groups except the normal control group that received distilled water as placebo on Day 0. At the end of the treatment period (Day 28), there was a significant decrease ($P<0.05$) in the SBP of groups C, D, E, F, and G compared to the positive control group B. The decrease in the SBP was much shown in group F, while groups E and F had almost equal percentage change in the SBP. Group B also decreased slightly when compared to group A and this could be used as a possible physiological homeostasis mechanism (Table 1).

Table 2 showed the antihypertensive effect of aqueous rich extract of *Solanum lycopersicon* on rat diastolic blood pressure (DBP) and it shows a significant ($P<0.05$) increase in the DBP on day 0 which was the hypertensive stage before commencement of the administration of the lycopene-rich extract. The treatment result also showed a significant decrease in DBP and the decrease was in a dose-dependent manner in which higher dosage of lycopene rich extract decreased the DBP and there was a statistical significant difference ($P<0.05$) between the positive control group B compared to the normal control, also, there were significant ($P<0.05$) differences between groups C, D, E and F compared to group B.

Table 3 shows a typical result of the antihypertensive effect of lycopene-rich extract of *Solanum lycopersicon* (LRESL) on HR in Wistar rats. The

Table 1: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on systolic blood pressure in Wistar rats (n=10).

Group	Day 0	Day 14	Day 28	Percentage Change
A	127.20±0.22	126.01±0.03	127.30±0.02	0.08
B	186.20±0.37	184.20±0.44*	175.20±0.30*	-6.27
C	188.45±0.29	138.30±1.20*$^{\beta}$	124.30±0.03$^{\beta}$	-51.60
D	178.30±0.34	129.20±1.30*$^{\beta}$	117.30±0.04$^{\beta}$	-52.00
E	206.45±0.78	143.50±0.37*$^{\beta}$	122.80±0.23$^{\beta}$	-68.11
F	192.40±0.83	133.20±1.38$^{\beta}$	109.20±0.45$^{\beta}$	-76.19
G	173.60±0.28	112.30±0.01$^{\beta}$	103.20±0.22$^{\beta}$	-68.22

Results were expressed as mean ± standard deviation (n=10);

* P<0.05 showed a statistical significant difference compared to the normal control (group A); $^{\beta}$ P<0.05 showed a statistical significant difference compared to the positive control (group B) using Tukey *post hoc* test for multiple comparison. Values with negative sign (-) indicate a decrease.

Table 2: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on DBP in Wistar rats.

Group	Day 0	Day 14	Day 28	Percentage change
A	78.20±0.01	76.00±0.00	77.30±0.01	-1.16
B	96.10±0.07*	94.20±0.04*	85.20±0.02*	-12.79
C	98.15±0.03*	88.30±1.30	74.30±0.00*$^{\beta}$	-32.00
D	88.10±0.04*	79.20±1.00	77.30±0.02$^{\beta}$	-13.97
E	96.12±0.07*	83.50±0.07	72.80±0.18$^{\beta}$	-24.26
F	92.40±0.03*	73.20±1.08	69.20±0.50*$^{\beta}$	-33.50
G	93.50±0.02*	62.30±0.00*$^{\beta}$	53.20±0.22*$^{\beta}$	-75.75

Results were expressed as Mean ± Standard deviation (n=10);

* P<0.05 showed a statistical significant difference compared to the normal control (Group A); $^{\beta}$ P<0.05 Showed a statistical significant difference compared to the positive control (Group B) using Tukey *Post hoc* test for multiple comparison.

Table 3: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on heart rate of Wistar rats.

Group	Day 0	Day 14	Day 28	Percentage Change
A	208.70±0.01	206.00±0.00	300.30±0.08	44.2
B	433.10±0.07	307.20±0.04	207.20±0.08	-109.03
C	305.00±.03	405.20±1.30	284.30±0.08	-728
D	288.30±0.04	330.50±1.00	307.90±0.02	6.37
E	406.34±0.07	208.50±0.07	372.80±0.20	-8.99
F	342.60±0.03	300.00±1.08	276.20±0.60	-24.04
G	333.30±0.02	350.30±0.00	283.20±0.37	-17.69

Results were expressed as Mean ± Standard deviation (n=10); Values without any superscript showed no statistical significant difference (P>0.05) for multiple comparisons.

results did not show any particular trend with respect to the rat heart rate and there was no significant difference (P>0.05) in the experimental groups A-G), but at the end of the study, there were a decrease or reductions in the heart rates of all test groups except for the control group A.

Table 4: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on serum total cholesterol (mg/dl) in Wistar rats.

Groups	Day 0	Day 14	Day 28	Percentage change
A	51.35±3.05	56.0±1.40	52.0±2.30	1.25
B	61.60±1.60	73±0.08	63.33±0.05	2.73
C	57.95±3.84	56.20±0.07	53.40±0.22	-8.52
D	57.12±5.45	54.40±0.19	53.10±0.14	-7.57
E	56.15±5.42	53.00±0.20	50.00±1.25	-12.30
F	61.36± 3.34	57.00±0.35	52.00±0.93	-18.00
G	60.20±3.34	53.00±0.50	49.00±0.01	-11.20

Results were expressed as Mean ± Standard deviation (n=10). Values without any superscript showed no statistical significant difference (P>0.05) for multiple comparison.

Table 5: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on triglycerides (mg/dl) in Wistar rats.

Groups	Day 0	Day 14	Day 28	Percentage change
A	98.33±1.89	97.40±1.50	97.10±1.50	-1.27
B	156.30±0.17*	179.04±1.20*	199.05±1.80*	21.48
C	158.30±0.19*	144.20±1.10*$^{\beta}$	134.90±2.10*$^{\beta}$	-0.17
D	160.20±0.25*	133.24±0.20*$^{\beta}$	118.52±1.20*$^{\beta}$	-35.17
E	159.18±0.38*	122.55±2.25*$^{\beta}$	100.50±3.24*$^{\beta}$	-58.34
F	163.00±0.77*	138.15±0.23*$^{\beta}$	108.25±1.23*$^{\beta}$	-50.58
G	156.10±0.69*	111.35±2.04*$^{\beta c}$	90.30±3.34*$^{\beta c}$	-72.87

Results were expressed as Mean ± Standard deviation (n=10);

* P<0.05 Showed a statistical significant difference compared to the normal control (group A): $^{\beta}$ P<0.05 Showed a statistical significant difference compared to the positive control (group B) using Tukey *Post hoc* test for multiple comparison.

Table 4 shows the antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on Serum total cholesterol in Wistar rats. The total cholesterol increased in the positive control and A compared to other groups, which recorded a decrease in the total cholesterol concentration. This decrease in the concentration of total cholesterol was recorded more in group F, followed by groups E and G, while groups C and D had almost equal concentration of total cholesterol.

Table 5 also depicts the antihypertensive effect of aqueous lycopene-rich extract *of Solanum lycopersicon* on serum triglycerides in Wistar rats. There was a significant (P<0.05) decrease in the serum triglyceride concentration of all hypertensive treated groups with the exception of the group A and B which are normal and positive control groups respectively. There were statistical significant differences (P<0.05) between the test groups and the normal control on day 0, while on day 14 there was a statistical significant (P<0.05) difference between the test groups compared to the normal and positive control groups respectively. On day 28, there were significant (P<0.05) differences between groups B,C, D,E, F, and G compared to the normal control group, while groups C-G also showed a significant difference compared to group B. The decrease in the triglyceride level was more in groups G, E, and F, respectively, while group B recorded a significant increase.

Table 6 also shows the antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on serum low-density lipoprotein cholesterol (LDL-C) in Wistar rats. The LDL-C concentration increased on Day 0, which is the hypertensive stage, and later decreased significantly

Table 6: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on low-density lipoprotein cholesterol (LDL-C) (mg/dl) in Wistar rats.

Groups	Day 0	Day 14	Day 28	Percentage change
A	98.33±1.89	97.20±1.45	97.10±1.95	-1.26
B	166.30±0.17	169.04±0.80	179.05±2.70	7.12
C	178.30±0.19	143.90±2.50	124.90±3.30	-42.75
D	160.20±0.25	142.40±0.05	108.52±0.20	-47.62
E	189.18±0.38	141.20±1.15	100.20±2.14	-88.80
F	173.00±0.77	156.25±1.90	138.25±1.83	-25.14
G	186.10±0.69	148.60±0.80	98.30±0.44	-89.31

Results were expressed as Mean ± Standard deviation (n=10); Values without any superscript showed no statistical significant difference (P>0.05) for multiple comparisons.

Table 7: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on high density lipoprotein cholesterol (HDL-C) (mg/dl) in Wistar rats.

Groups	Day 0	Day 14	Day 28	Percentage change
A	80.00±0.15	88.30±0.33	88.30±0.33	9.39
B	40.05± 0.19	38.40±2.00*	38.40±2.00*	-4.29
C	49.00±0.20	72.20±0.12*$^{\beta}$	72.20±0.12*$^{\beta}$	32.13
D	47.20±0.20	79.60±0.19$^{\beta}$	79.60±0.19$^{\beta}$	40.70
E	39.18±0.11	85.11±0.50$^{\beta}$	85.11±0.50$^{\beta}$	53.96
F	44.30±1.40	78.20±0.70$^{\beta}$	78.20±0.70$^{\beta}$	43.35
G	47.60±0.35	90.20±1.77$^{\beta cde}$	90.20±1.77$^{\beta cde}$	47.22

Results were expressed as Mean ± Standard deviation (n=10);

* P<0.05 Showed a statistical significant difference compared to the normal control (group A); $^{\beta}$ P<0.05 Showed a statistical significant difference compared to the positive control (group B); ^{cde}P<0.05 compared to (Group C, D and E respectively) Values with negative (-) signs indicate decrease in the parameters assayed.

(P>0.05) on Day 28 of the treatment. The LDL-C of group B significantly increased, while there was a significant decrease in the LDL-C of the normal control group and groups C, D, E, F, and G, respectively. Group G had the least concentration of LDL-C followed by groups E, D, C, and F, respectively, although there was no statistical significant difference (P>0.05) compared to the normal and positive controls respectively.

Table 7 depicts the effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on high density lipoprotein cholesterol in Wistar rats. There was a significant (P<0.05) increase in the HDL-C level of all test groups except for the positive control group on days 14 and 28, respectively. After the post-treatment period on day 28, assay of HDL-C showed a significant increase (P<0.05) in all treatment groups except for the hypertensive untreated group. The increase in HDL-C was more significant in groups E and G compared to the normal and positive control groups, respectively. The increase in the HDL-C concentration of the aqueous lycopene-rich extract was in a dose-dependent manner as the increment was seen in group E which received higher dosage than groups C and D respectively.

Table 8 shows the results of the serum cardiac arginase activity on the effect of lycopene rich extract of *Solanum lycopersicon* on Wistar rats. The serum cardiac arginase activity decreased significantly (P<0.05) in groups C, D, E, F, and G compared to the normal control group and the positive group, respectively. Group G recorded the least concentration of

Table 8: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicom* on serum cardiac arginase concentration (SCAr) in Wistar rats.

Groups	Day 0	Day 14	Day 28	Percentage change
A	67.00±0.01	62.20±0.01	56.28±0.03	-19.04
B	152.00±0.27	158.20±0.01*	162.20±0.05*	6.29
C	143.01±0.01	138.08±0.02*$^{\beta}$	135.04±0.20*$^{\beta}$	-5.90
D	154.00±0.36	136.00±0.01*$^{\beta}$	126.00±0.07*$^{\beta}$	-22.2
E	145.00±0.74	128.00±0.10*$^{\beta}$	118.00±0.30*$^{\beta}$	-22.88
F	163.20±0.54	144.20±0.07*$^{\beta}$	134.00±0.37*$^{\beta}$	-21.79
G	173.13±0.23	132.40±0.04*$^{\beta}$	112.60±0.06*$^{\beta}$	-53.76

Results were expressed as Mean ± Standard deviation (n=10);

* P<0.05 Showed a statistical significant difference compared to the normal control (group A); $^{\beta}$ P<0.05 Showed a statistical significant difference compared to the positive control (group b); Values with negative (-) signs indicate decrease in the parameters assayed.

Table 9: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicom* on serum Nitric oxide (NO) concentration (uMol/L) in Wistar rats.

Groups	Day 0	Day 14	Day 28	Percentage change
A	6.34±.0.01	6.32±0.11	6.02±0.12	-5.31
B	0.23±0.01	0.22±0.01*	0.18±0.01*	-27.78
C	0.32±0.00	4.22±0.04	4.27±0.05	92.51
D	0.56±0.03	5.90±0.00	7.85±0.13	92.86
E	0.78±0.03	6.85±0.01	7.99±0.34	90.19
F	0.43±0.07	4.40±0.00	6.90±0.22	93.77
G	0.74±0.02	8.34±0.02*$^{\beta}$	11.34±0.02*$^{\beta}$	93.47

Results were expressed as mean ± standard deviation (n=10);

*P<0.05 showed a statistical significant difference compared to the normal control (group A); $^{\beta}$P<0.05 compared to the positive control (Group B) using Tukey Post-hoc test for multiple comparison. Value with minus (-) sign shows a decrease.

cardiac arginase activity followed by groups F, D, E, A, and C, respectively, while the serum cardiac arginase activity increased in the hypertensive untreated group (B). The decrease in the different concentrations of the lycopene - rich extract was in a dose-dependent manner and there was a statistical significant difference (P<0.05) between groups B and G compared to the normal control.

Table 9 reflects the effect of lycopene-rich extract of *Solanum lycopersicon* on serum cardiac arginase activity. Moreover the serum nitric oxide concentration increased significantly in all test groups except for group B (Positive control). The increase in the different concentrations of the lycopene-rich extract was in a dose-dependent manner and there was a statistical significant difference (P<0.05) between groups B and G compared to the normal control.

Table 10 shows the decrease in body weight followed a dose-dependent pattern in the groups treated with the lycopene-rich extract of *Solanum lycopersicon*. Group E decreased more than groups D and C, respectively. At the end of the experimental study, there was a significant (P<0.05) decrease in the body weight of all test groups except for the normal control group which had a significant increase in the body.

Table 10: Antihypertensive effect of aqueous lycopene-rich extract of *Solanum lycopersicon* on body weight (g).

Groups	Day 0	Day 14	Day 28	Percentage Change
A	180.30± 14.0	183.10±10.50	187.20±12.00	3.82
B	183.20±13.50	181.40±9.50	180.40±10.20	-1.55
C	185.30±12.20	183.20±11.25	179.30±8.40	-3.34
D	181.40±10.20	178.70±9.80	175.60±10.30	-3.30
E	193.50±12.40	189.20±8.60	180.20±9.45	-7.38
F	205.65±8.50$^{*\beta}$	202.70±6.50$^{*\beta}$	193.60±12.30$^{*\beta}$	-6.22
G	253.50±12.50$^{*\beta}$	248.20±10.60$^{*\beta}$	241.50±13.80$^{*\beta}$	-4.97

Results were expressed as Mean ± Standard deviation (n=10);

* P<0.05 Showed a statistical significant difference compared to the normal control (group A); $^{\beta}$ P<0.05 Showed a statistical significant difference compared to the positive control (group B) using Tukey *Post hoc* test for multiple comparison. Values with down arrow signs show a decrease in the parameters.

DISCUSSION

This study investigated the effect and possible antihypertensive mechanism of the activity of aqueous lycopene-rich extract of *Solanum lycopersicon* on Wistar rats. Hypertension is a common debilitating illness among people in both developed and developing countries. The disease continues to be a leading cause of morbidity and mortality from coronary artery disease and stroke.[2] Fortunately, antihypertensive drugs are available to reduce blood pressure to the 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 or no side effects and easy availability.[24-25]

The screening of various plants according to their traditional uses and nutritional value based on their therapeutic value leads to the discovery of newer and safer alternatives for the management of hypertension. One of such plants of medicinal value is lycopene-rich *Solanum lycopersicon fruit, which* is a genus in the flowering plant belonging to the family *Solanaceae* (nightshades and its relatives) which is commonly known as tomatoes. This *Solanum lycopersicon* also acts as an antihypertensive drug because it contains many of the therapeutic carotenoids of which lycopene is the most abundant with no adverse effects. The previous pilot *in-vivo* studies suggested that the antihypertensive activity was highest at a dose of 800 mg/kg of aqueous extract of the plant.[15] The antihypertensive mechanism of aqueous lycopene-rich extract of *Solanum lycopersicon* was evaluated by using an 8% NaCl induced hypertensive model. The lycopene-rich extracts showed a significant decrease in SBP and DBP. Aqueous lycopene-rich extract did not interfere with pulse rate (i.e., normal heart rate) as there was some variation/ instability in the heart rate. The SBP and DBP were significantly higher in the hypertensive untreated rats compared to the hypertensive treated groups, and this is an agreement,[25] which stated that the mean values of SBP, DBP and heart rate were higher in the hypertensive untreated groups than in the treated groups and the antihypertensive properties of this plant were in a dose-dependent pattern and it is in agreement with Kohno *et al.*[25] The intake of lycopene-rich extracts of *Solanum lycopersicon* as medicine has been found to have potential benefits in the management of hypertension. A concomitant administration of lycopene-rich extracts might be helpful in better management of hypertension along with available antihypertensive drugs without any interference.

The serum lipid profile showed that the lycopene-rich extract *of Solanum lycopersicon* has anti-atherogenic properties owing to its ability to decrease total cholesterol, low-density lipoprotein-cholesterol (LDL-C), triglycerides and a marked elevation of high-density lipoprotein-cholesterol (HDL-C) level significantly compared to the normal control and this effect is in agreement with Palozza *et al.*,[26] which stated that Lycopene and tomato products reduced plasma LDL-C, and increased HDL-C and the effect was dependent on the dose and time of the administration. In addition to this, there was a decrease in the activity of cardiac arginase concentration as a result of lycopene present in the *Solanum lycopersicon* fruit, which reflects the elevation status of nitric oxide (NO) in the groups treated with lycopene-rich extract and the group that received standard drug as arginase decrease promotes the elevation/production of NO as vasodilator.[27] This is achieved via several potential mechanisms, including competition with nitric oxide synthase (NOS) for L-Arginine, uncoupling of NOS resulting in generation of NO· scavengers, superoxide and peroxynitrite, repression of translation and stability of inducible nitric oxide synthase (iNOS), protein, inhibition of iNOS via generation of urea and by sensitization of NOS to its endogenous inhibitor asymmetric dimethyl L-arginine.

However, if the effect of nitric oxide is impaired or absent, an increase in BP occurs. Endothelial dysfunction is a risk factor for the development of salt sensitivity and subsequent hypertension. Salt sensitivity is defined as a marked elevation in BP following a Na^+ load of ≥5 g and is characterized by an elevation of systolic BP of at least 10 mmHg within a few hours of ingestion. Salt-sensitive individuals have underlying endothelial dysfunction due to genetic or environmental influences. In response to a high salt load, these individuals generally manifest overproduction of transforming growth factor β (TGF-β), which increases the risk of fibrosis and oxidative stress, and have limited bioavailable nitric oxide.[2]

At the end of the experimental study, there was a significant decrease (P<0.05) in the body weight of all test groups except for the normal control group which had a significant increase in the body weight. The decrease in body weight followed a dose-dependent pattern in the groups treated with the lycopene-rich extract of *Solanum lycopersicon* and loss of body fluid to be able to eliminate or reduce the high concentration of sodium ion to restore the blood pressure to its normal physiological status.[28] Group E decreased more than groups D and C, respectively. This study is in agreement with Ani *et al.*[14] in which an increase in the dosage of *Solanum lycopersicon* administered to Wistar showed a significant decrease in the body weight of the animals in a dose-dependent manner.

CONCLUSION

In this study, LRESL showed an antihypertensive effect through its anti-hyperlipidemic, anti-atherogenic properties. LRESL was shown not only to reduce blood pressure but to increase serum nitric oxide levels as well as decreased cardiac arginase concentration as well as a measure of improved endothelial function. Therefore, this study suggests that the antihypertensive mechanism of *Solanum lycopersicon* was achieved via multiple mechanisms stated and this could be beneficial in the manufacturing of some pharmaceutical products that could be therapeutically important in the management of hypertension. It was concluded that the antihypertensive mechanisms of LRESL may involve anti-atherogenic events, vasodilatory, cardiac arginase reduction, and NO elevation as well as a decrease in body weight.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

LRESL: Lycopene Rich Extract of *Solanum lycopersicon*; **SBP:** Systolic Blood Pressure; **DBP:** Diastolic Blood Pressure; **SCAr:** Serum Cardiac Arginase; **SNO:** Serum Nitric Oxide; **ACE:** Angiotensin-Converting Enzyme; **LD50:** Lethal Dose at 50%; **TLC:** Thin Layer Chromatography; **NaCl:** Sodium Chloride; **NIBP:** Non-Invasive Blood Pressure; **BP:** Blood Pressure; **TGF-β:** Transforming Growth Factor-Beta; **TC:** Total Cholesterol; **TG:** Triglyceride; **LDL-C:** Low Density Lipoprotein Cholesterol; **HDL-C:** High Density Lipoprotein Cholesterol; **iNOS:** Inducible Nitric Oxide Synthase.

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