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Original Research Paper

Comparison Study between Rosuvastatin and Hibiscus Sabdariffa to Alleviate Atherosclerosis in Male Rabbits

Authors:
Ali Jasim Muhamed, Rzaq shailaan kaurshead, Adnan Mansour jasim
[1] *Department of Anesthesia Techniques, Hilla University College, Babylon, Iraq*
[2] *College Medical and Health Techniques, Al-Mustaqbal University*
[3]*College of Veterinary Medicine, AL-Qasim green University, Babylon 5013, IRAQ.*
Corresponding Author*:*
Adnan Mansour jasim
College of Veterinary Medicine, AL-Qasim green University, Babylon 5013, IRAQ.

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ABSTRACT:
Background: Cardiovascular diseases (CVDs) are important causes of elevated healthcare costs and disability and premature death. A significant proportion of this morbidity and mortality can be reduced by application a healthy system that includes health care and the use of effective treatments and great safety. **Objective**: This study aims to compare between hydroalcoholic extracts of Hibiscus sabdariffa and rosuvastatin in mitigating cardiovascular damage induced experimentally in male New Zealand rabbits. **Materials and Methods**: Twenty eight male local rabbits were randomly divided into four equal groups. The first group served as the control (NCG), the second group was induced with positive atherosclerosis untreated, The III group (A therogenic group and Rosuvastatin 0.88 mg/kg. The IV group (atherogenic and 100 mg/kg of Hibiscus sabdariffa Calyx extract daily throughout the experiment. The treatment was persistent for six weeks. **Results**: The study demonstrated that H. sabdariffa a significant enhancement in antioxidant activity (superoxide dismutase and catalase) and a reduction in levels cardiac enzyme (serum troponin I, LDL, CKMB, CRP and myoglobin). Additionally, the hawthorn extract led to clear reduction of total cholesterol, triglyceride, VLDL, heart rate and increased HDL. Moreover, Rosuvastatin appear improvement in among parameters with limited effect antioxidant activity. This study concluded that The extract of the H. sabdariffa plant has a role in protecting the heart from toxic effects by reducing cardiac enzymes, as well as increasing antioxidant factors, repairing heart cell tissue, and repairing damage to the blood vessel wall.

Keywords: Cardiovascular defect, rosuvastatin, Hibiscus sabdariffa, seum troponin

INTRODUCTION:

Cardiovascular diseases (CVDs) are predicted to account for 23.6 million deaths worldwide by 2030. They are one of the main causes of death worldwide(1). It has been demonstrated that a variety of metabolic risk factors, such as high blood pressure, lipid abnormalities, and hyperglycemia, have a significant impact on the onset and progression of CVDs (2) . Recent years have seen a significant increase in the financial burden of cardiovascular illnesses on the health care system, leading to greater rates of morbidity and mortality. Nevertheless, an excessive amount intracellular oxidative stress and lipid peroxidation may also result in molecular cell damage associated with a variety of physiological and pathological conditions. Additionally, research has shown that oxidative stress plays essential roles in the pathophysiology and development of cardiac problems. Although oxidative species (OS) have influenced proteins, lipids, and DNA, this has resulted in inflammatory processes and controlled cell death , which provides a fundamental understanding of the emergence of various cardiovascular diseases , which may be mitigated by suitable treatment(3) . According to many studies ultimate heart failure synonyms are associated with cardiac pathological conditions such as cardiomyocyte, deregulation of cell death, extracellular matrix alteration and hypertrophy.

Atherosclerosis is inflammatory disease with chronic state that result from in the major and small arteries and is typically linked to person suffering from hyperlipidemia or hypertension, dyslipidemia, diabetes, and autoimmune disease. (4) These factors can be affected by age, gender, and heredity. (5) For the purpose of hypertension control, the modern studies have been

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aimed to herbal extracts because of because of their lipid-absorbing, anti-inflammatory, and antioxidant qualities . As a result, many therapeutic agents such as synthetic medications and antioxidant-rich supplements—have shown helpful in managing or curing cardiac-associated illnesses caused by stress.

Hibiscus sabdariffa, sometimes known as roselle, is a member of the Malvaceae family and is widely planted around the world. Hibiscus sabdariffa contains polyphenols, which include phytochemicals including polysaccharides, anthocyanins, and certain organic acids. These phytochemicals support the plant's historic usage and, consequently, its many potential applications in contemporary therapy(6).

Additionally, the lower lipid agents in roselle for patients suffering from metabolic disorder has been established (7). The elevated levels of antioxidants identified in H. sabdariffa are additionally known to have anticancer (8), hypoglycemic (9), antipyretic , hypotensive , and antiproliferative effects (10). Additionally, it was shown by Najaf and associates that drinking tea made from H. sabdariffa might control blood pressure and glucose levels in the body (11). In 2018, Hibiscus sabdariffa was shown to have antiobesity and cholesterol-lowering properties in obese, hypercholesterolemic rats by Rason and the coauthor (12). Furthermore, tritone x induces atherosclerosis and efficacy hibiscus sabdariffa mitigate HFD and ROS, the goal of this study is to shed light on the potential of different fractions of to reduce oxidative stress in rabbit males. Recent study by noted that anthocyanins from H. Sabdariffa has an effective role in lowering blood pressure and oxidized low-density lipoprotein (OxLDL) with improvement HDL as well as antioxidant enzymes in patients consumption tea bag for 6 weeks . The study aimed to evaluate hydro alcoholic extract to mitigate atherosclerosis induced in rabbit as well as compared with rosuvastatin in improvement of parameters involved in this study.

METHODS OF RESEARCH AND MATERIALS USED:

This study was conducted from November 2023 to January 2024 in the animal house of College of Veterinary Medicine, Al-Qasim Green University. Rabbits were purchased from local market.

Plant Extraction:

Collection and preparation of Calyx of the Hibiscus sabdariffa were utilized. The apical part of plant callus was collected from the Hilla local market, and powdered by grinder. The fine powder were extracted according to method prescribed by [13] can be noted via 100 g per 250 ml of absolute ethanol then diluted to 70% , Hibiscus sabdariffa Calyx extract yield was 33%.

Animals:

Twenty-eight male Albino rabbits weighing between 1.2 and 1.4 kg and four to five months of age were bought for this investigation from the surrounding market. Following an ivermectin and enrofloxacin pretreatment procedures, the rabbits were randomly divided into four groups, with seven rabbits in each group. The groups were as follows: The group under control: Throughout the trial, the rabbits in this group were fed a regular meal and were given tab water every day. The atherogenic T2 group, or (T1) group: Rabbits in this group were fed both a conventional diet and a hyperlipidemic diet (HFD) supplemented with triton X. Rosuvastatin 0.88 mg/kg body weight (per human dose) and the T2 (A therogenic group). The (T3) group (atherogenic group rabbits): This group was treated with a drug at (100 mg / kg) of body weight of Hibiscus sabdariffa Calyx extract daily throughout the experiment. For six weeks, the treatment was ongoing and Blood samples were taken from the auricular vein for biochemical analyses at the conclusion of the six-week research, which involved stress and treatment. The blood serum was isolated and stored in the freezer until needed .

Induction atherosclerosis in rabbits:

In the current research rabbits was feed on a standard diet plus hyperlipidemic diet (HFD) at a concentration of 10% and 1.5% of hydrogen peroxide in tap water for 3 weeks then rabbits exposed to single dose 50mg/kg triton X 100 [14] [15] at the end of study .The atherogenic rabbits was selected according to s.c.troponin I ng/ml above (60 ± 3) as well as some 5 rabbit selected for histological section of aorta (16).

Determination of lipid profile Concentration:

The serum concentration of high-density lipoproteins (HDL-C), total cholesterol, and triglycerides, utilizing the Kit manufactured by the French company BIOLABO SA, low-density lipoproteins LDL determine according to method prescribed by.[17]

Determination of serum LDH, troponin I SOD, Catalase and Myoglobin. This ELISA reagent utilizes the Sandwich-ELISA technique, kits supplied from Sunlong Biotech Co., Ltd. (18).

Heart Rate Measuring: The microphone transducer was utilized for the estimation of the rabbits peripheral pulse rate.[19]

Statistical analysis Data were expressed as mean ± SE. Data were analyzed on a SPSS software version 14.0 using one-way ANOVA and Student t test. *P < 0.05, were used as the criterion for significance.

RESULT AND DISCUSSION:

Hibiscus sabdariffa and Rosuvastatin in the lipid profile:

The current study noted significant differences (P <0.05) in all lipid profile at atherosclerosis groups (T1,T2 and T3) compared with control group. Table 1 appears that there are significant differences (P <0.05) in the serum concentrations of TC (99 ±6.3 , 79 ± 10 and 68 ± 3.4 mg/dl) respectively compared with control group (53.6 ± 2.22). It was also showed that the TC serum concentrations in the group treated with fruits of Crataegus azarolus was significantly diminished as compared with Rosuvastatin. On the other aspect rabbits in (T2 and T3) fed on a high-fat diet and atherogenic triton X with dosage by the Rosuvastatin and extract respectively showed a significant reduction (P<0.05) in the serum concentration of TG (68.6 ± 8.9 and 76 ± 2.1) as compared to the untreated rabbits (T1) to recorded man value (178 ± 19.6). The results noted a significant decrease at (P<0.05) in HDL-C (22.3 ± 4.1) group of atherogenic rabbits that not received treatment compared to the control group (38.3 ± 2.6) on the other aspect clear elevation of HDL-C in hydro-alcoholic extract of fruits of Hibiscus sabdariffa and the drug as compared with Rosuvastatin showed a significant elevation (P <0.05) in the blood serum of HDL-c (38.32± 2.6 and 35.8 ± 4.2) rather than to the HLD positive control group. While the serum rabbits received extracts or of the Rosuvastatin showed a significant reduction in VLDL-c (13.7± 1.7 and 15.2 ± 0.34), respectively, compared to the (T1) group. The hydro- alcoholic extract of Hibiscus sabdariffa noted a significant reduction of VLDL with result mimic to control and there is no a significant between T2, T3 and NCG. The data of the present research recorded the role of the alcoholic extract of *Hibiscus sabdariffa* in lowering the heart rate of among treated rabbits, as well as role rosuvastatin in reduce the heart rate, and there was no variant's in range than control. Also, the Hibiscus sabdariffa has a major role as a hypotensive and making it very close to the normal range.

Table 1 : The influence of the medication in hydroalcoholic extract of Hibiscus sabdariffa and Rosuvastatin in the lipid profile in the serum Heart Rate in male rabbits.

Parameters / Groups	TC mg/dl	T.G mg/dl	HDL mg/dl	VLDL mg/dl	Heart Rate
NCG	53.6 ± 2.22 C	61.2 ± 2.8 B	38.3 ± 2.6 B	12.2 ± 0.8 A	172.2± 4.8 B
T1	99 ±6.3 A	178 ± 19.6 A	22.3 ± 4.1 D	31.6 ±13.9 A	215 ± 10.6 A
T2	79 ± 10 B	68.6 ± 8.9 B	38.32± 2.6 A	13.7± 1.7 A	183.5 ± 3.7 B
T3	68 ± 3.4 B	76 ± 2.1 B	35.8 ± 4.2 C	15.2 ± 0.34 A	179.5 ± 6 A
LSD	15.8	26.5	5.6	5.3	21.2

NCG : negative control group ; T1: positive atherogenic not received treatment
T2: atherogenic rabbits treated by Rosuvastatin ; T3 atherogenic rabbits treated by Hibiscus sabdariffa

Influence of Hibiscus sabdariffa and rosovastatin on the Production of Zinc and CRP:

The current study in figure (1) appear there is elevation in serum Zinc at (P≥0.05) with (T3) (53.4± 1.24) as compared with rabbits received rosovastatin to recorded mean value (49.8 ± 1.8) but remain there is a significant difference when compared with NCG (59 ± 1.14). In this current study on atherogenic rabbits, there was retardation in serum CRP levels in (t3) to mean value (1.13 ± 1.0.19) and there is no difference as compared with NCG, while administration of rabbits rosovastatin in (T2) and (T1) recorded significantly increased (p < 0.05) to (1.17± 0.21and 1.37 ± 0.17) respectively. In addition to SOD of rabbits received extract showed clear improvement but still there is significant a significant reduction in atherogenic rabbits when compared with(T2) and (T3) (61.4± 4.30 and 68 ± 1.04) respectively . Catalase serum activity showed significant elevation in treated groups (T3) received extract showed there is no significant difference as compared with NCG. The present data noted that extract showed restore the antioxidant ability via improvement of SOD and catalase (61.4 ± 4.30 and 30.2 ± 0.86) versus atherogenic rabbits not received therapy as well as that received rosovastatin has support different body function but still has less antioxidant capacity. In this study, compared with the

normal healthy rabbits in (NCG), the rabbits un received on rosovastatin under with HFD significantly improved the activities of antioxidant enzymes, such as catalase and SOD when compared with untreated rabbits (T1) fig (3,4) respectively.

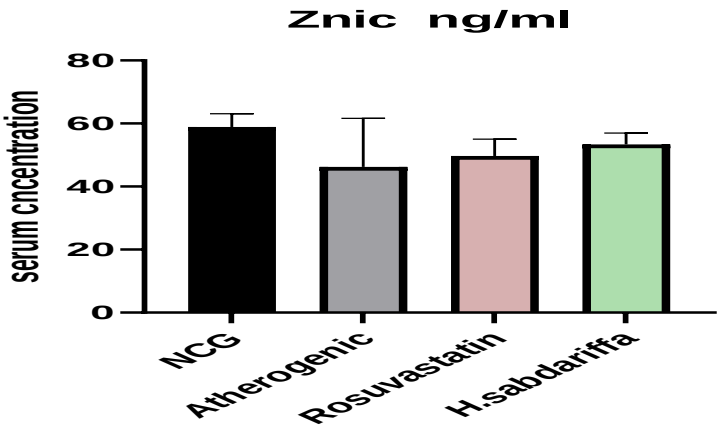

Figure (1) effect of *H. sabdariffa* and rosovastatin blood serum Zinc in atherogenic rabbits

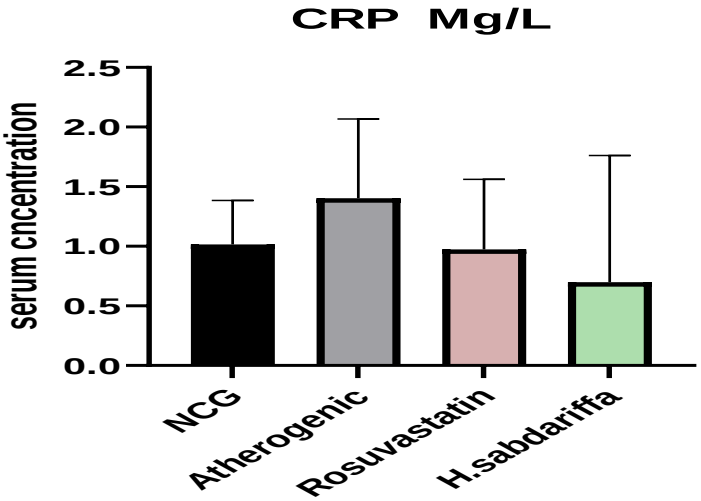

Figure (2) effect of *H. sabdariffa* and rosovastatin blood serum CRP in atherogenic rabbits

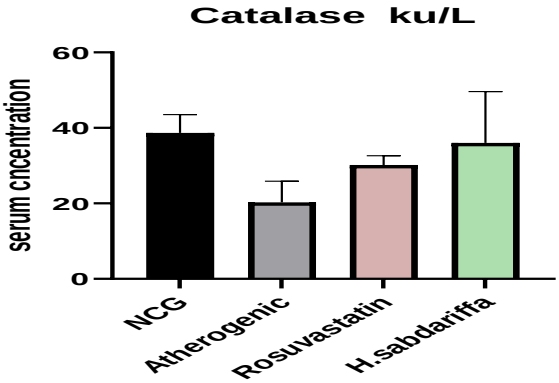

Figure (3) effect of *H. sabdariffa* and rosovastatin blood serum antioxidant Catalase in atherogenic rabbits

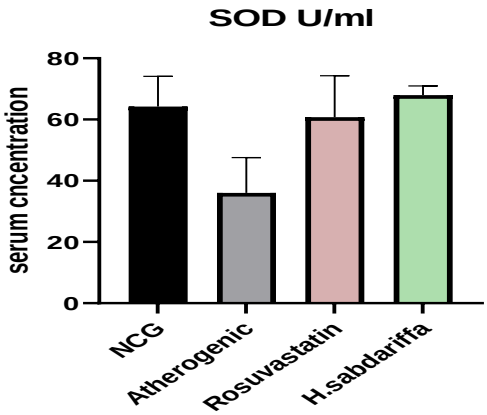

Figure (4) effect of *H. sabdariffa* and rosovastatin blood serum antioxidant SOD in atherogenic rabbits

Influence of Hibiscus sabdariffa and rosovastatin on the cardiac enzyme:

In the current study, there troponin I was a significant restore in serum troponin I levels in the rabbits received extract Hibiscus sabdariffa group compared with the(T1) while still there is no a significant difference in rabbits received rosovastatin in (T2) group Figure (7). Herein, the data of the present research recorded a significant improvement in the parameters of cardiac enzymes studied on rabbits exposed to strong antioxidants in addition to high-fat nutrition, as a clear and greater improvement was observed for the treated animals(T2,T3) when compared with untreated rabbits (T1), to recorded mean value (0.46±0.04 and 0.25±0.015) as compared with positive group(T1) (2.4 ±0.47) for CKMB from side as well as High levels of LDH in the blood may indicate the presence of inflammation in the body or damage to a vital organ such as the heart that is clear noted in current study specially in (T1) rabbit still not received any remedy as positive group to recorded men value (153.6±22.1) , rabbits received extract Hibiscus sabdariffa group showed clear reduction like health groups (93.1 ± 6.8 , 88.6 ±4.7) with no difference when compared with rosovastatin in (T3) group. Troponin I is one of the proteins found in the heart muscle. An increase in the level of troponin T has been linked to an increased risk of heart disease, especially atherosclerosis, and this test is considered the basic criterion for it. Treatment with the H؛ sabdariffa or rosovastatin led to a significant decrease in this enzyme at levels very close to the negative control, but there is a slight significant difference.

The current study's findings demonstrated that both cardiac enzymes (myoglobin and hs CRP) improved and increased when treated with a plant extract or the medication rosovastatin, to recorded mean value (0.33 ± 0.075, 0.41± 0.90,) (1.68 ± 0.10, 1.64± 0.05) respectively with a similar range as compared with NCG and the results were with a significant difference when compared with the positive control of untreated rabbits fig (8,9).

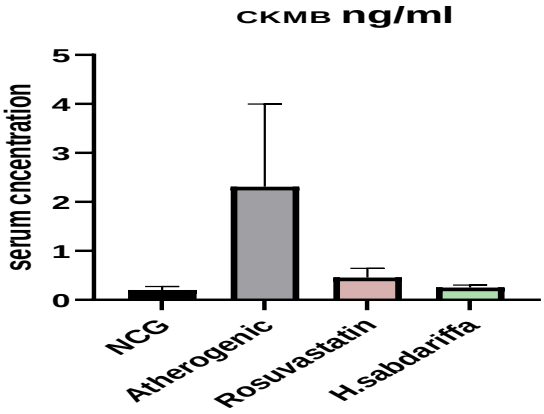

Figure (5) effect of *H. sabdariffa* and rosovastatin blood serum Creatine Kinase-MB in atherogenic rabbits

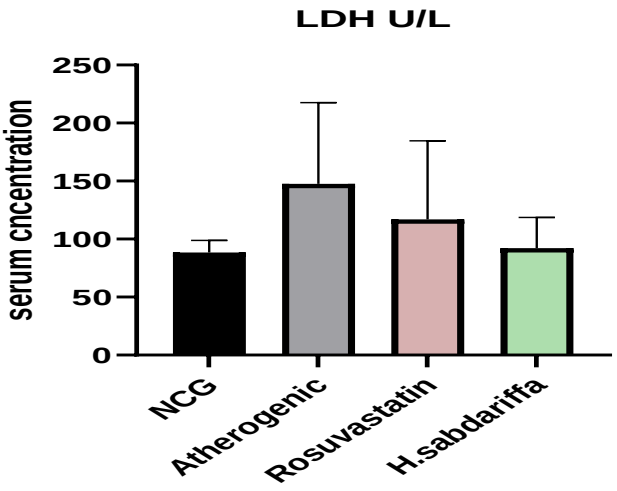

Figure (6) effect of *H. sabdariffa* and rosovastatin blood serum LDH in atherogenic rabbits

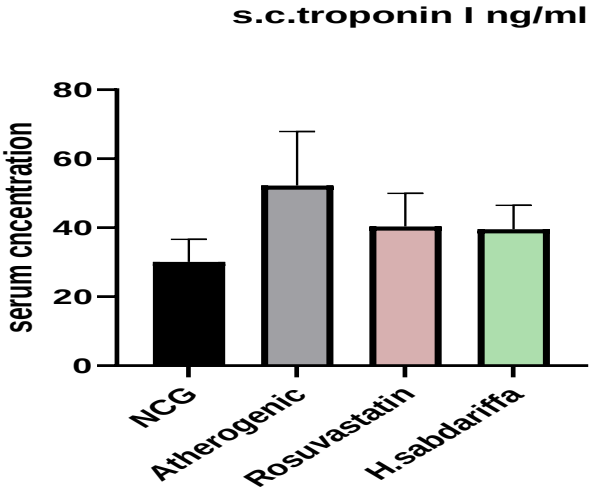

Figure (7) effect of *H. sabdariffa* and rosovastatin blood serum troponin I in atherogenic rabbits

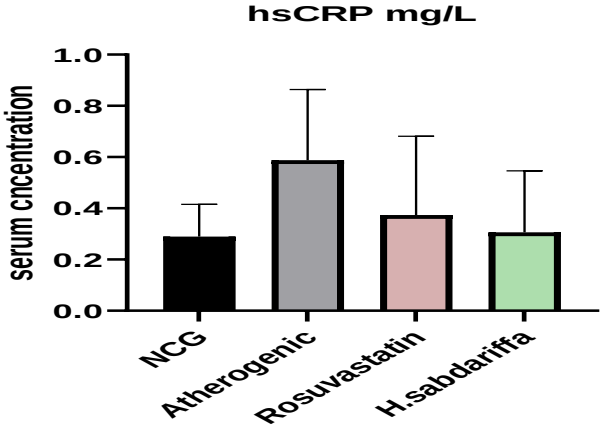

Figure (8) effect of *H. sabdariffa* and rosovastatin blood serum High-sensitivity C-reactive protein (hsCRP) in atherogenic rabbits

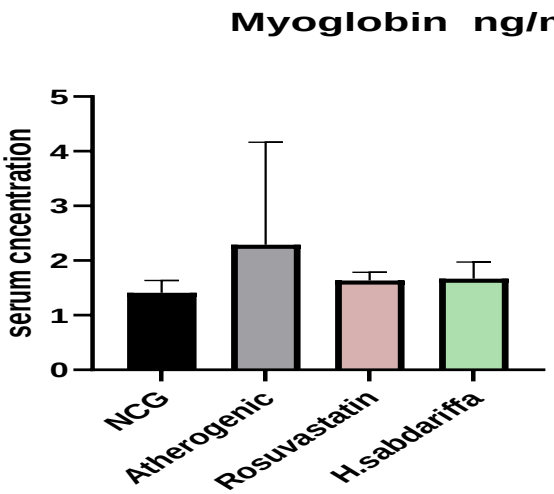

Figure (9) effect of *H. sabdariffa* and rosovastatin blood serum myoglobin in atherogenic rabbits

DISCUSSION:

Through emulsification, the nonionic surfactant Triton X-100 increases intestinal absorption of fat and stimulates the liver's production of cholesterol. Consequently, it prevents lipoproteins from being absorbed by other organ tissues, which raises blood cholesterol levels. This is accomplished by inhibiting lipoprotein lipase activity.[20] . Our results are consistent with several studies that have demonstrated that tritons cause both hyperlipidemia and dyslipidemia in rats. Triton X-100 induces acute hyperlipidemia and prevents the clearance of TG-rich lipoproteins in animal models(20). A decrease in VLDL and LDL catabolism was observed after the liver's increased production of VLDL due to hypertriglyceridemia brought on by the Triton X-100 injection.Pirmoghani and his co-authors (21) . It has already been determined that hyperlipidemia is a major factor in the development of atherosclerosis and cardiovascular illnesses. According to our research, Hibiscus sabdariffa has the potential to prevent hyperlipidemia by improving HDL cholesterol concentrations and preventing lipid profile alterations in the HFD and tritone X-induced groups (22). According to number of studies have demonstrated that HDL cholesterol has a positive function in lowering the atherogenic index and removing excess cholesterol from the tissue system and liver. [23] who reported that the low serum concentration of cholesterol in fruit extract may be the block of the hydroxy-methylglutaryl coenzyme A reductase (HMG-CoA) suitable for the building of TC in hepatic cells, within the cells. Furthermore, Hibiscus sabdariffa has essential role in potentiate the capacity of the lipoprotein lipase enzyme and thus minimize triglycerides in the blood rabbit .[24] Lactate dehydrogenase has role in metabolism, during the process of converting sugar into energy used by cells, and is found in many organs and tissues located throughout the body, including the liver, heart, pancreas, kidneys, skeletal muscles, and lymphatic tissue. , When damage to blood vessels or the heart occurs, this enzyme may be released into the bloodstream, causing its level to rise therefore highly increase in rabbits exposed to atherogenic agent and HFD .

The current study indicated the involvement of ascorbic acid and other antioxidants in reducing total cholesterol, triglyceride, and LDL levels and boosting HDL levels in blood to alleviate high levels of fat, namely oxidized LDL, and the development of arteriosclerosis. A recent study using rats as a model for H. sabdariffa's cardioprotective potential found that sodium fluoride induces cardiotoxicity. In contrast to the positive group, all extracted using different solvents revealed reduced cardiac biomarkers and sabdariffa increased tissue availability of HDL-c, LDH, and antioxidants, SOD, SOD, catalase, and CRP. GC-MS Investigation Significant levels of phyto-constituents, includingalpha-tocopherol, phytol, ethyl palmitate,methyl , and ethyl linolenate, which function as scavengers against Triton X-100, were found by GC-MS analysis of the ethanolic leaf extract of roselle (25). Among which, the total flavonoids contribute in the expression of two essential liver enzymes, HMG-CoA and cholesterol-7-alpha-hydroxylase (CYP7α), which are key enzymes for lipid synthesis.[26] There is information that the active ingredients in roselle extract lessen inflammation and oxidative stress, control lipid levels and prevent lipid accumulation—particularly of free cholesterol—in macrophages and the development of foam cells. Furthermore, the extract has a major effect in increasing intracellular calcium levels, inducing antiplatelet aggregation, protecting the vascular endothelium, and regulating endothelial dysfunction and relaxation. Clinical experiments have demonstrated that the alcoholic extract of roselle has a crucial role in resolving atherosclerosis along with other vascular disorders, and

it greatly lowers the harmful impacts of cardiovascular disease on blood lipids, blood pressure, and heart beat[27].

The current research investigation demonstrated the anti-oxidant properties of Hibiscus sabdariffa extract and the suppression of free radicals caused by the use of rosuvastatine and triton X100, which aids in accelerating the process of free radical metabolism and removal from the body while also encouraging organ regeneration. They can lower lipid oxidation and boost antioxidant capacity, which lowers vascular damage and helps avoid major cardiovascular consequences like hypertension [28] . The suggested mechanisms of these effects may be due to has potent antioxidant efficacy by the restoration of the normal value antioxidant enzymes' activities and nitric oxide production as well as the excretion of peroxide production to preserve the redox balance and hold vascular damage. In addition, the hawthorn can also reduce inflammation by minimizing hs-CRP. [29]

Lactate dehydrogenase-A (LDH-A), a crucial enzyme for glycolysis, has been linked in numerous studies to the migration and proliferation of VSMCs. Platelet-derived growth factor (PDGF)-induced VSMC activation led to cellular migration and proliferation. (30). The ability of anthocyanins in H. sabdariffa to block LDL oxidation, hence its antiatherosclerotic properties.The scientists demonstrated that H. sabdariffa inhibits CD36 receptor gene expression, which prevents macrophages from absorbing oxidized LDL(31, 32) . Numerous studies have shown that elevated blood levels of TC, TG, and LDL-c can trigger atherosclerosis and ischemic heart disease. Additionally, rosuvastatin pretreatment significantly improves the lipid profile, mostly by inhibition of HMG-CoA reductase (33, 34). Furthermore, the histological alterations in the pretreatment groups demonstrated a delay in the development of inflammation and myonecrosis, which may potentially be related to the anti-inflammatory and antioxidant characteristics of ellagic acid and rosuvastatin. Treatment with the H. sabdariffa or rosuvastatin led to an improvement in heart parameters by preventing the development or damage of tissues, especially blood vessels. This was observed through an improvement in the levels of important enzymes such as troponin, CKMB, hs CRP and myoglobin. The present study also noted that H. sabdariffa or rosuvastatin led to clear improvement of serum skin and CRP in atherogenic rabbits that may augmented by lipid profile as well as cardiac markers. Moreover, the majority of scientific evidence indicates zinc's beneficial effects on a number of physiological processes, including the production of NO, immunity cells, anti-oxidation, reducing inflammation, and anti-apoptosis. H. sabdariffa consider a natural source of anthocyanins, which are associated with cardiovascular protective by inhibited arachidonic acid-induced platelet aggregation, reduced calcium mobilization, and Vasorelaxation reduction was of aortic rings and endothelium versus inhibitors of nitric oxide synthase(35). Soto, Zuñiga-Muñoz (36) reported that H. sabdariffa potentiate total antioxidant capacity , ascorbic acid extra cellular super oxide dismutase, glutathione reductase , glutathione, glutathione peroxidase , glutathione-S-transferase , and reduce ROS in patients with aortic dilatation, endothelial dysfunction, and oxidative stress.

CONCLUSIONS:

The results of the present study confirmed H. sabdariffa has many active compounds work to suppression of oxidative factors, and protection of the heart from toxic effects on the heart through reduce of cardiac enzymes as well as increase Znic , SOD and catalase that support immune system with increase scavengers of free radical that give chance for repair tissue of cardiac cell and repair damage on vascular wall that may give promise chance in future for many studies to isolate important active compounds that have antihyperlipidemic effect .

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Ethical approval The Ethics Commission of Veterinary Medicine has authorized this research under reference number 533FD2.

Conflicts of Interest :

They have no conflicts of interest.

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