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# THE EFFECT OF BOILED CUMIN SEED EXTRACT (*CUMINUM CYMINUM* ) AND LEMON JUICE (*CITRUS LIMON*) ON SOME BIOCHEMICAL PARAMETERS AND AORTIC TISSUE IN MALE RATS EXPOSED TO A HIGH CHOLESTEROL DIET

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**ABSTRACT : The current study aimed to investigate the effect of cumin seed extract and lemon juice and to compare their effect with simvastatin on some biochemical parameters and aortic tissue of male rats fed a high cholesterol diet (2% g/kg). Biochemical parameters included estimation of lipid profile levels: Total cholesterol ,Triglycerides, High Density Lipoprotein, Low Density Lipoprotein, Very Low Density Lipoprotein and the immune enzymes, including Interleukin-1 beta and Endothelin-1. The study included 45 male laboratory Albino rats of the Sprague Dawley breed with weights ranging between 200-250 grams and divided into nine groups, each group included 5 rats for an experiment that lasted for 90 days, including, the first group control, the second group was given a standard diet rich in cholesterol. At a rate of (2% g/kg), the third group was given a high cholesterol diet and boiled cumin seed extract at a concentration of (250 mg/kg), the fourth group was given a high cholesterol diet and lemon juice at a concentration (5g/kg). The fifth group was given a high-cholesterol diet, boiled cumin seed extract (250 mg/kg) and lemon juice (5g/kg) together at the same concentrations, the sixth group was given a high-cholesterol diet (2% g/kg) and simvastatin at a rate of (10 mg/kg), The seventh group was given the standard diet and boiled cumin seed extract (250 mg/kg), the eighth group was given the standard diet and lemon juice (5g/kg), the ninth group was given the standard diet and boiled cumin seed extract (250 mg/kg) and lemon juice ( 5 g/kg) together. The results showed a significant increase in the biochemical variables, including TC,TG, LDL-C, VLDL-C and the immune enzymes IL-1β and ET-1, in the group exposed to a high-cholesterol diet. Groups treated with boiled cumin seed extract and lemon juice showed a decrease in the levels of TC, TG, LDL-C, VLDL-C while the group treated with simvastatin showed a significant decrease in the levels of TC, TG, LDL-C, V LDL-C and immune enzymes. IL-1β and ET-1. Histopathological findings were revealed the aorta of rats in the cholesterol-only group showed an accumulation of a large amount of cholesterol between the smooth muscle fibers with hemorrhage in the endothelial layer, and improvement in the histological picture of the aortic of rats of groups treated with boiled cumin seed extract and lemon juice.**

***Key words :*** Cholesterol, interleukin-1-beta, endothelin-1, cumin seed extract, lemon juice, simvastatin.

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## INTRODUCTION

Diet has a significant impact on human health, as many health problems have arisen, especially those related to metabolism and the digestive system (Ditu *et al*, 2018). Many diseases have emerged, including hypercholesterolemia. An increase in cholesterol levels This term is often used as a synonym for dyslipidemia (Ramchoun *et al*, 2020), which is one of the biggest risk factors for the development of Cardiac Heart Disease (CHD) (Harisa *et al*, 2016) and is characterized by elevated cholesterol levels. Total TC, Triglycerides (TG) with an increase in one or more types of lipoproteins, including very low-density lipoproteins for cholesterol and low-density lipoproteins for cholesterol with a decrease in high-density lipoproteins of cholesterol (Surya *et al*, 2017). Among the therapeutic interventions for hypercholesterolemia are synthetic chemical drugs. In vitro, which has cholesterol-lowering efficacy, but it has some side effects of drugs (Huang and Freter, 2016). The world has turned to research in developing effective alternatives for lowering cholesterol that are safer, more effective and less expensive, namely medicinal plants

(Karuna *et al*, 2018). Cumin seed belongs to the family Apiaceae (Zarandi *et al*, 2017). Cumin contains different types of compounds, including carbohydrates, proteins, fiber, oils and some vitamins, including (B1), (B2) and (B3) Niacin, C, Alpha-tocopherol (E), flavonoids, Tannins, Saponin, Alkaloids, glycosides and many minerals, including Iron Fe, Calcium Ca, Sodium Na and Selenium Se. As well as phenols, Aldehydes, including Cuminaldehyde (Mohamamadizadeh *et al*, 2020), cumin seeds are used as anti-inflammatory (Sakhaee *et al*, 2016) and have anti-cancer activity, antioxidant properties and the ability to inhibit human platelet aggregation (Mohan *et al*, 2015). Citrus limon is one of the most important types of citrus that belongs to the family of Rutaceae, where lemon juice is the active compounds, the most important of the flavanones are Hesperidin, Naringin and Rutin and it also contains the choreteins and carotenoids, it is rich in vitamin C known as ascorbic acid (Klimek-Szczykutowicz *et al*, 2020). Lemon juice is rich in Iron, Fe, Manganese Mn, Selenium Se, and Zinc Zn (Czech *et al*, 2020). Lemon juice is used to treat indigestion problems and stomach ulcers and prevent the formation of kidney stones (Al-Qudah *et al*, 2018) and anti-oxidant, anti-inflammatory, lowering-cholesterol and lipolytic have an effect on the Digestive System and the Cardiovascular System (Klimek-szczykutowicz *et al*, 2020).

### Aim of the study

1. Estimation of the lipid profile, which includes total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol.
2. Estimation of some immune enzymes, including interleukin-1-beta and endothelin-1.
3. Study of histological variables in the aorta.

## MATERIALS AND METHODS

### Preparation of high-cholesterol food

20 g of pure cholesterol powder of white color prepared from (Direvo Industrial biotechnology) company) was mixed with 1 kg of standard diet, at an amount of 2% g/kg (Oboh *et al*, 2015).

### Prepare the boiled extract of cumin seeds

Cumin seeds were obtained from the grasses of the city of Ramadi, Iraq. The cumin seeds were ground, then 300 ml of distilled water was added to 20 g of seed powder and placed over a hot plat with magnetic stirrer and left to boil for 20 minutes, then left to cool and filtered with gauze pieces to obtain the extract in the refrigerator (Al-julud, 2017).

### Preparation of lemon juice

Lemon fruits were obtained from the local markets of the city, after which the fruits were washed well and cut in half and squeezed manually. The juice was obtained, instantaneously prepared on the same day of dosing (Jaiswal *et al*, 2015).

### Animals used in the study

45 albino males rates of the type Sprague Dawley were used, their ages ranged between (12-14) weeks, and their weights (200-250) grams, they were placed in cages prepared for this purpose at a temperature of (25 $\pm 3^0$C) with a light period of 12 hours and a period of darkness of 12 hours, the standard diet and water were given adequately. The animals were randomly divided into (9) groups in each group (5) animals. The first control group was given water and food, the second group was given a high-cholesterol diet at (2% g/kg), the third group was given a high-cholesterol diet (2% g/kg) and dosed with cumin extract (250 mg/kg), the fourth group was given a high-cholesterol diet. Cholesterol (2% g/kg) and dosed with lemon juice (5 g/kg), the fifth group was given a high-cholesterol diet (2% g/kg) and dosed with cumin extract and lemon juice together in the same concentrations, the sixth group was given a high-cholesterol diet (2% g /kg) dosed with Simvastatin at a rate of (10 mg/kg). The seventh group was given a standard diet and cumin extract only at a concentration of (250 mg/kg), the eighth group was given a standard diet and lemon juice at a concentration (5g/kg), the ninth group was given the standard diet, cumin extract and lemon juice in the same concentrations. After the end of the experiment for a period of 90 days, the animals starved for 24 hours. After anesthesia, the animals were sacrificed and blood was collected using the heart puncture method. The blood serum was obtained using a centrifuge at a speed of 3000 revolutions per minute for a period of (15 minutes) and the serum was saved. At -20°C, the aorta was removed, washed with physiological solution, and placed in 10% formalin solution until tissue excision was performed.

### Biochemical examinations

The tests included estimating the levels of total cholesterol, triglycerides, high-density lipoproteins for cholesterol, low-density lipoproteins for cholesterol and very low-density lipoproteins for cholesterol, as a ready-made kit from the French company Biolabo was used. For cholesterol, as for the immune enzymes that included interleukin-1-beta and endothelin-1, they were measured using an enzyme-linked immunosorbent assay (ELISA) and a kit supplied by Calbiotech of America.

### Tissue sections

Histological sections of the aorta were made according to sequential steps based on Bancroft and Stevens (1999). Washing, Dehydration, clearing, Embedding and infiltration and sectioning trimming were carried out on it, cutting with a thickness of 5 microliters, and finally hematoxylin and eosin dye was used.

### Statistical analysis

The significant differences between the means were tested using the least significant difference test L.S.D. At the probability level of 0.05. Analysis of variance was analyzed using the ANOVA Table using the SPSS statistical program.

## RESULTS

### Analysis of the lipid profile

Figs. 1, 2 showed that high cholesterol diet increases the level of TG.TC, LDL, VLDL and decreases the level of HDL. The second group compared to the first. The level of TG, TC, LDL, VLDL decreased and the level of HDL increased in the treated groups. plants and drug compared to the first and second group.

The values expressed in each row are mean ± standard deviation and the number of rats/5 in the group.

The different letters indicate the significant difference at the probability level ($P \leq 0.05$).

The values expressed in each row are mean ± standard deviation and the number of rats/5 in the group.

The different letters indicate the significant difference at the probability level ($P \leq 0.05$).

### Analysis of the level of the immune enzymes interleukin-1-beta and endothelin-1

Fig. 3 showed that high-cholesterol nutrition increased the level of IL-1β and ET-1 in the second group compared to the first. The level of IL-1β and ET-1 was decreased in the groups treated with plants and the drug. Compared to the first and second group.

The values expressed in each row are mean ± standard deviation, and the number of rats/5 in the group.

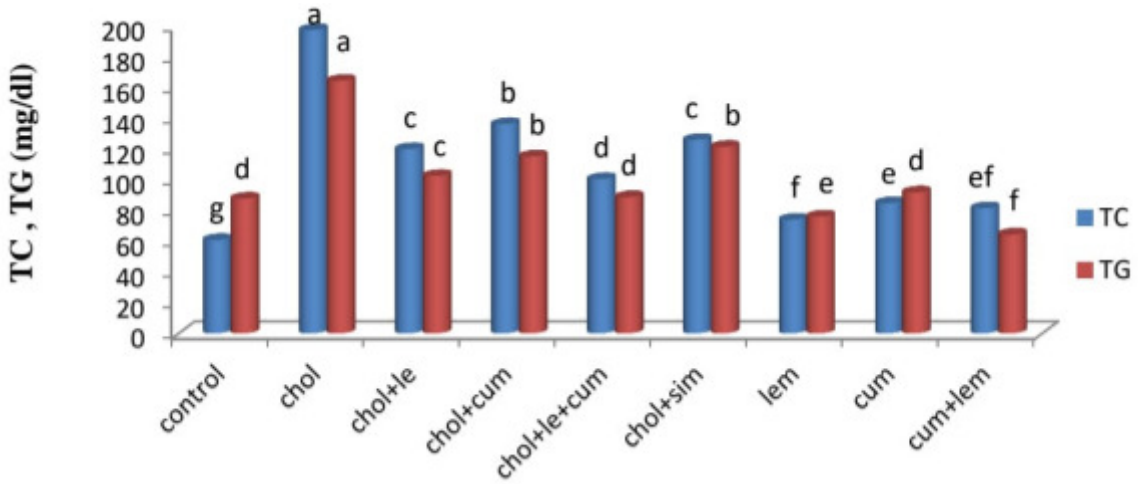


**Fig. 1 :** shows the effect of cumin extract, lemon juice and simvastatin on the level of TC and TG in the blood serum of rats.

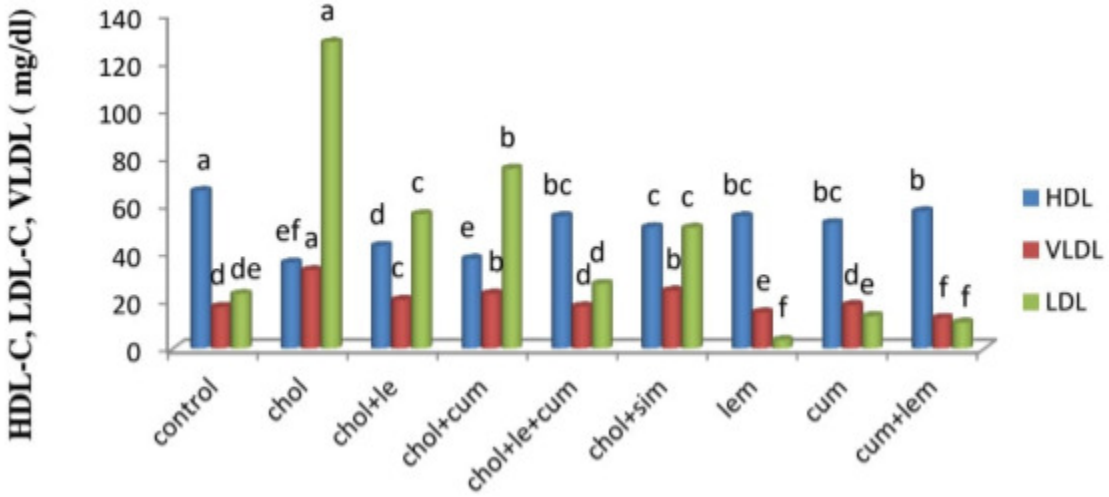


**Fig. 2 :** shows the effect of cumin extract, lemon juice and simvastatin on the level of HDL, LDL and VLDL in the blood serum of rats.

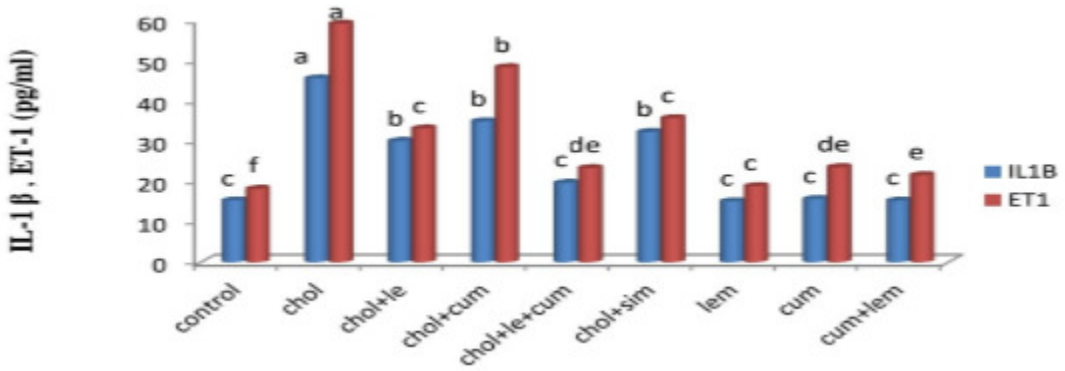


**Fig. 3 :** shows the effect of cumin extract, lemon juice and simvastatin on the level of IL-1â and ET-1 in the serum of rats.

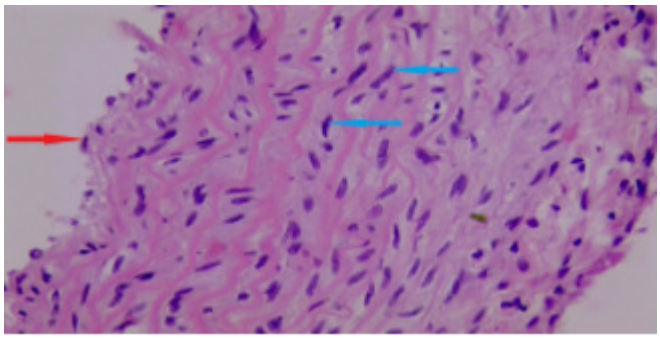

**Fig. 4 :** Section of the aorta in the control group showing the endothelium EN (red arrow) and smooth muscle fibers SM(blue arrow) H&E, X 400.

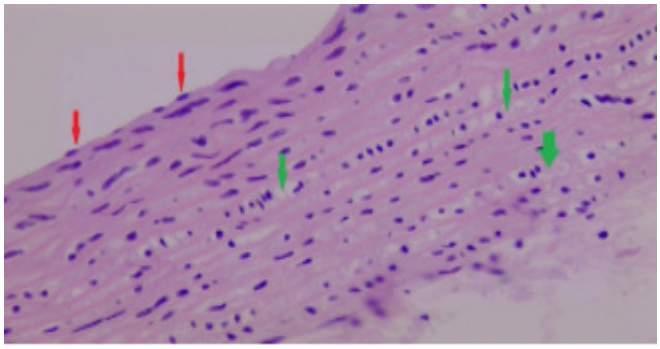

**Fig. 5 :** A section of the aorta in the cholesterol-treated group showing the accumulation of a large amount of CHOL cholesterol between the smooth muscle fibers SM (green arrow) with the endothelial layer EN (red arrow) H & E, X400.

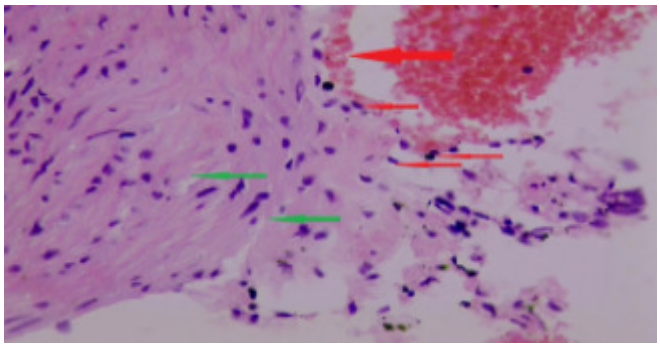

**Fig. 6 :** A section of the aorta in the cholesterol-treated group showing the accumulation of CHOL cholesterol in the endothelial layer EN (green arrow) with the inner layer rising towards the lumen with its layer affected by hemorrhage H on its surface (red arrow) H & E, X 400.

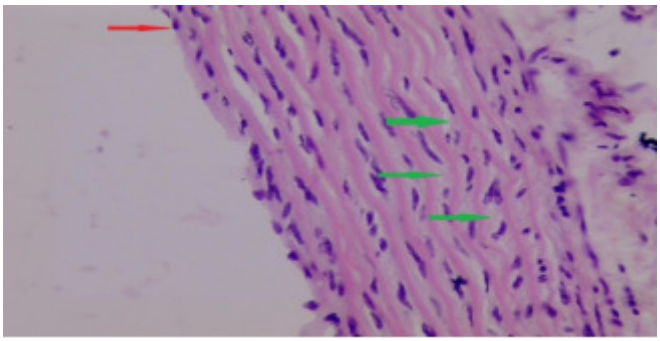

**Fig. 7 :** Section of the aorta in the cholesterol-treated group and cumin seed extract showing the normal histological structure with the accumulation of CHOL cholesterol between the SM smooth muscle fibers in the middle layer Media layer (green arrow) with the inner lining EN (red arrow) H & E, X 400.

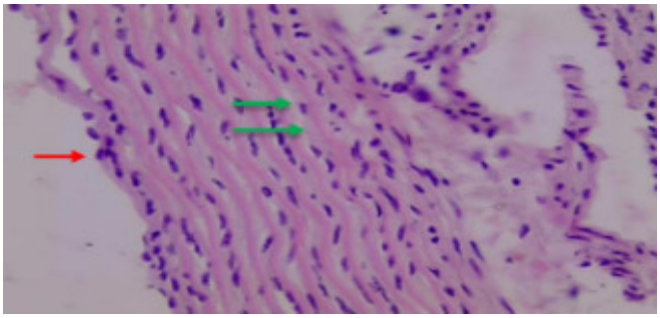

**Fig. 8 :** A section of the aorta in the group treated with lemon juice shows a very small accumulation of CHOL cholesterol (green arrow) between the SM smooth muscle fibers with the inner lining EN (red arrow) 400 X, H & E.

The different letters indicate the significant difference at the probability level ($P \leq 0.05$).

## Histological study of the aorta

Microscopic examination of the histological sections of the aorta in the control group showed the normal pattern of the artery layers (Fig. 4), represented by the endothelial inner layer and the middle layer by smooth muscle fibers. However, the cholesterol-treated group showed an accumulation of cholesterol in a large amount with bleeding as shown in Figs. 5, 6. In the cholesterol-treated group and cumin extract showed little accumulation of cholesterol (Fig. 7). In the group treated with cholesterol and lemon juice, there was very little

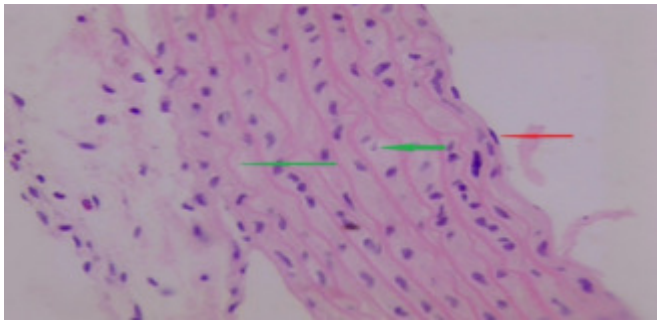

**Fig. 9 :** Sections of the aorta in the cholesterol-treated group, lemon juice and cumin seed extract together showing the accumulation of cholesterol CHOL between smooth muscle fibers SM in the media layer (green arrow), endothelium EN (red arrow) 400 X, H & E.

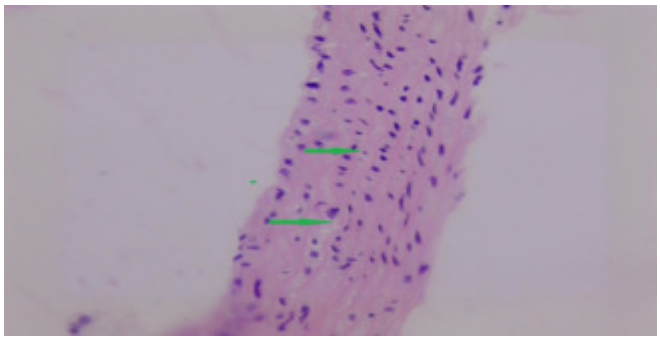

**Fig. 10 :** A section of the aorta in the cholesterol-treated group and Simvastatin shows a very small accumulation of CHOL (green arrow) between smooth muscle fibers SM 400 X, H & E.

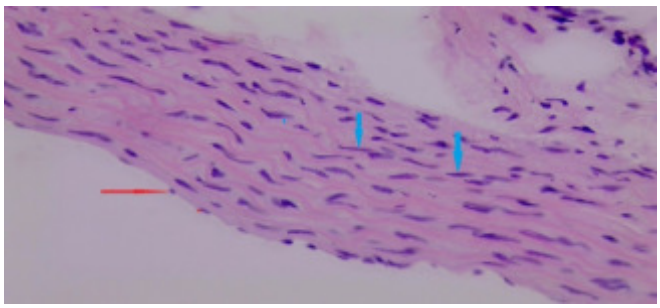

**Fig. 11 :** Section of the aorta in the group treated with boiled cumin seed extract showing the normal histological structure where the artery line is mediated by endothelial cells (endothelial cells) EN (red arrow) with the middle layer consisting of smooth muscle fibers SM (blue arrow) H&E, X 400.

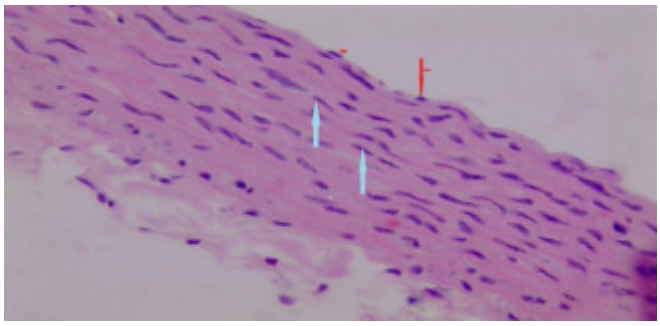

**Fig. 12 :** Section of the aorta in the group treated with lemon juice only, showing the normal histological structure of the artery, the inner lining EN (red arrow) with smooth muscle fibers SM (blue arrow) H & E, X 400.

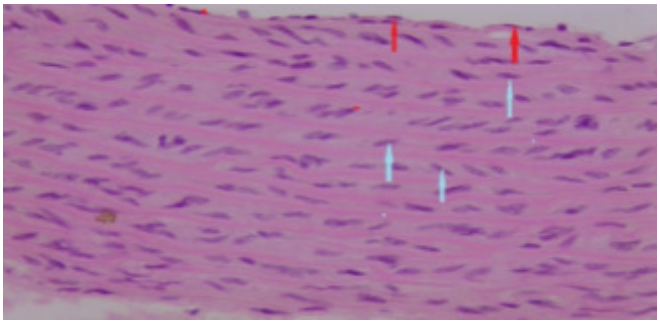

**Fig. 13 :** Section of the aorta in the group treated with cumin seed extract and lemon juice together showing the normal histological structure of the artery, the inner lining EN (red arrow) with smooth muscle fibers SM (blue arrow) H & E, X 400.

cholesterol accumulation between the smooth muscle fibers (Fig. 8). In the group treated with cholesterol, cumin extract and lemon juice together, a significant improvement appeared in the composition of the layers of the artery (Fig. 9). In the cholesterol-treated group and simvastatin, a little accumulation of cholesterol between smooth muscle fibers showed (Fig. 10). While in the group treated with cumin extract only (Fig. 11), the group treated with lemon juice (Fig. 12) and the group treated with cumin extract and lemon juice together (Fig. 13). The normal structure of the arterial layers of the endothelial layer and smooth muscle fibers.

## DISCUSSION

The increase in the nutritional content of cholesterol and its absorption by the intestine stimulates the liver to produce large amounts of molecules responsible for transporting cholesterol in the bloodstream. (Hassan, 2013), a high cholesterol food leads to the activation of the enzyme HMG-CoA reductase, which in turn stimulates the conversion of HMG-CoA to Mevalonate and increased blood cholesterol by the liver, as well as inhibiting the enzyme lipoprotein lipase (LPL) responsible for plasma lipolysis (Harnafi *et al*, 2008). The current study agrees with Naik *et al* (2018), highlighting the role of plants in alternative treatment because the plant has many medicinal and therapeutic properties as a result of containing many effective compounds. Whereas, cumin seeds contain a high percentage of fiber (about 15-45%), which works to adsorb dietary fats and bile acids with these fibers and merge with them in the intestine and then lose bile acids by excreting them with the feces (Rathore *et al*, 2013). Lemon juice contains pectin fibers and selenium, which inhibit the enzyme HMG-COA reductase and increase the formation of bile acids and their excretion with waste (Marounek *et al*, 2007). The mechanism of action of statins inhibits cholesterol through inhibiting the enzyme HMG-CoA- reductase competitively

in the liver and converted to mevalonate, the primary initiator of cholesterol synthesis (Laufs *et al*, 2016). As for triglycerides, their high level is due to the increased intake of foods rich in fats, which leads to an increase in the production of chylomicrons in the intestine. Serious as cardiovascular disease (Liu *et al*, 2017). It appears that lemon juice contains Carotenoids, Vitamin C, Naringin and Hesperidin that inhibit hepatic enzymes responsible for building TG (Burke *et al*, 2018). As for low-density lipoproteins and very low-density lipoproteins, a significant increase was observed at the probability level of $P \leq 0.05$. In the cholesterol-treated group, compared with the rest of the studied groups, the increase in VLDL-C may result from a defect in the work of the enzyme lipopritein lipase, which converts TG to fatty acids and thus contribute to a high level in the blood serum and in the meantime, Intermediate Density Lipoprotien (IDL) is formed, which quickly turns into LDL-C (Hall and Hall, 2020). Cumin seeds contain flavonoids, vitamin E, and fiber, all of which reduce the level of LDL-C and VLDL-C and increase the concentration of HDL-C in the blood serum (Dhandapani *et al*, 2000). The flavonoids and limonoid present in the juice reduce the formation of TG, which is the building block of LDL-c (Gordon, 1997). The effectiveness of the plants was proven in improving the level of HDL to better levels than its value in the group treated with the drug, which was its value, HDL-C has an inhibitory role in cholesterol, as it captures excess cholesterol from the blood and peripheral tissues and transports it to the liver, where it is broken down into bile acids (Ahmed, 2020). Vitamin C prevents the oxidation of HDL-C, as well as E, K and A, which are powerful antioxidants with a On reducing oxidative processes and removing free radicals, which works in reducing LDL-c oxidation and inhibiting the formation of foam cells (Chang *et al*, 2004). The results of the current study agree with Narges and Gholamreza (2016), Idoko *et al* (2017).

The group treated with cholesterol only showed a significant increase at the probability level ($P \leq 0.05$), while the groups treated with cholesterol and the mixture of plants had improved the level of IL-1β better than the level of the drug Simvastatin, this is due to a high cholesterol diet that led to the accumulation of fat in the liver associated with a defect in the liver. The function of hepatocytes led to steatosis, which stimulated and activated the inflammatory process, causing an increase in the secretion of cytokines, including IL-1 beta and TNF-α (ElMahdy *et al*, 2020). Alkaloids found in cumin seeds act as anti-inflammatory that have an important role In regulating endothelial nitric oxide (ON) expression, improving endothelial function, and relieving pro-inflammatory cytokines including TNF-α and IL-6 (Srinivasan, 2018), Lemon juice contains Hesperidin, a type of flavonoid, that has pharmacological activities as anti-hepatitis, removes free radicals and reduces lipid peroxidation (Mahmoud *et al*, 2019). While there was a significant increase in ET-1 level in the cholesterol-treated group only compared to the groups. Treatment with plants and the drug Simvastatin as well as control, as it is a vital indicator for the detection of cardiovascular diseases, high blood pressure and atherosclerosis (Jankowich and Choudhary, 2020). Excess cholesterol generates free radicals that cause damage to the cell membrane, leading to the infiltration of an enzyme from endothelial cells ET-1 (Li *et al*, 2013) Hesperidin stimulates endothelial nitric oxide (eNO) production in aortic endothelial cells and reduces monocyte adhesion (Chen *et al*, 2020).

Vitamin E has a role in protecting against coronary heart disease through its ability to reduce free radicals and Ox-LDL-C formation, as well as enhancing the immune system's defense mechanism (Lewis *et al*, 2019).

Microscopic examination revealed the accumulation of cholesterol with hemorrhage in the aortic tissue. This is due to the fact that a diet rich in cholesterol contributes significantly to the development of inflammatory conditions in the tissue and cellular degeneration, which leads to the formation of atherosclerotic lesion. The damage to the epithelial cells of the artery is due to the rise in LDL-c and its accumulation. In the lining of the artery, it is oxidized and devoured by macrophages to turn into lipid-laden foam cells and cause streak fat (plaque) in the artery wall (Rojková, 2021).

As for the group treated with cholesterol and the mixture of plants, it shows a better improvement in the composition of the tissue layers, as for the drug group, a similar structure appears, a little accumulation of cholesterol between muscle fibers. Cumin seeds contain antioxidants such as flavonoids, polyphenols, tannins and cuminaldehyde that have an effective role in reducing LDL-C oxidation and foam cell formation (Farrokhi and Samani, 2014). Lemon juice contains flavonoids and limonoids, which are antioxidants that scavenge free radicals ROS and prevent the oxidation of LDL-C that has a disruptive action on arterial walls (Idoko *et al*, 2017).

## CONCLUSION

The importance of cumin and lemon plants in the prevention and reduction of diseases caused by the high level of harmful fats in the body, such as heart disease and arteriosclerosis due to the high capacity of plants to scavenge free radicals by the action of their active compounds and that hypercholesterolemia has a negative

effect on the tissues of some organs for male rats, such as the aorta.

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