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Effect of rosuvastatin and Senna Makki on some physiological and biochemical parameters in male Rabbits with Hyperlipidemia

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Abstract
This study was conducted in the College of Veterinary Medicine / University of Tikrit. The study included 20 male rabbits, their ages ranged between (3-4) months and their weights ranged between (1-1.25 kg). The study continued for sixty days, starting from (1-3-2022 to 1-5-2022). The animals were randomly divided into 4 groups, each group consisting of 5 rabbits. It was noted from the current study that the effect of fats was clear by causing a significant decrease (p<0.05) in the levels of (the total number of white blood cells, the total number of RBC, the concentration of hemoglobin, and the number of platelets), while rosuvastatin caused a significant increase in (the number Total RBC, Hb concentration, platelet count, and packed cell volume) within the same group compared to when the trial started. The aqueous extract of the senna makki plant had a clear role in restoring the levels of blood parameters to normal compared to the fat-treated group. Regarding biochemical measurements (HDL, LDL, and glucose). We conclude from this study that senna makki is the best natural compound used for the purpose of controlling most biochemical parameters in the body and preserving blood components from harmful effects, despite the role played by rosuvastatin, senna makki is considered the most effective compound. Sometimes it's better because it's free of artificial chemicals.

Keywords: Rosuvastatin, Senna makki, physiological and biochemical parameters, male rabbits, hyperlipidemia

Introduction
Nutrition is one of the important factors that affect a person's health and physical and mental condition. The quality of food is essential for human health, protecting it from diseases, and helping it perform its various vital functions [1]. Chronic diseases and their dangers to human health are related to bad food, therefore nutrients are one of the most important reasons that help to recover the body from many diseases, and it may become a contributing factor to the infection of a particular disease, the food that eating or the diet that we follow in our life controls our health and affects the various parts of our body [2]. Liver cells synthesize cholesterol with the help of the enzyme HMG-CoA reductase. Many experiments have been conducted to find out how to inhibit the action of this enzyme and proved that statin has an inhibition action on this enzyme that is considered the keystone for cholesterol synthesis [3]. Currently, Statins are among the most widely used medications to treat high blood fat levels, which lead to the prevention of many diseases, including kidney, liver, and heart diseases [4]. Despite the benefit offered by this drug in reducing fat and protecting the body from clots and diseases related to high cholesterol, many side effects caused by statins have appeared on the human body, especially in the elderly represented by problems in the central nervous system, strokes, epilepsy, dementia, and other risks that are still under investigation [5]. The current study was designed for the following objectives:

1. Comparison between fat-burning drugs that work with different mechanisms and medicinal herbs in reducing weight for those animals.
2. Explanation of the effects of the treatments used in the experiment on some physiological and biochemical parameters of developing rabbits.

Materials and Methods

Laboratory animals were obtained from Tikrit University/College of Veterinary Medicine with a number of 20 male rabbits, their ages between [3-4] months and weights between (1-1.25 kg), the study continued for sixty days. and they were placed under controlled conditions. In terms of ventilation and temperatures, which ranged between 22-30 °C, humidity of up to 50%, and lighting period (12:12 hours) inside the animal house. The animals are provided with filtered water, and the specialized ration designed for each group is given. The animals were placed in cages 10 days before the actual experiment to help them adapt and get used to the place, and 3 rabbits were isolated out of the previous number. A preliminary test was conducted to confirm the ability of free fats to raise cholesterol within a dose of 1 ml per day, and by taking blood samples from the eye area before and after lactation that lasted for a week, we found a significant increase in total cholesterol, identical to the results obtained in the study [6]. The drug rosuvastatin, known commercially as the Crestor drug, was used and the concentration of the active substance (rosuvastatin) in it was 20 mg /kg, according to the data of the Swedish manufacturer. It was ground well and made into a powder. 0.04 mg was taken from it dissolved in water and then dosed to animals according to the requirements of the experiment. The aqueous extract of Senna Makki was prepared according to the modified method by [7], 150 gm of crushed leaves were taken and placed in 1500 ml of distilled water (DW) for four hours under room temperature, after which the mixture was filtered by filter papers and the aqueous was used to feed the groups in our study. The rabbits were randomly divided into 4 groups, each group of 5 rabbits. After the conditioning period, which lasted for ten days, the rabbits were treated daily for a period of 60 days, with special treatments for each group, and they were administered orally using the medical syringe and some with the diet as well as following.

1. Control group: The rabbits were treated with DW and fed on a standard diet.
2. Fat group: The rabbits were treated by giving DW and given the fat mixed with the ration at 400 mg/kg in a concentration of animal weight for a period of 60 days throughout the experiment period.
3. Rosuvastatin group: it was fed on a high-fat diet at 400 mg/kg a concentration of animal weight for 60 days, and on day 30 it was treated with rosuvastatin at a concentration of 20 mg/kg of animal weight for a period of 30 days until the end of the experiment.
4. Senna Makki group: it was fed on a high-fat ration at a concentration of 400 mg/kg of animal weight for 60 days, and on day 30 it was treated with Senna Makki at a concentration of 10% for a period of 30 days until the end of the experiment.

Samples collection

Blood was drawn from all groups from the eye socket before starting the experiment (at time 0). Then, after the end of the specified period of the experiment, the rabbits were prevented from eating for about one day. (1-2) ml of blood was taken for the purpose of conducting blood tests. Then the animals were slaughtered and 3 ml were taken from each animal and placed in tubes containing anticoagulant for biochemical testing. The serum was obtained by centrifuging at 3000 revolutions per minute and kept at (-20) C in new and clean plastic tubes (Plane Tubes) until needed.

Count blood parameters

We used in our study Vet. Hematology coulter to count complete blood picture.

Count biochemical parameters

- **Determination of HDL_C concentration in blood serum:** We estimate High-density lipoprotein by using a specialized Kit supplied (Randox Company).
- **Determination of Low-Density Lipoprotein in blood serum:** We estimate Low-density lipoprotein by using a specialized Kit supplied (Syrbio Company).
- **Determination of glucose concentration in blood serum:** We estimate Glucose by using a specialized Kit supplied (Plasmatec Company).

Statistical analysis

The experiment was carried out according to the Complete Randomized Design (CRD) within the SAS (2001). In the case of significant differences Duncan's test was used to determine the significant differences, and a two-way variance test was conducted at a probability level of 0.05.

Results

Blood parameters

Table 1: Shows the effect of lipid treatment and the effect of rosuvastatin and aqueous extract of senna maki on hematological parameters (white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb) concentration, number of platelets, packed cells volume) before the experiment time (zero) and after Complete the experiment (after 60 days of dosing).

Values represented by Mean ± Standard error No. of rabbits in each group = 5 rabbits Different in small letters in the same column indicate significant differences ($p \leq 0.05$) between groups Different in capital letters in the same row indicate significant differences ($p \leq 0.05$) between groups					
Groups Parameters	**Time**	**Control G.**	**Fat G.**	**Fat + rosuvastatin G.**	**Fat + Senna Mekki G.**
WBC ($\times 10^3$ cell/ml^3)	0	7.2 ±1.5 *a A*	7.1 ± 1.3 *a A*	7.4 ±0.4 *a A*	7.2 ± 1.1 *a A*
WBC ($\times 10^3$ cell/ml^3)	After 60 days	7.7 ±1.4 *a A*	6.8 ± 1.2 *b B*	6.2 ± 0.2 *b B*	7.3 ± 1.5 *a A*
RBC ($\times 10^6$ cell/ml^3)	0	5.3 ± 0.7 *a A*	5.8 ± 0.8 *a A*	5.5 ± 0.7 *b B*	5.7 ± 0.7 *a A*
RBC ($\times 10^6$ cell/ml^3)	After 60 days	5.9 ±0.8 *a A*	4.1 ± 0.6 *b B*	6.1 ± 0.5 *a A*	5.7 ± 0.3 *a A*
Hb (g\dl)	0	12.5 ±1.7 *a A*	12.8 ± 1.3 *a A*	12.3 ± 1.1 *b A*	12.6 ± 1.2 *a A*
Hb (g\dl)	After 60 days	*13.2 ±1.4* a A	*9.7 ± 1.2* b B	*13.7 ±1.3* a A	*12.5 ± 1.7* a A

PLT × 10^6 \ µl	0	292 ± 14.3 *a A*	267 ± 12.1 *a A*	277 ± 12.3 *b A*	285 ± 11.3 *a A*
PLT × 10^6 \ µl	After 60 days	298 ± 13.7 *a A*	211 ± 11.1 *a B*	293 ± 12.7 *a A*	292 ± 14.3 *a A*
PCV (%)	0	36 ± 2.1 *a A*	34 ± 2.4 *a A*	35 ± 3.1 *b A*	36 ± 3.2 *a A*
PCV (%)	After 60 days	37 ± 3.1 *a A*	28 ± 1.4 *b B*	39 ± 4.2 *a A*	35 ± 2.1 *a A*

Levels of high-density lipoproteins in studied group

Table 2: Shows the effect of treatment with fat and the effect of rosuvastatin and aqueous extract of Senna Mekki on the level of high-density lipoproteins before the experiment, time (zero) and after completing the experiment (after 60 days of dosing)

Values represented by Mean ± Standard error No. of rabbits in each group = 5 rabbits Different in small letters in the same column indicate significant differences ($p \leq 0.05$) between groups. Different in capital letters in the same row indicate significant differences ($p \leq 0.05$) between groups.					
Groups Parameters	**Time**	**Control G.**	**Fat G.**	**Fat + rosuvastatin G.**	**Fat + Senna Mekki G.**
HDL (mg/dl)	0	52.13±3.5 *a A*	50.56± 2.1 *a A*	49.65 ± 1.9 *a A*	50.53 ±2.9 *a A*
HDL (mg/dl)	After 60 days	55.21 ±2.7 *a A*	41.22 ± 1.7 *b B*	50.33 ±2.9 *a A*	51.22 ±3.1 *a A*

Levels of low-density lipoproteins in studied group

Table 3: Shows the effect of treatment with fat and the effect of rosuvastatin and aqueous extract of senna maki on the level of low-density lipoproteins before the experiment time (zero) and after completing the experiment (after 60 days of dosing)

Values represented by Mean ± Standard error No. of rabbits in each group = 5 rabbits Different in small letters in the same column indicate significant differences ($p \leq 0.05$) between groups. Different in capital letters in the same row indicate significant differences ($p \leq 0.05$) between groups.					
Groups Parameters	**Time**	**Control G.**	**Fat G.**	**Fat + rosuvastatin G.**	**Fat + Senna Mekki G.**
LDL **(mg/dl)**	0	*±1.6 18.33* a A	*19.52* ±1.8 b A	*20.36 ±1.6* b A	*20.14* ± 1.8 a A
LDL **(mg/dl)**	After 60 days	*±2.3 20.13* a B	*33.14* ± 2.8 a A	*28.46 ±2.6* a A	*21.22* ± 2.1 a B

Levels of glucose in studied group

Table 4: Shows the effect of treatment with fat and the effect of rosuvastatin and aqueous extract of senna maki on glucose level before the experiment, time (zero) and after completing the experiment (after 60 days of dosing)

Values represented by Mean ± Standard error No. of rabbits in each group = 5 rabbits Different in small letters in the same column indicate significant differences ($p \leq 0.05$) between groups. Different in capital letters in the same row indicate significant differences ($p \leq 0.05$) between groups.					
Groups Parameters	**Time**	**Control G.**	**Fat G.**	**Fat + rosuvastatin G.**	**Fat + Senna Mekki G.**
Glucose (mg/dl)	0	71.1± 2.5 *a A*	±3.2 71.6 *b A*	±3.5 72.3 *b A*	3.2 72.8 ± *a A*
Glucose (mg/dl)	After 60 days	74.7 ± 2.3 *a B*	±4.2 83.3 *a A*	85.4 ± *1.5* *a A*	74.4 ±4.2 *a B*

Discussion

Blood parameters: The current study indicated that the studied levels of all WBC, RBC, Hb concentration, platelets, and packed cells volume) in the control group did not significantly differ ($p \leq 0.05$) between the two treatment times (at time zero and 60 days of the experiment), while the results of the current study showed that treating rabbits with a diet containing fat led to a significant decrease in (WBC, RBC, Hb concentration, platelets and packed cells volume) and that this decrease in blood components occurs when their loss is greater than their production (8), and that the lack of RBC is reflected on the concentration of Hb in the blood and its level decreases [9] and due to the presence of a positive significant correlation coefficient between each of RBC and the concentration of Hb and PCV, we notice a decrease in the three parameters and our results agreed with [10] who revealed that blood cells can be exposed to lysis as a result of exposure to oxidative stress by treating rabbits with a diet containing fat which indicated to the formation of deposits called Heinz bodies inside the RBC, which helps to degrade them and thus reduce their number in the bloodstream [11]. The results we obtained differed with [10], which showed that an increase in the level of fats in the blood will lead to an increase in the level of RBC and an increase in the concentration of hemoglobin and the average volume of cells due to the high viscosity caused by fatty substances in the serum. As for the results of the group Dosed and treated with rosuvastatin, the results were in agreement with what [12] mentioned regarding the lack of effect of statin drugs on the rate of hemoglobin concentration in terms of its ability to reduce but that sometimes it may increase the rate of hemoglobin concentration due to the acidic nature of the drug that lowers

the pH of the blood But he did not address in his study the effect of the drug on the rate of RBC and corpuscular volume, and the results also agreed with [13] who showed the ability of statin drugs to increase the value of the (total number of white blood cells, red blood cells, hemoglobin concentration, and packed cells volume) in the blood after interruption of cholesterol synthesis through inhibition of the enzyme HMG (hydroxymethyl glutaryl coenzyme) which it is necessary in the synthesis process and activation circulation cycle. [14] indicated that the use of rosuvastatin leads to a decrease in the level of white blood cells due to the role that this drug plays in reducing the secretion of C-Active Protein through its effect on the reduction of the enzyme HMG-CoA, which plays an critical role in the production of cholesterol in the liver. That is due to the similarity in patterns of molecular between rosuvastatin and the enzyme that replaces it. Thus, statins reduce the production of mevalonate, which is in the sequence is the second molecule that ends with the production of cholesterol. This is what we found in our current study. As for the group treated with an aqueous extract of senna makki, it was completely identical to the results mentioned by [15], who showed that senna makki because of its ability to enhance the body's immunity and has a protective factor, it will become more resistant to diseases and therefore the white cells will return to their normal proportions over time, as the results we obtained agreed with the study of [16], indicating that the senna makki compounds contain a high amount of antioxidants which prevent the decomposition of RBC and preserve their walls by preventing lipid peroxidation. Which is likely to be formed due to the presence of free radicals as these antioxidant compounds scavenge and analyze free radicals. Thus, the use of senna Makki, if used in moderate doses, contributes to the return of levels (RBC, Hb concentration, platelet count, and packed cells volume) to their normal state, and this is what we have reached in our current study, and as shown in Table No. (1).

Levels of high-density lipoproteins in the studied group

This study showed that the level of high-density lipoproteins in the control group did not significantly differ ($p \leq 0.05$) between the two treatment times (before and after 60 days) of the experiment and between the studied groups at time zero due to both groups eating the same diet without making any changes to them. While it was observed that high-density lipoproteins decreased when rabbits were treated with cholesterol, the reason for low HDL-chol may be because it works to reverse the transfer of cholesterol from tissues to liver tissues. Low HDL-chol is due to liver disease or high levels of cholesterol, triglycerides, and LDL-chol [17]. When the concentration of triglycerides and cholesterol increases in tissues and blood vessels, this leads to a reduction in the efficiency of HDL-chol in transporting cholesterol. Also, the oxidation of LDL and the demolition of internal cholesterol in the body leads to a decrement in the HDL level, which is significant for the process of transporting cholesterol and thus reducing its level in the blood vessels [18]. For the group that was treated with rosuvastatin, a significant decrease in the level of high-density lipoproteins was observed in the group treated with rosuvastatin at a time of 60 days compared to zero time. The results agreed with [19] who reported that statin compounds stimulate the secretion of different enzymes (proteolytic, amylolytic, and lipolytic), which helps in the digestion of nutrients in the gut, which in turn improves metabolic processes within the intestine which in turn helps the process of losing weight and returning high-density lipoproteins (HDL) to normal. It was also observed that there is a significant difference in the level of high-density lipoproteins in the group treated with senna mekki at times zero and 60 days and with the group treated with fat, while there is no significant difference between the level of high-density lipoproteins in the group treated with senna mekki after the end of the experiment when compared with The control group, as this group was treated with the diet containing fat for thirty days and then used the aqueous extract of senna mekki, which led to decrease the level of high-density lipoproteins when compared with the fat-treated group and returning to its normal level when compared with the control group. Oue results that we obtained agreed with (20) showed that the extract of senna mekki contains antioxidant compounds that inhibit the synthesis of high-density lipoproteins in the cells that synthesize it in the liver, as shown in Table No. (2).

Levels of low-density lipoproteins in studied group: The current study indicated that the level of low-density lipoproteins in the control group did not differ significantly ($p \leq 0.05$) between the two treatment times (before the experiment and after 60 days of the experiment) and between the studied groups at time zero for each of the parameters due to the group eat the same diet without making any changes to them. Also, in the results of the current study, a significant increase in low-density lipoproteins was observed when cholesterol was treated in rabbits, as the role of LDL is known as a major transporter of cholesterol from the liver to tissues, which contains a high percentage of cholesterol and this increase leads to Arteriosclerosis [21] The increase in the level of LDL can be explained by the increase in the level of malondialdehyde (MDA) resulting from oxidative stress due to cholesterol intake, which is accompanied by an increase in the level of low-density lipoproteins in the blood serum because malondialdehyde works to oxidize lipoproteins Low density and converting it to the oxidized form [22]. The increase may be attributed to the oxidation of the high-density protein receptors [23]. The research indicates that MDA and 4-Hydroxynenonal are the most involved in the oxidation of low-density lipoproteins and very low-density lipoproteins, which are due to the cause of atherosclerosis, or the reason may be attributed to the role of free radicals in oxidation Fats and their decomposition or the effect of stress and the increase of free radicals work to increase the oxidation of low-density lipoproteins, which will affect the cardiac and smooth muscles and will negatively affect the protein metabolism inside the cell. Thus, stress is responsible for causing chronic diseases such as atherosclerosis [24]. The results also agreed with [25] which showed that a fatty diet will have a significant impact on health in terms of cholesterol formation and an increase in the proportion of bad from of it and increase the level of triglycerides in the blood serum and plaque formation inside the arteries, which leads to impeding the flow of blood inside the vessels, which results in many diseases and [26] emphasized that statin drugs, if used for a long time it has the ability to reduce low-density and very low-density lipoproteins through Inhibition and reduction of the enzyme HMG-CoA, and this reduction will activate the protein factor so it is transferred from the endoplasmic reticulum to the Golgi apparatus, which will activate the receptors of these low-density proteins, especially VLDL and increasing the number of these receptors will eventually lead to the absorption and destruction of this protein and reduce the level of its presence as indicated by [27]. In the group that was

treated with senna makki, it was noted that the use of senna extract after the end of the experiment (30 treatment days) Contributed to return the level of low-density lipoproteins to normal when compared with the control group and with time zero from the start of the experiment. The results also agreed with [28], who showed the ability of the active substances in senna, antioxidants and flavonoids, and its content of cynarin and chlorogenic consisting of a mixture of quinic and caffeic acid, which are necessary to restore low-density lipoproteins to the normal level when compared with the control group as shown in Table (3).

Levels of glucose in studied group: The current study indicated that the sugar level in the control group did not differ significantly ($p \leq 0.05$) between the two treatment times (before the experiment and after 60 days of the experiment) and between the studied groups at time zero for each of the parameters due to the group eating the same diet without making any changes to it, as it was noted. Treating rabbits with cholesterol led to a significant increase in glucose concentration, which may be due to the fact that oxidative stress affects epinephrine, which increase the blood sugar level by stimulating glycogenolytic enzymes, thus turning glycogen into glucose-6-phosphate (Glucos-6- phosphate) under the influence of the enzyme Glucos-6-phosphatase or due to an increase in oxygen and thus an increase in the active types of oxygen that attack the β-cells that secrete insulin, which leads to a defect in the function of these cells, which leads to a halt Consumption of glucose and stimulating the process of its formation and glycogenolysis [29]. It was also noted through this study that the use of rosuvastatin caused a significant increase in glucose level when compared with the control group after the end of the experiment for both groups due to effect of rosuvastatin on β-cells and causes decrease in the level of insulin which causes increase in the level of glucose. On the other hand, it causes increase in the level of glucose [30, 31] also indicated that the use of the aqueous extract of senna makki contributes to the return of the sugar level to normal and the reason for this is to restore and improve the insulin situation in the body and increase the consumption of carbohydrates through the activation of the amylase enzyme responsible for the destruction of carbohydrates, which contributes to reduce high blood sugar level, and this is what we found in our current study, and as shown in Table (4)

Conclusion

We conclude from this research that senna makki aqueous extract has preventive and therapeutic antioxidant properties, as evidenced by its decreased the harmful effects of rosuvastatin on the some physiological and biochemical parameters, as well as improvements in the state of oxidative stress, the level of fat in the blood and weight loss.

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Conflict of interest

In this scientific work, there is no conflict of interest.

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