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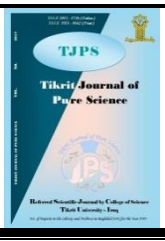

Synthesis of new thioester derivative of aspirin and study its effect on some biochemical parameters in blood serum of rabbits

Zaid Abdalkader Dawood[1] , Firas Shawqi Algburi[2] , Nazar Ahmad Naji[1]

Department of chemistry. College of science. Tikrit University, Tikrit . Iraq

Department of biology. College of science. Tikrit University, Tikrit . Iraq

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Corresponding Author:

Name: Zaid Abdalkader

E-mail:

zaid.abdulqader.dawood.chem@st.tu.edu.iq

dr.firas.shawki@tu.edu.iq

Tel:

ABSTRACT

This presented work was included synthesis of new thioester derivatives by reaction of Aspirin (a non-steroidal anti-inflammatory drugs) (NSAIDs) and Captopril as a carrier which is used as an antihypertensive drug and an inhibitor for angiotensin-converting enzyme (ACE). Aspirin was converted into acid chloride of aspirin then reacted with SH group of captopril to afforded of 1-(3-((2-acetoxybenzoyl)thio)-2-methylpropanoyl)pyrrolidine-2-carboxylic acid and characterized by FT-IR and ^{1}HNMR spectroscopy. The effect of synthesized compound was studied on some biochemical parameters in the blood serum of rabbits. Results of this study indicated: significant increase in the level of total fucose, total protein and globulin. Non- significant increase in the level of albumin, creatinine, glutathione and uric acid, significant decrease in level of Triglycerides and non-significant decrease in the level of Cholesterol, and malondialdehyde.

Introduction

Most of the drugs have undesired properties, therefore many scientists and researchers are trying to enhancing and increasing of drug efficiency through performing some of the modifications[1]. The prodrug is a chemical modification that include adding some of the group which usually calling promoiety with the parent drug to improve its properties. The additive group must be possessing specific advantages such as no toxic, no side effects and deleting easily out the body. The design of prodrug solving of several problems of an original drug such as stability, target specificity and bioavailability[2].

Captopril is one of the drugs that inhibit of ACE enzyme, which is responsible for increasing blood pressure[3]. Thus preventing heart failure and myocardial infarction[4]. also captopril catalyzing to accumulation of bradykinin through inhibition of bradykininase enzyme[5]. Recently, many studies were revealed captopril reduce and slow developing of some cancer types such as prostate cancer, lung tumor[6],[7].

Aspirin or acetyl-salicylic acid is a nonsteroidal anti-inflammatory drug (NSAID), widely used as an antipyretic, analgesic, and anti-inflammatory. The effect of aspirin is summarized by blocking of prostaglandins pathway which are participating in the formation of inflammation and prevents the formation of thromboxane, which prevents the aggregation of blood platelets and thus contributes to the prevention of thrombus formation and increases blood flow in clotting cases[8]. This occurs due to the inhibition of COX enzymes, which are responsible for the conversion of arachidonic acid into prostanoids and thromboxane[9]. However, the majority of today's some NSAIDs are associated with side-effects such as gastrointestinal (GI) ulceration because of the acidity of the carboxyl group [10].

Protein in the plasma is made up of albumin and globulin, the globulin in turn is made up of α1, α2, β1, β2 and γ globulins. Many serum protein are synthesized in the liver , but the blood cells and lymphocyte of the immune system synthesized immunoglobulins and proteins of complement system are synthesized by macrophage as well as hepatic cells[11].

Carbohydrates form one of the major groups of biological macromolecules in living organisms. Many

biological processes, including protein folding, stability, immune response, and receptor activation are regulated by glycosylation. Fucosylation of proteins regulates such processes and is associated with various diseases including autoimmunity and cancer. Fucose is a simple monosaccharide resemble of galactose with replacing of OH group at C6 carbon by hydrogen atom, only L-isomer exist in nature and human body, increasing of fucose level lead to some disease such as immunity disease and inflammations[12] whereas deficient of fucose level causing Leukocyte Adhesion Deficiency type II(LADII)[13].

Glutathione (GSH) is a tripeptide that consist of three amino acids glutamine, glycine and cysteine[14], GSH play a pivotal role as antioxidant agent and scavenging of free radical species consequently prevention of cell damage[15].

Malondialdehyde(MDA) is endogenous product by lipid peroxidation process of membrane poly unsaturated acids and used as a biomarker to increasing of oxidative stress level[16].

Creatinine is a non-protein nitrogenous biomolecule that afforded from the ultimate metabolism of nitrogen through elimination of water molecule from creatine compound and used as indication to kidney disease[17].

Uric acid is a resultant compound through metabolism pathway of purines (guanine and adenine) in liver and act as a significant antioxidant agent by inhibition of lipid peroxidation[18].

Triglycerides (T.G) and cholesterol are biochemical molecules belongs to lipids, when their concentration increase causing multiple disease such as hypertensive, stroke and heart failure therefor researchers are trying to design new organic molecules make to decreasing their levels in blood[19],[20].

Aim of the work: synthesis of a new organic compound by linking of aspirin with captopril then estimate its effect on some significant biochemical parameters that are related to hypertension (TG and cholesterol) and oxidative stress (GSH, MDA, Uric acid)**.**

Materials and methods

All chemicals used in this work were purchased from (Sigma Aldrich, Merck, BDH, BIOLABO) completion of reactions followed up by thin layer chromatography (TLC) using silica gel GF 254(type 60) pre-coated aluminum sheets, Merck (Germany) and visualized by iodine vapor.

IR spectra were recorded on a FT-IR-8400S from SHIMADZO company in KBr pellets at Tikrit university/Iraq. ^{1}HNMR spectra were recorded on Bruker 400MHz by using DMSO-d^{6} at Al Al-Bayt University/ Jordan. Chemical shifts are reported as δ (ppm) relative to tri methyl silane (TMS) as internal reference.

General procedure for the synthesis of 2-(chlorocarbonyl)phenyl acetate hydrochloride:

In 100 mL of round bottom flask 4 g (0.0223mol) of aspirin was dissolved with 4 mL of thionyl chloride, then refluxed in water bath at 70 ^{o}C for 1h, the condenser was removed and heated at 60 ^{o}C for 3 min to removing an excess of thionyl chloride[21], colorless liquid (72%).

General procedure for synthesis of General procedure for synthesis of 1-(3-((2-acetoxybenzoyl)thio)-2-methylpropanoyl)pyrrolidine-2-carboxylic acid:

8.444 gm (0.04 mol) of captopril was dissolved in pyridine and added dropwise with stirring into acid chloride of aspirin in an ice bath. The mixture of reaction left overnight with stirring at room temperature. 100 mL of distilling water was added into the reaction mixture and extracted three times by chloroform (3x100mL) then the organic layer was washed by solution (95:5)(H_2O:HCl) to removing of pyridine remains and extracted again by chloroform(3x100), dried by MgSO4, filtered and the solvent was removed by rotary evaporator. The product was purified by column chromatography, semisolid (41%) R_f= 0.673 (benzene: chloroform) (4:1).

Animals used:

In this study, two groups of domestic rabbits were taken each group contains nine rabbits at the weight (>or = 2Kg), then left for one week in cages at the same conditions. Before 24h from starting the test, the rabbits were kept without food (fastened), but they were allowed free access to water *ad libitum*, under constant temperature 30^{o}C. One group taken of the synthesized compound with dose (35 mg/Kg), DMSO was used as a solvent and another group was used as a control.

Samples collection and preservation:

5 mL of blood was withdrawn by a disposable syringe from the heart of the rabbit, then kept in clean and sterilize plastic tubes, left at room temperature. The blood serum was separated by centrifuge (4000Xg) for 15 min to obtaining of serum free from any remains of red blood cells, then the serum withdrawal by micropipette and stored at (-20 ^{o}C) in the refrigerator until to perform biochemical tests.

Estimation of Total Fucose(TF) level in Blood Serum

This method depends on the direct interaction between concentrated sulfuric acid and serum components, carbohydrates in the serum react with the SH group of the amino acid cysteine and form a colored product that can be measured in two wavelengths (430 and 396) nm. The difference in wavelengths represents the concentration of fucose and is directly proportional to the size of the methyl group present in the solution[22], the concentration of total fucose calculated by the following equation:-

$$\text{Total Fucose. (mg /dL)} = \frac{\text{At (430- 396)}}{\text{Ast (430- 396)}} \text{ standard Conc(10mg /dL)}$$

At= absorbance of sample that bounded with cystien, Ast= absorbance of standard solution that bounded with cystien.

Estimation of Total protein(TP) level in blood serum:

TP level in blood serum can be estimated by reaction of serum sample containing protein with potassium tartrate solution. Copper (Cu^{2+} ions in alkaline medium), which is known as Biuret Reagent to afford a violet-colored complex. The intensity of its absorption depends on the number of peptide bonds present in the protein; the absorption intensity measured at a wavelength (550nm).

Protein + Cu^{2+} + OH^- $\longrightarrow$ violet complex

the concentration of total protien calculated by the following equation:-

$$\text{Total protien Conc. (g /L)} = \frac{\text{(A)sample}}{\text{(A)standard}} \text{ standard Conc(60 g /L)}$$

Estimation of albumin (ALB) level in blood serum:

This method include reaction of albumin with Bromo cresol green in buffer solution at pH= 4.2 to formation a colored complex, the intensity of color represent of albumin concentration. The absorbance of solution measured at 630 nm and the concentration of albumin calculated according to the following equation:

$$\text{Albumin Conc. (g /L)} = \frac{\text{(A)sample}}{\text{(A)standard}} \text{ standard Conc(50 g /L)}$$

Estimation of Globulin(Glu) level in serum:

Globulin was estimated according to the following eqution:

Conc. Globulin = Conc. Total protein – Conc. Albumin

Estimation of GSH level:

GSH level was estimated through reduction of [5,5-dithio bis(2-nitro benzoic acid)](DTNB) by (SH) group of glutathione to the formation of yellow complex and measured at 412 nm[23], the concentration of glutathione calculated according to the following equation:

$$conc.of\ Glutathione\ (\mu mol/L) = \frac{A\ at\ 412\ nm}{Eo \times L} \times 10^6$$

E_o = Extinction Coefficient = 13600 $M^{-1}.cm^{-1}$, L = Light path 1 cm.

Estimation of MDA level: MDA is a final product of lipid peroxidation, MDA level was estimated through the reaction with thiobarbituric in an acidic medium to afford colored yield measured at 532 nm[24] the concentration of malondialdehyde calculated according to the following equation:

$$\text{Conc. of Malondialdehyde } (\mu mol/L) = \frac{Atest - Ablank}{Eo \times L} \times D \times 10^6$$

E_o = Extinction Coefficient = 1.56* 10^5 $M^{-1}.cm^{-1}$, L = Light path 1 cm. D = Dilution factor = 6.7 [A = Absorbance]

Estimation of Creatinine level in Blood Serum:

Creatinine level was estimated by colorimetric method through reaction of creatinine with sodium picrate solution to afford creatinine picrate as a red solution that measured at 490 nm at two time through two minutes and the concentration of creatinine calculated according to the following equation:

$$\text{Creatinine Conc. (mg /dL)} = \frac{(A_2 - A_1)\text{sample}}{(A_2 - A_1)\text{standard}} \text{ standard Conc(2mg /dL)}$$

Estimation of uric acid concentration:

The uric acid concentration was estimated by using colorimetric method through oxidation of uric acid by uricase enzyme to convert it to allantoin, H_2O_2 and CO_2 hydrogen peroxide react with 4-amino anti pyrine and dichlorohydroxyl benzene sulfonate (DHBS) to formation of quinon as a red color solution that measured at 520 nm and the concentration of uric acid calculated according to the following equation:

$$\text{Uric acid. Conc (g/L)} = \frac{\text{(A)sample}}{\text{(A)standard}} \text{ standard Conc(n)}$$

Standard Conc. (n) = 595 µmol / L (100 mg / dL).

Determination of Cholesterol level in serum:

Cholesterol level was estimated by (kits) from BIOLABO company through using enzymetic method that include conversion of cholesterol and esters of cholesterol into Quinoneimine (purple color) that measured at 500nm and the concentration of cholesterol calculated according to the following equation:

$$\text{Cholesterol. Conc (mg / dL)} = \frac{\text{(A)sample}}{\text{(A)standard}} \text{ standard Conc(200 mg/dL)}$$

Determination of T.G level in serum:
Triglycerides level was estimated by (kits) from BIOLABO company through hydrolysis of triglycerides into fatty acids and glycerol, glycerol phosphorylated by ATP and glycerol kinase enzyme to afford of glycerol-3-phosphate which oxidized by glycerol-3-phosphate oxidase into dihydroxyacetone phosphate and H_2O_2, then H_2O_2 react with p-chlorophenol and 4-aminoantipyrine in presence of peroxidase to formation of Quinoneimine as a colored product measuring at 500 nm, and the intensity of color proportional with concentration of triglyceride. the concentration of uric acid calculated according to the following equation:

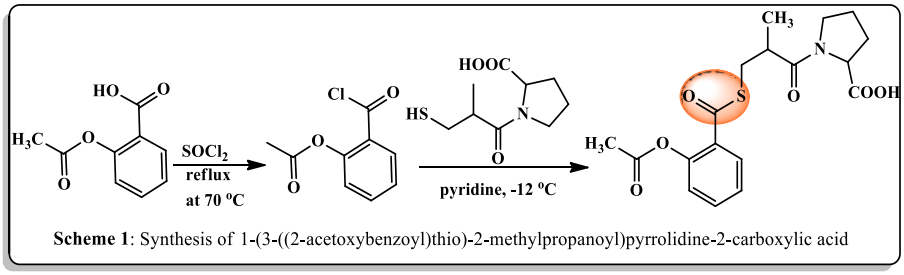
$$\text{Triglycerides. Conc (mg / dL)} = \frac{\text{(A)sample}}{\text{(A)standard}} \text{ standard Conc(200 mg/dL)}$$

Statistical analysis was conducted out by using IBM SPSS Statistics 17 program.

Results and discussion

Organic part:

Aspirin was converted into aspirin chloride via reaction of aspirin with thionyl chloride, then aspirin chloride was linked with captopril through **SH** group to generate thioester functional group as shown in scheme 1 as the following:



Scheme 1: Synthesis of 1-(3-((2-acetoxybenzoyl)thio)-2-methylpropanoyl)pyrrolidine-2-carboxylic acid

The structure of the new synthesized compound was elucidated through available spectral methods, FT-IR spectroscopy fig.(1) was provided the following information: absence of bending vibration frequency of (**S-H**) group at (2594) cm^{-1}, abroad peak was observed at (3500-3200) cm^{-1} indicating to stretching vibration frequency of (**O-H**) of the carboxyl group, the peak at (3070) cm^{-1} indicate to stretching vibration of (**C-H**) aromatic, the peaks at (2975, 2877) cm^{-1} were attributed to (**C-H**) aliphatic, The peaks of stretching vibration frequency of (**C=O**) groups were observed at (1743 - 1639) cm^{-1} and the peak at (754) cm^{-1} attributed to (**C-S**).

^{1}HNMR spectrum of synthesized compound fig.(2) was revealed the presence of broad singlet signal at chemical shift δ =11.17 ppm corresponding to the proton of the carboxyl group, the multiplet signals at range δ =6.9-7.9 ppm attributed to the aromatic protons, the chemical shifts of aliphatic protons labeled in the structure of the synthesized compound in figure(2).

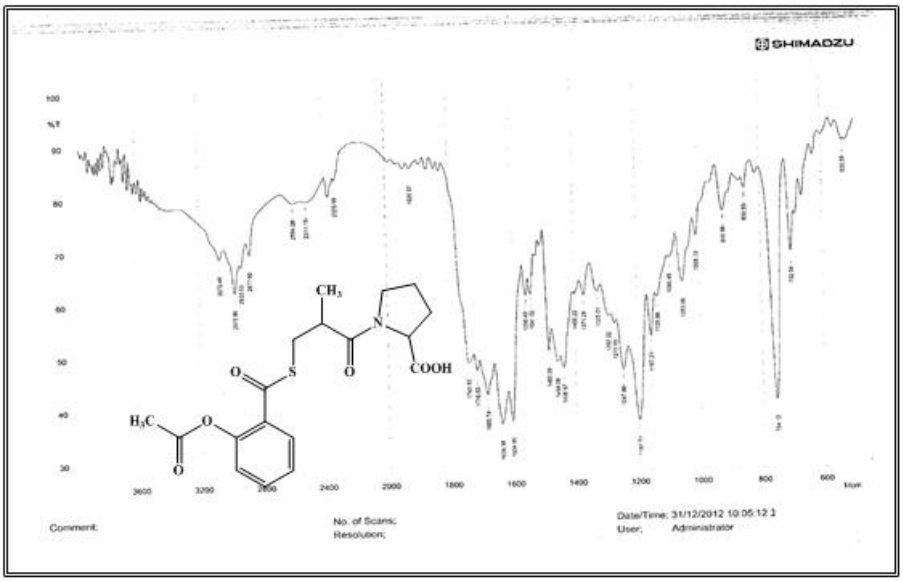


Fig. 1: IR spectrum of synthesized compound

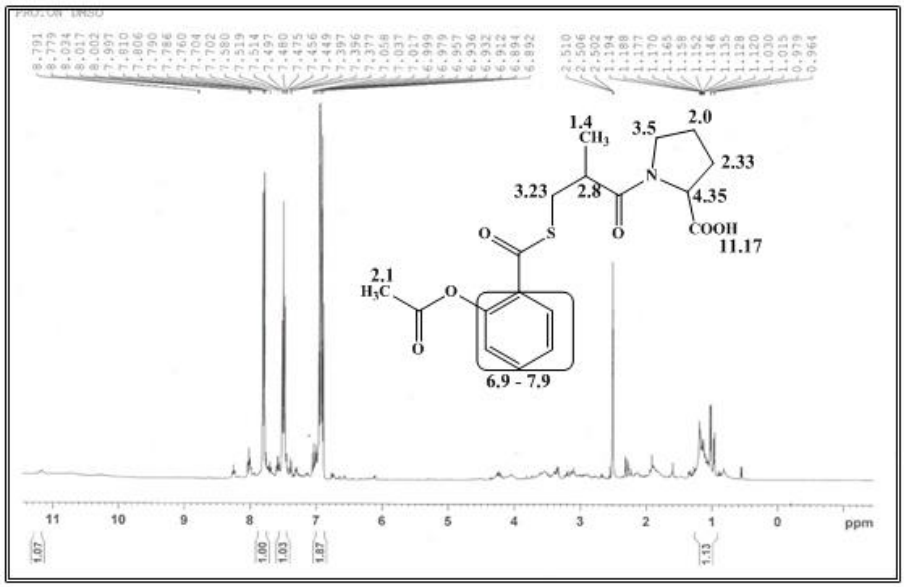


Fig. 2: ^{1}HNMR spectrum of synthesized compound

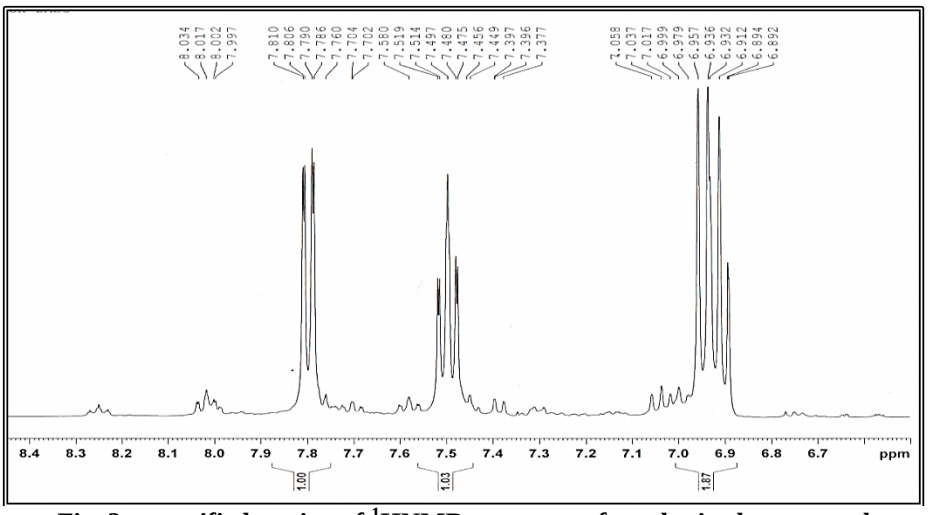


Fig. 3: magnified section of ^{1}HNMR spectrum of synthesized compound

Biochemical part:

This part included study effect of the synthesized compound on the level of some biochemical parameters, which comprised: TF, TP, ALB, Glu, GSH, MDA, Creatinine, Uric acid, Cholesterol and T.G, the obtained results shown in the following table:

Biochemical parameters	**N**	**Biochemical groups (mean±SD)**		**P-value**
		Control	**Test**	
TF (mg/dL)	**9**	3.531±0.687	5.225±2.203	0.028
TP (g/L)	9	74.044±2.275	77.611±2.135	0.662
ALB (g/L)	9	51.165±0.880	53.068±1.788	0.143
Glu (g/L)	9	23.070±2.610	24.287±3.41	0.011
GSH (µmol/L)	9	4.402±1.364	5.908±1.418	0.577
MDA (µmol/L)	9	6.28±2.153	5.108±1.364	0.056
Creatinine (µmol/L)	9	91.275±7.124	116.597±13.487	0.585
Uric acid µmol/L	9	934.798±27.119	950.881±18.065	0.121
Cholesterol mg /dL	9	68.98±3.429	64.178±3.512	0.489
TG (mg /dL)	9	171.266±8.884	148.466±6.130	0.0216

The results obtained in the above table were indicated that:

A significant increase in TF level at a (P<0.05). fucosylation of glycoproteins (the addition of L-fucose at the terminal end of the oligosaccharide chain) is one of the most important features that mediate several specific biologic functions. The reason for the increase in the level of TF in the blood

may be attributed to the increasing activity of fucose transferase enzyme[25],[26] or it could be related to different rates of synthesis or to the post-synthetic selection of the fucosylated glycoforms [27].

Also, there was a significant increase in the concentration of Glu at a P-value equal to 0.011, it's not clear exactly what causes for this elevated in levels.

A non-significant decrease in TP, ALB, MDA, GSH, creatinine, uric acid, and cholesterol levels. These results correspond with I. A. Ibrahim.*et.al*. [28] .

A significant decrease in the TG level by the effect of the synthesized compound at a P-value equal to 0.0216, this decrease in TG level may be attributed to the release of captopril[29] .

Conclusion

The new synthesized compound was prepared in reasonable yield and characterized by FT-IR and ^{1}HNMR, the effect of the synthesized compound was studied on some biochemical parameters in the blood serum of rabbits. Results of this study indicated to: significant increase in the level of total fucose, total protein and globulin. non- significant increase in the level of albumin, creatinine, glutathione and uric acid, significant decrease in level of Triglycerides and non-significant decrease in the level of Cholesterol, and malondialdehyde.

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تحضير مشتق ثايواستر جديد للاسبرين ودراسة تاثيره على بعض المتغيرات الكيموحيوية في مصل دم الارانب

زيد عبدالقادر داود[1] ، فراس شوقي عبدالرزاق[2] ، نزار احمد ناجي[1]

[1]قسم الكيمياء ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق

[2]قسم الكيمياء ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق

الملخص

تضمن هذا البحث تحضير مشتق ثايواستر للاسبرين (مضاد التهابات غير ستيرويدي) والكابتوبريل (دواء مضاد لارتفاع ضغط الدم ومثبط للانزيم المحول للانجيوتينسين) كحامل. حيث تم تحويل الاسبرين الى كلوريد الحامض للاسبرين ومن ثم مفاعلته مع مجموعة SH للكابتوبريل ونتج المركب 1-(3-((2-اسيتوكسي بنزويل)ثايو)-2- مثيل بروبانويل)بايرولدين-2- حامض الكاربوكسيل وتم تشخيصه بواسطة اطياف FT-IR و ^{1}H-NMR. تم دراسة تاثير المركب المحضر على بعض المتغيرات الكيموحيوية في مصل دم الارانب ودلت النتائج على: ارتفاع معنوى في مستوى كل من الفيوكوز الكلي، البروتين الكلي والكلوبيولين. زيادة غير معنوية في مستوى الالبومين، الكرياتنين،الكلوتاثايون وحامض اليوريك. انخفاض معنوي في مستوى الكليسيريدات الثلاثية وانخفاض غير معنوي في مستوى كل من الكوليستيرول والمالون ثنائي الالديهايد.