EFFECT OF PARTIAL PURIFIED LOVASTATIN FROM *ASPERGILLUS TERREUS* A50 ON LIPID PROFILE AND LIVER ENZYMES *IN VIVO*

A.J. Al-Sa'ady[1] G. M. Aziz[2] M. J. Al-Obaidi[3]
Assist. Prof. Prof. Assist. Prof.
[1,2] Dept. Biotechnology Coll. Sci. University of Baghdad
[3] Tropical-Biological Research Unit Coll. Sci. University of Baghdad
E-mail: lafta@sc.uobaghdad.edu.iq

ABSTRACT

This study was designed to determine the effect of partial purified lovastatin on the lipid profile and liver functions in rabbits. The rabbits were divided into six groups, each group containing four rabbits, and the lipid profile and liver functions were checked at zero, 30, 60, and 90 days. The parameters of the cholesterol, high-density lipoprotein (HDL), triglycerides (TG), low-density lipoprotein (LDL), very- low-density lipoprotein (VLDL), blood bilirubin (BB), and liver enzymes (ALP, ALT and AST) were determined separately. Determination of parameters was made before treatment with any medication and after treatment with cholesterol (4 g/kilo/day), standard lovastatin (0.4 mg/kilo/day), cholesterol plus standard lovastatin 4g+0.4mg/kilo/day), partial purified lovastatin (0.4 mg/kilo/day), and cholesterol plus partial purified lovastatin (4g+0.4mg/kilo/day). The findings showed that partial purified lovastatin have influence on lipid profile and liver function with significant differences (positive effect) (P≤0.05) in the mean of cholesterol, TG, HDL-C, LDL-C, VLDL-C, ALP, ALT, AST and BB levels in compression with the control group, but some of them were higher than the normal value. In addition no significant differences (P≥0.05) in lipid profile and liver function enzymes activity if treatment with standard or partially purified lovastatin.

Key words: lovastatin, lipid profile, liver function, in-vivo.

مجلة العلوم الزراعية العراقية -2022 :53(5):1003-1010 الساعدي وأخرون

تأثير اللوفستاتين المنقى جزئيا من فطر *Aspergillus terreus* A50 على نسق الدهون و وظائف الكبد في الجسم الحي

علي جبار الساعدي[1] غازي منعم عزيز[2] محمد جابر العبيدي[3]
أستاذ مساعد أستاذ أستاذ مساعد
[2،1] قسم التقنيات الاحيائية – كلية العلوم – جامعة بغداد
[3] وحدة الابحاث البايولوجية للمناطق الحارة–كلية العلوم–جامعة بغداد

المستخلص

صممت هذه الدراسة لقياس تأثير اللوفستاتين المنقى جزئيا على مستوى الدهون ووظائف الكبد في الارانب. قسمت الارانب الى ست مجاميع كل منها يحوي اربعة افراد وتم قياس مؤشرات مستوى الدهون ووظائف الكبد في الاوقات (صفر، 30، 60، 90 يوم). شمل قياس مؤشرات مستوى الدهون كل من الكوليسترول والبروتين الدهني عالي الكثافة HDL و الدهون الثلاثية TG والبروتين الدهني واطئ الكثافة LDL والبروتين الدهني الواطئ جدا للكثافة VLDL والبلروبين BB وانزيمات الكبد الثلاث AST , ALT , ALP بشكل منفصل. تم قياس المؤشرات قبل المعاملة بأي دواء و بعد المعاملة بالكولسترول(4 غم/كغم/ يوم)، ,اللوفستاتين القياسي (0.4 ملغم/كغم/ يوم)، والكولسترول مع اللوفستاتين القياسي (4غم+0.4 ملغم/كغم/يوم)، واللوفستاتين المنقى جزئيا (0.4 ملغم/كغم/ يوم) والكولسترول مع اللوفستاتين المنقى جزئياَ (4غم+0.4 ملغم/كغم/يوم). أظهرت النتائج بأن اللوفاستاتين المنقى جزئياً له تأثير على مستوى الدهون و وظائف الكبد مع فروق معنوية (P≤0.05) في معدلات الدهون الثلاثية والبروتينات الدهنية عالية الكثافة وواطئة الكثافة والواطئة جدا للكثافة والبلروبين وانزيمات الكبد الثلاثة بالمقارنة مع مجموعة السيطرة ولكن بعضها كان اعلى من الحد الطبيعي . بالاضافة لم تكن هناك فروق معنوية (P≥0.05) في مؤشرات مستوى الدهون ووظائف الكبد عند المقارنة بين اللوفستاتين المنقى جزئيا واللوفستاتين القياسي.

الكلمات المفتاحية: لوفستاتين، مستوى الدهون، وظائف الكبد، الجسم الحي.

Received:15/3/2021, Accepted:16/6/2021

INTRODUCTION

Lovastatin is a polyketide component that is produced during its secondary metabolism by certain fungi (17). Lovastatin, also recognized as inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), also known as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitors, are a class of lipid-lowering medications that reduce illness and mortality in those who are at high risk of cardiovascular disease (13). Whereas the statins act as competitive inhibitors for HMG-CoA reductase, a rate constraining advances of cholesterol biosynthesis (1,9). Statins inhibit the change of HMG-CoA to mevalonic acid in the mevalonate pathway. In this metabolic pathway, mevalonate is changed over into sterol isoprenoids, various hydrophobic atoms and non-sterol isoprenoids low-density lipoprotein (LDL) bearers of cholesterol assume a key significant role in the advancement of atherosclerosis and coronary heart illness by means of the instruments portrayed by the hypothesis of lipid (12). Lovastatin is viable in bringing down LDL cholesterol as are generally utilized for essential counteraction in individuals at high danger of cardiovascular disease, just as in optional avoidance for the individuals who have created cardiovascular illness (8). Statin has various applications. The effect of statins on the prevention morbidity and mortality of various infectious diseases has been examined in many studies (4,18). Lovastatin effectively improves endothelial activity, preserves plaque stability, adjusts inflammatory responses, and prevents the production of thrombus with which all kinds of artery- can be cured, and it has been proposed that the consequence of lipid core shrinkage of the atherosclerotic plaque prevents plaque rupture that would otherwise cause intramural haemorrhage and additional (11). Clinical studies showed that lovastatin has the ability to reduce morbidity and mortality rates in multiple sclerosis patients (14,15). Also, decreases inflammatory response and cytokine activation of the superfamily GTPases Ras thereby helping to treat kidney disorders. Exact mechanism of action is not yet understood, but it helps to prevent kidney damage which is particularly associated with glomerulonephritis (2). This study is the first in Iraq to provide important local alternatives used in medical treatment. The aim of this study to determine the effect of partial purified lovastatin from *A.terreus* A50 on some biomarkers of lipid profile and liver functions *in-vivo*.

MATERIAIS AND METHODS

Experimental animals: Twenty-four adult male rabbits with weight of 1400-1800gm were obtained from Al-Nahrain University Biotechnology Research Center, Baghdad, Iraq. The animals were acclimated to laboratory conditions for two weeks before experimentation. All rabbits were fed with a standard pellet diet and water. Care and use of animals were conducted under supervision of the Biotechnology department, college of science, Baghdad University, Iraq.

Experimental design

In this work the animals were divided into six main groups and each group contain four rabbits, after two weeks of acclimatization. The rabbits earned standard diet in group 1 and without any medication. For group 2, the rabbits supplemented orally for 3-month diet with 4 g/kilo/day of cholesterol. In group 3, the rabbits orally supplemented the diet with standard lovastatin for 3 months at a dosage of 0.4 mg/kilo/day. For group 4, the rabbits for 3 months orally supplemented the diet with partial purified lovastatin at a dosage of 0.4 mg/kilo/day. In group 5, the rabbits supplemented orally for 3 months diets with 4 g/kilo/day of cholesterol and standard lovastatin at a dosage of 0.4 mg/ kilo/day. In group 6, the rabbits supplemented orally for 3 months with 4 g/kilo/day of cholesterol and partial purified lovastatin at a dosage of 0.4 mg/kilo/day (3,7)

Serum collection

Four blood samples were collected from each rabbit in each group (from the ear of the rabbit) using centrifuge tube at zero time, after 30, 60, and 90 days through the experimental period (3 months). Then collection of blood samples from the animals (from the ears of the rabbit) use centrifuge tubes. Serum was isolated for 10 min by centrifugation at 5000rpm. from coagulant blood, and then rapidly frozen for further biochemical analysis at 20 ºC.

Biochemical analyses

The tests that performed in this work were, Aspartate transaminase (AST), Alkaline phosphatase (ALP), alanine transaminase (ALT), and bilirubin, as well as, lipids profile including; cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and very low-density lipoprotein cholesterol (VLDL-C). These tests were estimated by using kits from Linear, Spanish as followed.

Statistical analysis

All results acquired in this analysis were analysed using a one-way ANOVA test and post comparison was performed with Descriptive statistics, Non parametric analysis, Mann Whitney for independent samples, and Duncan test. The values were measured as mean ±SD and P≤0.05 values were considered statistically relevant (16,19).

RESUITS AND DISCUSSION

Effect of lovastatin on lipid profile and liver enzymes (at zero time, after 30, 60, and 90 days): In this work all animals in the experiment were clinically healthy, and there were no adverse clinical results. Each sample examined with several tests, before treatment with lovastatin and other treatments. The results in zero time showed that the Mean ±SD of cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, ALP, ALT, AST and bilirubin test for 24 normal rabbits were 66.94±2.12 mg/dl, 37.64±1.34 mg/dl, 30.69±2.25 mg/dl, 28.73±3.68 mg/dl, 7.53±0.27 mg/dl, 18.12±0.61 U/l, 51.27±2.66 U/l, 28.13±1.76 U/l and 0.23±0.097 mg/dl, respectively (Table 1). The findings of statistical analysis showed that there were no significant differences between the various tests of rabbit groups in zero time (p≤0.05) (Table 2).

Table1. The means of various tests for rabbit males at zero time.

Test	N	Mean	Std. Deviation	Minimum	Maximum
Cholesterol (mg/dl)	24	66.94	2.12	61.73	70.47
Triglyceride (mg/dl)	24	37.64	1.34	33.81	39.76
Bilirubin (mg/dl)	24	0.23	0.097	0.03	0.47
HDL-C (mg/dl)	24	30.69	2.25	25.87	36.38
LDL-C (mg/dl)	24	28.73	3.68	20.87	34.60
VLDL-C (mg/dl)	24	7.53	0.27	6.76	7.95
ALP (U/ml)	24	18.12	0.61	16.13	18.82
ALT (U/ml)	24	51.27	2.66	44.60	56.80
AST (U/ml)	24	28.13	1.76	24.50	32.60

Table2. Statistical analysis for the different zero-time tests

Groups (N=4)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Cholesterol (mg/dl)	67.65±2.35	67.56±0.51	68.40±1.52	66.18±1.94	64.90±3.33	66.94±1.05
Triglyceride (mg/dl)	38.53±1.03	37.46±1.84	37.76±0.42	37.18±0.60	37.55±2.61	37.34±0.67
Bilirubin (mg/dl)	0.23±0.09	0.12±0.06	0.31±0.12	0.18±0.06	0.28±0.06	0.24±0.07
HDL (mg/dl)	31.41±3.9	29.69±2.71	31.01±1.31	29.62±1.98	32.15±1.21	30.23±1.58
LDL (mg/dl)	28.53±6.01	30.38±2.19	29.84±2.57	29.12±3.73	25.24±3.87	29.25±2.25
VLDL (mg/dl)	7.71±0.21	7.50±0.37	7.60±0.08	7.44±0.12	7.51±0.52	7.47±0.14
ALP (U/ml)	18.31±0.34	17.86±0.57	18.15±0.6	18.41±0.40	17.54±0.99	18.42±0.23
ALT (U/ml)	51.93±1.23	50.13±3.93	51.93±3.23	51.35±4.02	51.28±2.23	50.98±1.67
AST (U/ml)	29.09±1.02	26.98±1.81	27.80±1.86	28.95±2.56	28.08±1.04	27.93±2.1

Group (G) 1= control ; G2= with treatmentcholesterol; G3 with treatment standard lovastatin ; G4= treatment with partial purified lovastatin ; G5= with treatment cholesterol and standard lovastatin ; G6= with treatment cholesterol and partial purified lovastatin

After 30 days of treatment, the data in Table (3) for the administration of oral partial purified lovastatin shows significant changes (p≤0.05) in lipid profile and AST tests compared to control group, suggesting its effect at the dose applied. Although oral standard lovastatin has a significant effect (p≤0.05) in lipid profile, ALP and AST tests compared to control group after 30 days of treatment. In the Table (3) the results of the group treatment with partial purified lovastatin plus cholesterol was produced significant differences in lipid profile and liver enzymes more effect than standard lovastatin plus cholesterol, which showed significant change in liver enzymes, cholesterol and LDL-C tests, in comparison with control after 30 days of treatments, and some of the significant differences were within the normal values of testes. The treatment with lovastatin caused a positively change in most parameters if compared to hypercholesterolemia rabbits group. Additionally, the hypercholesterolemic

rabbits (cholesterol treatment) showed a significant increase in lipid profile and in the activity of serum AST and ALT enzymes and LDL. The outcomes reviled to that standard and partial purified lovastatin were reduced the cholesterol, triglyceride, LDL-C, VLDL-C levels and increasing of HDL-C level in rabbits after one month of treatment compared with control group. In addition, the data showed no significant differences between using standard or partial purified lovastatin on the most tests in Table (3). The lipophilic lovastatin diminishes cholesterol synthesis and is a safe and bible treatment for the avoidance of cardiovascular illnesses. Along these lines, lovastatin is a powerful hypercholesterolemic drug used for bringing down blood cholesterol (22).

Table 3. Effect of standard and partial purified lovastatin on lipid profile and liver enzymes in rabbits serum after 30 days of different treatments

Groups (N=4)	G1		G2		G3	
	Mean ±SD	p-value	Mean ±SD	p-value	Mean ±SD	p-value
Cholesterol (mg/dl)	(66.65±1.23) a	0.205	(83.05±0.46) c	0.000▲	(55.85±1.15) e	0.000▼ *
Triglyceride (mg/dl)	(37.87±0.56) a	0.092	(45.24±0.3) c	0.003▲*	(32.16±0.56) b	0.001▼ *
Bilirubin (mg/dl)	(0.17±0.03) a	0.149	(0.130±0.01) a	0.67	(0.34±0.07) b	0.395
HDL (mg/dl)	(29.61±0.9) a	0.327	(28.15±0.32) a	0.343	(33.88±0.42) dc	0.037▲
LDL (mg/dl)	(29.22±1.73) a	0.771	(45.85±0.67) c	0.001▲ *	(15.54±0.69) d	0.001▼ *
VLDL (mg/dl)	(7.57±0.11) a	0.092	(9.05±0.06) c	0.003▲ *	(6.43±0.11) b	0.001▼ *
ALP (U/ml)	(18.25±0.28) a	0.547	(18.58±0.23) a	0.154	(19.62±0.5) bd	0.002▲ *
ALT (U/ml)	(51.35±0.65) a	0.144	(65.86±1.16) c	0.003▲	(55.78±0.89) b	0.087
AST (U/ml)	(28.84±0.56) a	0.523	(33.84±1.04) c	0.009▲ *	(31.70±0.91) b	0.015▲ *
Groups (N=4)	G4		G5		G6	
Cholesterol (mg/dl)	(57.78±0.44) b	0.004▼ *	(68.99±1.1) f	0.043▲ *	(71.33±0.34) d	0.003▲
Triglyceride (mg/dl)	(33.48±0.26) b	0.002▼ *	(39.02±2.2) a	0.092	(38.68±0.91) a	0.013▲ *
Bilirubin (mg/dl)	(0.20±0.04) a	0.206	(0.345±0.07) b	0.512	(0.210±0.03) a	0.379
HDL (mg/dl)	(33.02±1.34) bc	0.003▲	(31.92±1.18) b	0.383	(32.24±1.37) b	0.008▲
LDL (mg/dl)	(18.06±1.43) b	0.003▼ *	(29.27±2.01) a	0.038▲ *	(31.35±1.6) a	0.031▲ *
VLDL (mg/dl)	(6.70±0.05) b	0.002▼ *	(7.80±0.44) a	0.092	(7.74±0.18) a	0.013▲ *
ALP (U/ml)	(19.51±0.3) bc	0.006▲*	(19.33±0.35) cd	0.020▲ *	(19.30±0.36) b	0.021▲ *
ALT (U/ml)	(53.81±2.06) b	0.088	(54.69±0.55) b	0.041▲ *	(55.40±0.58) b	0.004▲ *
AST (U/ml)	(31.80±0.98) b	0.111	(30.23±0.85) d	0.003▲ *	(31.78±1.09) b	0.021▲ *

Group (G) 1= control ; G2= with treatmentcholesterol; G3 with treatment standard lovastatin ; G4= treatment with partial purified lovastatin ; G5= with treatment cholesterol and standard lovastatin ; G6= with treatment cholesterol and partial purified lovastatin; Different small letter(s) denote significant differences between groups; p-value refer to effect of treatment on tests; p<0.05= significant differences; (*) within the normal value; (▲) increase; (▼) decrease

The effect of standard and partial purified lovastatin on blood lipid profile and liver enzymes in rabbits are shown in table (4) after 60 days of treatment. Data in Table 4 illustrate the mean values of various tests in the control group and five treated groups along the experimental time. After 60 days of treatment a significant ($p \leq 0.05$) elevation in cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, ALP, ALT, AST and bilirubin test were observed in animal received partial purified lovastatin (0.4 mg/kilo/day). At the same period of the experiment, oral administration of standard lovastatin in group 3 caused a significant ($p \leq 0.05$) differences in the cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, ALP, ALT and AST level in compared to control group. After 60 days of experiment there was also a significant ($p \leq 0.05$) change in all tests levels except bilirubin when use standard and partial purified lovastatin plus cholesterol as compared to control. From these data can be deduce that the treatment with standard and partial purified lovastatin were effect on lipid profile as positively effect. In addition, the data were showed that there are significant differences among groups which treatment with dosage of standard and partial purified lovastatin on the most tests in Table 4, as well as could observe that standard lovastatin was more effect (significant effects) than partial purified lovastatin on most the tests. Standard and partial purified lovastatin plus cholesterol recorded a decrease ($P \leq 0.05$) in lipid profile in rabbit serum and increase ($P \leq 0.05$) of HDL levels compared to group that treated with only cholesterol for 60 days of treatment. The findings revealed that used of standard and partial purified lovastatin no cause liver

damage because they effect on the liver enzymes and bilirubin within the range values.

Table 4. Effect of standard and partial purified lovastatin on lipid profile and liver enzymes in rabbits serum after 60 days of different treatments

Groups (N=4)	G1		G2		G3	
	Mean ±SD	p-value	Mean ±SD	p-value	Mean ±SD	p-value
Cholesterol (mg/dl)	(66.65±1.23) a	0.205	(92.88±0.56) c	0.000▲	(47.85±0.74) e	0.000▼*
Triglyceride (mg/dl)	(37.88±0.56) a	0.092	(55.87±0.72) c	0.001▲	(25.10±0.46) e	0.000▼
Bilirubin (mg/dl)	(0.17±0.03) a	0.149	(0.17±0.01) a	0.291	(0.34±0.07) c	0.395
HDL (mg/dl)	(29.61±0.89) a	0.327	(22.16±0.59) c	0.008▼*	(39.36±0.11) e	0.001▲
LDL (mg/dl)	(29.47±1.93) a	0.681	(59.55±0.5) c	0.000▲	(3.47±0.63) e	0.000▼
VLDL (mg/dl)	(7.58±0.11) a	0.092	(11.17±0.14) c	0.001▲	(5.02±0.09) e	0.000▼
ALP (U/ml)	(18.25±0.27) a	0.547	(22.18±0.51) c	0.003▲*	(19.68±0.6) b	0.001▲*
ALT (U/ml)	(51.35±0.65) a	0.144	(81.32±0.53) c	0.000▲	(60.54±0.48) d	0.013▲*
AST (U/ml)	(28.84±0.56) a	0.523	(46.10±0.28) c	0.000▲*	(38.91±0.6) d	0.001▲*
Groups (N=4)	G4		G5		G6	
Cholesterol (mg/dl)	(50.19±0.34) b	0.000▼*	(90.32±0.44) f	0.001▲	(78.00±0.51) d	0.000▲*
Triglyceride (mg/dl)	(27.87±0.53) b	0.000▼	(53.03±0.46) f	0.002▲	(42.48±0.69) d	0.000▲*
Bilirubin (mg/dl)	(0.44±0.06) b	0.024▲*	(0.32±0.06) c	0.531	(0.31±0.07) c	0.187
HDL (mg/dl)	(37.50±0.55) b	0.004▲	(23.91±0.38) f	0.001▼*	(28.73±0.36) d	0.151▼*
LDL (mg/dl)	(7.12±0.95) b	0.001▼*	(55.80±0.75) f	0.001▲	(40.78±0.58) d	0.001▲*
VLDL (mg/dl)	(5.57±0.11) b	0.000▼	(10.61±0.09) f	0.002▲	(8.50±0.14) d	0.000▲*
ALP (U/ml)	(19.85±0.12) b	0.003▲*	(22.18±0.51) c	0.001▲*	(20.58±0.25) d	0.001▲*
ALT (U/ml)	(58.99±0.43) b	0.031▲ *	(56.22±0.53) e	0.000▲*	(60.54±0.48) d	0.003▲*
AST (U/ml)	(36.66±0.36) b	0.010▲*	(47.87±0.48) e	0.000▲*	(39.42±0.28) d	0.002▲*

Group (G) 1= control ; G2= with treatmentcholesterol; G3 with treatment standard lovastatin ; G4= treatment with partial purified lovastatin ; G5= with treatment cholesterol and standard lovastatin ; G6= with treatment cholesterol and partial purified lovastatin; Different small letter(s) denote significant differences between groups; p-value refer to effect of treatment on tests; p<0.05= significant differences; (*) within the normal value; (▲) increase; (▼) decrease

As shown in table (5) after 90 days of treatment, serum cholesterol levels, triglyceride, HDL-C, LDL-C, VLDL-C, ALP, ALT, AST and bilirubin were significantly changed (P≤ 0.05) with standard and partial purified lovastatin treated groups as compared to the control group. Treatments by standard and partial purified lovastatin altered the ALP, ALT, AST, and bilirubin levels and keep they're within the normal values as compared to the control group. While they recorded a decrease (P≤ 0.05) of lipid profile in serum and increase (P≤ 0.05) of HDL-C levels compared to control group of rabbits after 90 days of treatment. Standard and partial purified lovastatin plus cholesterol recorded a decrease (P≤ 0.05) of lipid profile in serum and increase (P≤ 0.05) of HDL-C levels compared to group that treated with only cholesterol. The outcomes in table (5), demonstrated that the treatment with partial purified lovastatin were affects to reduce cholesterol, triglyceride, LDL-C and VLDL-C as significant differences (P≤ 0.05), increase (P≤ 0.05) HDL-C, and significant change of ALP, ALT, AST enzymes, as well as bilirubin level with keep their (liver functions) within the normal value. From these data can conclude that the partial purified lovastatin does not affect the liver and not cause any damage. The results of group that treatment only with cholesterol revealed that there was a significant increase in serum cholesterol, triglyceride, LDL-C, VLDL-C, ALP, ALT, AST and bilirubin (P≤0.05) in compared to control and other treated groups, while HDL-C level shows significant decrease in each period. Also, there were no significant differences (P≤0.05) in serum lipid profile and liver functional enzymes activity if treatment with standard or partial purified lovastatin as compared with one another. In addition, the control group was not differed (no significant differences) in each period and remained constant.

Table 5. Effect of standard and partial purified lovastatin on lipid profile and liver enzymes in rabbits serum after 90 days of different treatments

Groups (N=4)	G1		G2		G3	
	Mean ±SD	p-value	Mean ±SD	p-value	Mean ±SD	p-value
Cholesterol (mg/dl)	(67.63±0.54) a	0.983	(105.36±1) c	0.000▲	(53.61±1.08) b	0.000▼*
Triglyceride (mg/dl)	(37.87±0.56) a	0.092	(68.14±0.6) c	0.000▲	(20.68±0.95) b	0.000▼*
Bilirubin (mg/dl)	(0.168±0.03) a	0.149	(0.30±0.09) a	0.029▲*	(0.73±0.07) b	0.008▲*
HDL (mg/dl)	(29.61±0.9) a	0.327	(9.66±0.5) c	0.001▼	(44.85±1.14) e	0.001▲
LDL (mg/dl)	(30.45±1.19) a	0.522	(82.07±1.4) c	0.000▲	(4.62±0.55) b	0.000▼
VLDL (mg/dl)	(7.57±0.11) a	0.092	(13.63±0.12) c	0.000▲	(4.14±0.19) b	0.000▼
ALP (U/ml)	(18.25±0.28) a	0.547	(27.46±0.38) c	0.000▲	(22.55±0.63) e	0.000▲*
ALT (U/ml)	(51.35±0.65) a	0.144	(104.28±1.12) c	0.000▲	(60.30±0.97) b	0.002▲*
AST (U/ml)	(28.84±0.56) a	0.523	(57.33±0.38) c	0.000▲	(44.90±1.07) e	0.000▲*

Groups (N=4)	G4		G5		G6	
Cholesterol (mg/dl)	(53.23±0.21) b	0.001▼*	(79.37±1.54) e	0.008▲*	(84.15±0.57) d	0.000▲
Triglyceride (mg/dl)	(21.42±0.44) b	0.000▼*	(46.64±0.97) e	0.012▲*	(49.43±0.38) d	0.000▲*
Bilirubin (mg/dl)	(0.78±0.09) b	0.002▲*	(0.76±0.09) b	0.002▲*	(0.74±0.17) b	0.024▲*
HDL (mg/dl)	(43.22±0.46) b	0.001▲	(28.36±0.65) ad	0.017▼*	(28.49±0.1) d	0.110▼*
LDL (mg/dl)	(5.73±0.48) b	0.001▼	(40.68±1.58) e	0.009▲*	(45.78±0.52) d	0.001▲*
VLDL (mg/dl)	(4.28±0.09) b	0.000▼	(9.33±0.19) e	0.012▲*	(9.89±0.08) d	0.001▲*
ALP (U/ml)	(20.32±0.28) b	0.001▲*	(22.47±0.68) e	0.000▲*	(21.47±0.72) d	0.007▲*
ALT (U/ml)	(61.13±0.5) b	0.003▲*	(91.92±1.15) e	0.000▲	(66.56±1.14) d	0.000▲
AST (U/ml)	(40.82±0.5) b	0.003▲*	(48.91±0.46) f	0.000▲*	(46.18±1.6) d	0.001▲*

Group (G) 1= control ; G2= with treatmentcholesterol; G3 with treatment standard lovastatin ; G4= treatment with partial purified lovastatin ; G5= with treatment cholesterol and standard lovastatin ; G6= with treatment cholesterol and partial purified lovastatin; Different small letter(s) denote significant differences between groups; p-value refer to effect of treatment on tests; p<0.05= significant differences; (*) within the normal value; (▲) increase; (▼) decrease

Lovastatin is 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor, whereas the lovastatin act as competitive inhibitors for HMG-CoA reductase, a rate constraining advance of cholesterol biosynthesis. Lovastatin hinder the change of HMG-CoA to mevalonic acid in the mevalonate pathway, lead to reducing lipid levels (1,17). Serum total bilirubin concentrations have been shown to be inversely associated with the risk for cardiovascular disease (CVD). The explanation for this association is not fully understood. In contrast, bilirubin was for a long time regarded as cytotoxic, in particular for its role in neonatal jaundice. It is only since the end of the 1980s that a physiological role for bilirubin functioning has emerged as a potent antioxidant. In fact, *in vitro* evidence suggests that LDL-C can be protected from oxidation by bilirubin. Therefore, low bilirubin concentrations could be a reflection of a heightened oxidative state and increased consumption of bilirubin. Furthermore, bilirubin has been shown to have anti-inflammatory properties. However, these results point to potential beneficial effects of bilirubin toward the chronic inflammatory state currently associate with atherosclerosis (12). Mouafi *et.al.* (12) demonstrated that lovastatin had a significant change ($P \leq 0.05$) in total lipid serum (TL), triglycerides (TG), total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C) low density lipoprotein cholesterol (LDL-C), and phospholipids (PL) as well as increased of the high-density lipoprotein cholesterol (HDL-C), in hypercholesterolemic rats supplemented with 0.4% cholesterol for three months. On the other hand, lovastatin treatment to hypercholesterolemic rats enhanced lipid profile in hepatic tissues, plus lovastatin treatment increased hepatic enzyme levels AST and ALT compared to hypercholesterolemic rats. Kusmana *et.al.* (8) found that lovastatin from *Aspergillus flavus* was decreased total cholesterol and triglycerides content. It was also proposed that LDL-C content reduced and high-density lipoprotein HDL levels remain naturalistic, whereas HDL-C will frustrate atherosclerotic disease as it acts as a carrier of excess

cholesterol from cells to the liver. Hamad and Mahmood (6), found that in a number of participants taking lovastatin or simvastatin therapy, there was a slight elevation of ALT, AST and ALP behaviours and concentrations of bilirubin above the upper normal limit values. A significant elevation in the simvastatin group of ALT and bilirubin compared to the control group and a significant elevation in the lovastatin group of ALT, AST and bilirubin compared to the control group. Patient stratification by age, duration of treatment and dosage showed a good correlation between some of the hepatic parameters and age, treatment duration and dose, although some of these elevations were not statistically significant. Garrett, *et.al*. (5), indicated that lovastatin therapy was associated with a mild effect on the liver and the effect was related to age, length of therapy and dose variables. Periodic monitoring of biochemical hepatic parameters through lovastatin and simvastatin therapy may be of benefit for detecting any noticeable elevation of these parameters. Taleb *et.al*. (21), they clinically examined the total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), blood bilirubin (total and direct), and liver enzyme tests (ALT and AST), in patients treated with atorvastatin (10-40 mg/day), before and after treatment for 3 and 6 months. Their findings showed a significant increase ($P \leq 0.05$) in mean of ALT, AST, total bilirubin, and direct bilirubin levels after 3 months, but they were higher than the normal value with insignificant relationship after 3 months. Taghadosi *et.al*. (20) demonstrated that lovastatin could reduce cholesterol, TG, LDL-C and increase HDL-C significantly whereas exercise revealed significant effect only on LDL-C. In addition, studies done by other researchers show that lovastatin 20 mg /day for 10 weeks reduces TG as much as 10 %. There is a 10 % reduction in LDL-C and 15 % increase in HDL-C with exercise (6). In a study in US, total cholesterol was reduced by 14-28 % due to lovastatin (16). Maji *et.al*. (10), state that the statins frequently increase hepatic transaminase rates asymptomatically but are not associated with hepatotoxicity. Statins are safe and well-tolerated like rosuvastatin, lovastatin, etc. The benefits of extensive use of statin in lowering cardiovascular risk greatly outweigh the risks involved (12).

REFERENCES

1. Alenghat, F.J. and A.M. Davis, 2019. Management of blood cholesterol. Jama. 321 (8): 800

2. Al-Sa'ady, A., and G. Aziz, 2021. Immobilization and application of partial purified lovastatin produced from local isolate *Aspergillus terreus* A50 using solid state fermentation. Iraqi J. of Agricultural Sci, 52(2): 377-391

3. Buemi, M., M. Senatore, F. Corica, C. Aloisi, A. Romeo, E. Cavallaro, F. Floccari, D. Tramontana, and N. Frisina, 2002. Statins and progressive renal disease. Medicinal Research Reviews. 22: 76-84

4. EL-Wakf, M.A., H.A. Ibrahim, H.A. Hassan, H.M. Serag and H.S. Gumaih, 2010. Favorable alteration of cardiovascular disorders with virgin olive oil compared to refined olive oil in atherosclerotic male rats. J. Egypt. Ger. Soc. Zool. 61(A): 25-47.

5. Garrett, I.R., G.E. Gutierrez, G. Rossini, J. Nyman, B. McCluskey, A. Flores, and G.R. Mundy 2007. Locally delivered lovastatin nanoparticles enhance fracture healing in rats. Journal of Orthopaedic Research. 25: 1351-1357

6. Hamad, Z.S. and I.H. Mahmood 2007. Comparative effects of lovastatin and simvastatin on liver function tests in hyperlipidaemia plants. The Medical Journal of Basrah University. 25(1): 21-26

7. Houmard, J.A., N.J. Bruno, R.K. Bruner, M.R. McCammon, R.G Israel and H.A. Barakat, 1994. Effects of exercise training on the chemical composition of plasma LDL. Arteriosclerosis, Thrombosis, and Vascular Biology. 14: 325–330

8. Kusmana, D., Y. Raflianti, and W. Mangunwardoyo, 2012. The effect of lovastatin produced from *Aspergillus flavus* UICC 360 on decreasing cholesterol level in blood of rattusnovergicus L.Sprague dawley strain. International Journal of Science and Research. 2(3): 1-5.

9. Lewington, S., G. Whitlock, R. Clarke, P. Sherliker, J. Emberson, J. Halsey, N. Qizilbash, R. Peto, and R. Collins, 2007.

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 370 (9602): 1829–39.

10. Maji, D., S. Shaikh, D. Solanki, and K. Gaurav, 2016. Safety of statins. Indian Journal of Endocrinology and Metabolism. 17(4): 636-647.

11. Maryam, H., S. Maqsood, A. Jabbar, and A. Ali, 2017. Production of lovastatin from fungal sources and its medical applications. European Journal of Pharmaceutical and Medical Research. 4(6): 148-158

12. Mouafi, F.E., M.M. Elkomy, and M.M.A. Elsoud, 2016. Optimization of lovastatin production under sub-merged fermentation and its effect on cholesterol blood level in rats. Journal of Innovations in Pharmaceutical and Biological Sciences. 3(4): 33-42.

13. Novotny, L., and L. Vitek .2003. Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. Bulletin of Experimental Biology and Medicine. 228: 568-571

14. Nurhayati *et al*. 2019. Protein efficiency in Japanese quail (coturnix-coturnix japonica) fed fermented palm kernel cake by *Aspergillus niger*. Iraqi J. of Agricultural Sci, 50(2): 377-391

15. Ohm, T.G. and V. Meske, 2006. Cholesterol and statins. Acta Neurol Scand Suppl, 185: 93-101

16. Pettit, R. K. 2009. Mixed fermentation for natural product drug discovery. Applied Microbiology and Biotechnology. 83(1): 19-25

17. Praveen, V.K., S.D. Bhargavi, and J. Savitha, 2015. Lovastatin production by *Aspergillus terreus* (KM017963) in submerged and solid-state fermentation: A comparative study. American Journal of Pharmacy and Health Research, 3(7): 116-126

18. Prisant, L.M., M. Downton, L.O. Watkins, H. Schnaper, R.H. Bradford, A.N. Chremos, and A. Langendorfer, 1996. Efficacy and tolerability of lovastatin in 459 African Americans with hyper-cholesterolemia. The American Journal of Medicine. 78: 420-424

19. Snedecor, G. W. and W.G. Cochran, 1982. Statistical Methods. 7th Ed. The State University Press American, Iowa. 1:677

20. Taghadosi, M., B.J. Fath-Gharib, and A. Piroozmand, 2013. Comparing the effect of lovastatin and exercise on serum lipid profile in hyperlipidaemia patients. International Journal of Medical and Biomedical Studies. 2(1): 18-32

21. Taleb, M.H., I.M. Almasri, N.I. Siam, A.A. Najim, and A.I. Ahmed, 2014. The effect of atorvastatin on liver function among patients with coronary heart disease in gaza strip. Pharmacology and Pharmacy. 5: 781-788.

22. Yassein, S. N., 2020. Comparative study of pathogenicity between *Aspergillus fumigatus* and *Penicillium chrysogenum* in mice. Iraqi J. of Agricultural Sci, 51(1):267-283.