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

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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 (ALT, AST 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, ALT, ALP, 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.
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 intramura1 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 AS0 on some biomarkers of lipid profile and liver functions in-vivo.

MATERIALS 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 °C.
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 kits.

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).

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           | 28.07   | 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-C (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-C (mg/dl)      | 28.53±0.01 | 30.38±2.19 | 29.84±2.57 | 29.12±3.73 | 25.24±3.87 | 29.25±2.25 |
| VLDL-C (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 | 28.92±2.56 | 28.08±1.04 | 27.93±2.1  |

Group (G) 1= control ; G2= with treatment cholesterol; 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

RESULTS 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, 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).

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 lip 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 lip 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 |
|--------------|----|----|----|
| Cholesterol (mg/dl) | Mean ±SD | p-value | Mean ±SD | p-value | Mean ±SD | p-value |
| Mean ±SD | p-value | Mean ±SD | p-value | Mean ±SD | p-value |
| G1 | (66.65±1.23) a | 0.205 | (83.05±0.46) c | 0.001 ▲ | (55.85±1.15) e | 0.000 ▲ |
| G2 | (37.87±0.56) a | 0.092 | (45.24±0.3) c | 0.003 ▲ | (32.16±0.56) b | 0.001 ▲ |
| G3 | (0.17±0.03) a | 0.149 | (0.130±0.01) a | 0.67 | (0.34±0.07) b | 0.395 |
| HDL (mg/dl) | Mean ±SD | p-value | Mean ±SD | p-value | Mean ±SD | p-value |
| Mean ±SD | p-value | Mean ±SD | p-value | Mean ±SD | p-value |
| G1 | (29.61±0.9) a | 0.327 | (28.15±0.32) a | 0.343 | (33.88±0.42) de | 0.037 ▲ |
| G2 | (29.22±1.73) a | 0.771 | (45.58±0.67) c | 0.001 ▲ | (15.54±0.69) d | 0.001 ▲ |
| G3 | (7.57±0.11) a | 0.092 | (9.05±0.66) c | 0.002 ▲ | (6.43±0.11) b | 0.001 ▲ |
| Triglyceride (mg/dl) | Mean ±SD | p-value | Mean ±SD | p-value | Mean ±SD | p-value |
| Mean ±SD | p-value | Mean ±SD | p-value | Mean ±SD | p-value |
| G1 | (33.84±1.04) c | 0.004 ▲ | (31.70±0.91) b | 0.003 ▲ | (3.45±0.07) a | 0.021 ▲ |
| G2 | (65.86±1.16) c | 0.144 | (83.05±0.46) c | 0.004 ▲ | (15.54±0.69) d | 0.001 ▲ |
| G3 | (28.84±0.56) a | 0.523 | (38.68±0.91) a | 0.013 ▲ | (83.05±0.46) c | 0.004 ▲ |

Group (G) 1= control ; G2= with treatment cholesterol; 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≤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≤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≤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≤ 0.05) in lipid profile in rabbit serum and increase (P≤ 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 Mean ±SD | p-value | G2 Mean ±SD | p-value | G3 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 treatment cholesterol; 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 Mean ±SD | p-value | G2 Mean ±SD | p-value | G3 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±1.11) 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 ▲ |

Group (G) 1= control; G2= with treatment cholesterol; 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 function 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≤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

1008
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≤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 asymptotically 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).

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