Results

✓ Organ Weight:

Table (1) and figure (1) summarized the mean relative organ weights. The heart relative weight showed a significant ($P<0.01$) and a non significant ($P> 0.05$) increases in the cholesterol and simvastatin treated groups, respectively compared to that of the control group. Heart relative weight of the HS-gp decreased significantly ($P<0.01$) compared to that of the cholesterol treated group.

All treated groups showed significant decreases ($P<0.05$) in lungs relative weights compared to that of the control group. HS-gp showed a significant decrease in lung relative weight ($P<0.05$) in relation to those of other treated groups.

Cholesterol and simvastatin treated groups showed significant increases ($P<0.001$) in liver relative weights compared to that of the control one, while HS-gp showed significant decreases ($P<0.05$, $P<0.01$ and $P<0.01$) compared to control, cholesterol and simvastatin groups, respectively.

Spleen relative weights showed significant decreases in cholesterol ($P<0.05$), simvastatin ($P<0.05$) and HS ($P<0.01$) treated groups in relation to the control one. Spleen relative weights of HS-gp showed significant decreases ($P<0.001$) compared to other treated groups.

There were non significant changes ($P>0.05$) in the kidneys relative weights in all treated groups compared to that of the control group and also between the treated groups.

There were significant decreases in testes relative weights of all treated groups compared to that of the control group ($P<0.01$ for cholesterol, $P<0.05$ for simvastatin and $P<0.001$ for HS treated groups). In addition, HS-gp showed significant decreases ($P< 0.001$ & $P<0.01$) in testes relative weights % compared to cholesterol and simvastatin treated groups respectively.

✓ Hematological parameters:

Table (2) and figures (2, 3 & 4) illustrated the effect of cholesterol, simvastatin and both of them on WBCs count, RBCs count, hemoglobin content, hematocrit value (PCV), blood indices (MCV, MCH and MCHC) and platelets count.

WBCs count showed non significant increases in cholesterol and simvastatin treated groups related to the control group ($P> 0.05$), while WBCs of the HS-gp showed significant decreases ($P<0.001$) in relation to those of the control group and other treated groups (Table 2 & Fig 2).

RBCs count in cholesterol treated group and HS-gp showed significant increases ($P<0.05$ & $P<0.01$ respectively) compared to that of the control

group, while RBCs count of simvastatin treated group showed non significant increases (P> 0.05) in relation to that of the control group (Table 2 & Fig 2).

Blood Hb concentration showed non significant increases (P> 0.05) and non significant decreases (P> 0.05) in HS-gp and both cholesterol and simvastatin treated groups, respectively compared to that of the control group (Table 2 & Fig 2).

Hematocrit value (PCV) was increased significantly in all treated groups in relation to that of the control group (P<0.01, P<0.05 and P<0.001 for cholesterol, simvastatin and HS treated groups respectively). Hematocrit value of HS-gp showed a significant increase (P<0.05) compared to simvastatin treated group (Table 2 & Fig 3a).

There was a significant decrease (P<0.05) and non significant increases in MCV of cholesterol treated group and both simvastatin and HS treated groups, respectively in relation to that of the control group. Simvastatin and HS treated groups showed significant increases (P<0.01 &P<0.05, respectively) in MCV compared to cholesterol treated group, while HS-gp showed a significant decrease in MCV (P<0.05) compared to that of simvastatin treated group (Table 2 & Fig 3b).

MCH was decreased significantly (P<0.001) in cholesterol treated group compared to that of control group while simvastatin and HS treated groups showed non significant increase (P>0.05) and decrease (P>0.05), respectively compared to that of the control group. MCH was increased

significantly (P<0.001) in simvastatin and HS treated groups compared to that of cholesterol treated group (Table 2 & Fig 3c).

MCHC was decreased significantly (P<0.001) in cholesterol treated group compared to that of the control group, while simvastatin and HS treated groups showed non significant decrease (P>0.05) and increase (P>0.05), respectively in MCHC values compared to that of the control group. MCHC was increased significantly (P<0.001) in simvastatin and HS treated groups compared to that of cholesterol treated group (Table 2 & Fig 4a).

Blood platelets count showed significant decreases (P<0.05, P<0.01 and P<0.01 for cholesterol, simvastatin and HS treated groups, respectively) in relation to that of the control group. Blood platelets count of HS-gp showed a significant decrease (P<0.05) in relation to that of cholesterol treated group (Table 2 & Fig 4b).

✓ Respiratory Functions of Blood

I. Blood gas parameters:

A- Blood oxygen:

1. Blood oxygen partial pressure (PO_2):

Blood PO_2 of male rat was affected by the administration of cholesterol, simvastatin or both of them. Table (3) and figure (5) demonstrated the significant increases (P<0.001) of arterial PO_2 (P_aO_2) of the cholesterol treated group compared to that of the control, simvastatin and HS treated

groups with % differences of 15.24, 18.14 and 17.00, respectively. Venous PO_2 (P_vO_2) of the cholesterol and HS treated groups decreased significantly ($P<0.001$ & $P<0.05$ respectively) compared to the control group, while P_vO_2 of simvastatin treated group showed significant increases ($P<0.001$) in relation to those of other groups. Arterio-venous difference of PO_2 ($P_{(a-v)}O_2$) of the cholesterol treated group was significantly high ($P<0.001$) compared to those of control, simvastatin and HS treated groups with % difference of 44.50, 99.60 and 36.90, respectively. $P_{(a-v)}O_2$ of the simvastatin treated group was decreased significantly ($P<0.001$) compared to those of the control and HS treated groups. Alveolar PO_2 (P_AO_2) was increased significantly in all treated groups in relation to that of the control group ($P<0.001$ for cholesterol and HS treated groups & $P<0.01$ for simvastatin group). The P_AO_2 of the HS treated group showed significant increase ($P <0.001$, $P< 0.001$ and $P< 0.01$) compared to those of the control, cholesterol and simvastatin treated groups, respectively. Alveolar-arterial gradient of PO_2 ($P_{(A-a)}O_2$) of cholesterol treated group was significantly low ($P< 0.001$) compared to those of the control and treated groups, while P_AO_2 of simvastatin and HS treated groups showed significant increases ($P< 0.001$) in relation to that of the control group. The percentage of venous admixture (% shunt) value was significantly decreased ($P< 0.001$) in cholesterol treated group compared to those of the control and those of other treated groups, while simvastatin and HS treated groups showed significant increases ($P< 0.001$) in % shunt in relation to that of the control group.

2. Blood oxygen saturation %:

There were significant increases (P< 0.001) in arterial blood oxygen saturation % of the simvastatin group in comparison with control group and both cholesterol and HS treated groups, while cholesterol treated group showed non significant increases (P> 0.05) compared to control and HS treated groups (Table 3 & Fig 6). Also, venous blood oxygen saturation % of simvastatin treated group was significantly higher than those of the control, cholesterol and HS treated groups, while cholesterol treated group showed significant decreases (P< 0.001) compared to control and HS treated groups. The (a-v) difference of blood oxygen saturation % was significantly high (P<0.001) in cholesterol treated group compared to other groups, while that of simvastatin treated group showed significant decreases (P<0.001) compared to other groups (Table 3 & Figure 6).

3. Oxygen content:

Arterial blood oxygen content (C_aO_2) was non significantly high in HS treated group in relation to other groups. C_aO_2 of cholesterol and simvastatin treated groups were non significantly low in comparison with control group. On the other hand, venous blood oxygen content (C_vO_2) of cholesterol treated group was significantly decreased (P< 0.001) in relation with all other groups, while that of simvastatin treated group showed significant increases (P< 0.001) compared to other groups. There were significant increases (P<0.001) in the a-v difference of the oxygen content ($C_{a-v}O_2$) of cholesterol treated group compared to other groups, while $C_{a-v}O_2$ of simvastatin treated group showed significant decreases (P<0.001) compared to other groups. $C_{a-v}O_2$ of HS treated group showed significant increases

(P<0.001) compared to those of control group and simvastatin treated group, while it was significantly decreased (P<0.001) compared to that of cholesterol treated group (Table 3 & Figure 7a).

4. Blood oxygen-carrying capacity:

There were non significant differences (P> 0.05) in blood O_2 carrying capacity between the control and treated groups. There were non significant decreases (P> 0.05) in oxygen-carrying capacity of cholesterol and simvastatin treated groups compared to the control and HS treated groups. The blood O_2 carrying capacity of HS treated group showed non significant increases in relation to other groups (Table 3 & Figure 7b).

B- Blood carbon dioxide partial pressure (PCO_2):

All treated groups showed significant decrease (P<0.01, P<0.05 & P<0.001 for H-gp, S-gp and HS-gp, respectively) in arterial PCO_2 (P_aCO_2) in comparison with control group. Moreover, P_aCO_2 of HS treated group was significantly lower (P< 0.001 & P< 0.01 for H-gp and S-gp, respectively) in relation with those of other treated groups. On the other hand, venous PCO_2 (P_vCO_2) was significantly high (P<0.001) in all treated groups in relation with control group. P_vCO_2 of HS treated group showed significant increases (P<0.05 &P<0.001 respectively) compared to cholesterol and simvastatin treated groups. P_vCO_2 of cholesterol treated group was significantly higher (P< 0.05) than simvastatin treated group. $P_{(a-v)}CO_2$ gradient was significantly high (P<0.001) in HS group in relation with all other groups, while P(a-

v)CO_2 of cholesterol and simvastatin treated groups were significantly higher ($P< 0.001$ & $P< 0.01$ respectively) than that of the control group (Table 3 & Figure 8).

II. Blood acid-base status parameters:

Table (4) and figure (9-12) summarize the effect of cholesterol, simvastatin or both of them on blood acid-base status parameters of male Wister rats.

A- Blood pH:

Data presented in table (4) and figure (9) showed significant increases ($P<0.001$) in arterial blood pH of simvastatin treated group compared to that of other groups; moreover, cholesterol treated group showed significant ($P< 0.01$) and non significant ($P> 0.05$) increases compared to those of control and HS treated groups, respectively. Venous blood pH was significantly decreased ($P<0.001$) in cholesterol treated group compared to those of other groups, while simvastatin treated group exhibited significant increases ($P< 0.001$, $P< 0.001$ & $P< 0.01$ for C-gp, H-gp & HS-gp, respectively) compared to other groups. The (a-v) difference of blood pH was significantly high ($P< 0.001$, $P< 0.001$ & $P< 0.05$ for H-gp, S-gp & HS-gp, respectively) in all treated groups in comparison to that of the control group. The (a-v) difference of blood pH of cholesterol and simvastatin treated groups were significantly higher ($P< 0.001$) than that of HS treated group.

B- Blood bicarbonate:

Arterial blood $HCO3^-$ of cholesterol, simvastatin and HS treated groups showed significant decreases ($P<0.05$, $P<0.001$ & $P<0.001$respectively) in relation to the control group, while cholesterol treated group it was significantly higher ($P<0.01$ & $P<0.001$) than those of simvastatin and HS treated groups. Venous blood HCO_3^- was significantly increased ($P<0.001$) in both simvastatin and HS treated groups compared to those of control and cholesterol treated groups. The venous blood HCO_3^- of cholesterol treated group was non significantly lower ($P> 0.05$) than that of the control group, and it was the lowest value among other groups. The (a-v) difference in blood HCO_3^- was significantly higher in all treated groups ($P< 0.05$, $P<0.001$ & $P< 0.001$ for H-gp, S-gp and HS-gp, respectively) in relation with that of the control group, while that of the cholesterol group showed significant decrease ($P< 0.001$) compared to simvastatin and HS treated groups (Table 4 & Figure 10).

C- Total carbon dioxide (TCO_2):

It was obvious from the data presented in table (4) and figure (11) that there was significant increases ($P<0.05$, $P<0.001$ & $P<0.001$ for C-gp, H-gp and HS-gp respectively) in arterial blood TCO_2 of the simvastatin treated group in relation with that of other groups, while arterial blood TCO_2 of HS treated group was significantly lower ($P<0.001$) than that of other groups. Arterial blood TCO_2 of cholesterol treated group showed significant

decreases ($P<0.05$) compared to that of the control group. Venous blood TCO_2 was significantly high ($P<0.001$) in simvastatin and HS treated groups in relation to cholesterol and control groups. On the other hand, venous blood TCO_2 of cholesterol treated group showed non significant decrease ($P> 0.05$) from that of the control group. The (a-v) difference of TCO_2 was significantly higher ($P<0.001$) in HS treated group than those of other groups. Cholesterol treated group showed significant increase ($P<0.05$) and decrease ($P<0.05$) in the (a-v) difference of TCO_2 compared to control and simvastatin treated groups, respectively (Table 4 & Figure 11).

D- Base excess (BE):

Base excess (BE) of the arterial blood showed significant decreases ($P< 0.001$, $P< 0.001$ & $P< 0.01$ for C-gp, S-gp & HS-gp, respectively) in cholesterol treated group in comparison to those of other groups. Arterial blood BE of HS treated group showed significant declines ($P<0.01$) in relation with the control and simvastatin treated groups. Venous blood BE was significantly higher ($P<0.001$) in simvastatin and HS treated groups than those of the control and cholesterol treated groups, while that of the cholesterol treated group showed a significant decrease ($P<0.001$) compared to that of the control group. The (a-v) difference in BE was significantly declined ($P<0.001$) in simvastatin and HS treated groups in comparison to both control and cholesterol treated groups, while cholesterol treated group showed non significant decrease ($P> 0.05$) in relation with that of the control group (Table 4 & Figure 12).

III. Blood oxygen equilibrium curve (OEC):

Figure (13 and 14) showed that the OECs and Hill's plot respectively of treated groups were found to be shifted to the right compared to that of the control group. The blood oxygen half saturation pressure (P_{50}) of cholesterol and simvastatin treated groups were significantly higher ($P<0.01$) than that of the control group, while that of HS treated group was non significantly higher ($P> 0.05$) than that of the control group but significantly lower ($P<0.05$) than that of cholesterol treated group. This data were presented in table (6). Hill's constant (n value in Hill's equation) was significantly higher ($P<0.01$, $P<0.05$ & $P< 0.01$ for C-gp, H-gp and HS-gp, respectively) in simvastatin treated group than other groups with differences % of 43.91, 43.91 and 46.62 for control, cholesterol and HS treated groups, respectively.

✓ Biochemical Parameters:

I. Serum glucose:

Table (6) and figure (15) showed the effect of cholesterol, simvastatin or both of them on serum glucose of male Wister rats. The glucose level of cholesterol treated group was significantly higher ($P<0.001$) than those of control and simvastatin treated groups with % differences of 32.47 and 37.91, respectively. The glucose level of HS treated group was significantly higher ($P<0.001$, $P<0.01$ & 0.001) than those of other groups with % differences of 67.49, 26.44 and 74.37 for control, cholesterol and simvastatin treated groups, respectively.

II. Serum proteins:

Table (7) and figure (16) showed the effect of cholesterol, simvastatin or both of them on serum proteins of male Wister rats.

Serum total protein was significantly higher ($P<0.001$, $P<0.01$ & $P<0.001$ for H-gp, S-gp and HS-gp respectively) related to control group. Serum total protein of simvastatin treated group was significantly decreased ($P<0.01$) in comparison to those of cholesterol and HS treated groups with % difference of 14.31 and 16.28, respectively.

Serum albumin content of simvastatin and HS treated groups were significantly higher ($P<0.01$ & $P<0.001$ respectively) than that of control group with % differences of 12.75 and 24.25, respectively. Serum albumin

of HS treated group was significantly higher ($P<0.01$ & $P<0.05$) than those of other treated groups with % differences of 15.31 and 10.2 for cholesterol and simvastatin treated groups, respectively.

Serum globulin contents of all treated groups were significantly higher ($P<0.001$, $P<0.05$ and $P<0.01$ for H-gp, S-gp and HS-gp respectively) than that of the control group. Serum globulin of cholesterol treated group was significantly higher ($P<0.001$) than those of the other treated groups with % differences of 60.48 and 34.67 for simvastatin and HS treated groups, respectively.

III. Lipid profile:

Table (8) and figures (17, 18 and 19) summarized the effect of cholesterol, simvastatin or both of them on serum lipid profile of rats.

Serum triglyceride showed significant increases ($P<0.001$, $P<0.01$ & $P<0.001$) in cholesterol treated group in relation to those of other groups with % differences of 82.59, 79.67 and 115.75 for control, simvastatin and HS treated groups, respectively. Serum triglyceride levels increased and decreased non significantly ($P> 0.05$) in simvastatin and HS treated groups, respectively, compared to that of the control group (Table 8 & Figure 16).

Serum total cholesterol was recorded to be significantly higher ($P<0.001$, $P<0.001$ & $P<0.01$) in cholesterol treated group in relation to that of all other groups with % differences of 53.82, 49.61 and 34.88 for control, simvastatin and HS groups, respectively. The increases of total cholesterol in

simvastatin and HS treated groups were non significant compared to that of control group (Table 8 & Figure 17).

Serum HDL-cholesterol was significantly higher ($P<0.001$, $P<0.001$ & $P<0.01$) in HS treated group compared to those of all other groups with % differences of 160.74, 231.29 and 34.51 for control, cholesterol and simvastatin treated groups, respectively; while that of cholesterol treated group showed significant declines ($P<0.01$, $P<0.001$ & $P<0.001$) in relation to C-gp, S-gp and HS-gp respectively. Moreover, serum HDL-C of simvastatin treated group showed significant increases ($P<0.001$) compared to control and cholesterol treated groups (Table 8 & Figure 17).

In contrast to serum HDL-cholesterol, serum LDL-cholesterol was significantly higher ($P<0.001$) in cholesterol treated group in relation to those of control, simvastatin and HS groups, while LDL-C of simvastatin and HS treated groups showed significant declines ($P<0.001$) in relation to those of control and cholesterol groups (Table 8 & Figure 17).

VLDL-cholesterol showed significant increases ($P<0.001$) in cholesterol treated group in relation to those of control, simvastatin and HS groups (Table 8 & Figure 17).

LDL/HDL-cholesterol ratio was found to be higher in cholesterol treated group and lower in HS treated group compared to that of the control group (Table 8 & Figure 18).

Liver total cholesterol was significantly increased in all treated groups ($P<0.001$, $P<0.05$ & $P<0.05$ for H-gp, S-gp and HS-gp respectively)

compared to that of control group (Table 8 & Figure 19). Liver total cholesterol of HS treated group showed significant increases (P<0.05) in relation to control and simvastatin treated groups with % differences of 31.61 and 13.24, respectively. The increase of liver cholesterol in cholesterol treated group was significantly high (P<0.001 & P<0.05) other treated groups with difference % of 41.68 and 25.11 compared to simvastatin and HS treated groups, respectively (Table 8 & Figure 19).

IV. Serum and liver transaminases:

The effect of cholesterol, simvastatin or both of them on serum and liver transaminases (aspertate aminotransferase, AST and alanine aminotransferase, ALT) activities were recorded in table (9) and figure (20).

Serum AST showed non significant increases (P> 0.05) in simvastatin and HS treated groups compared to that of control group, while serum AST of cholesterol treated group showed non significant decreases (P> 0.05) compared to that of control group (Table 9 & Figure 20a).

Serum ALT of HS treated group showed significant increases (P<0.001, P<0.01 & P<0.001) compared to C-gp, H-gp and S-gp, resectively. Serum ALT decreased non significantly (P> 0.05) in cholesterol and simvastatin treated groups compared to that of control group (Table 9 & Figure 20a).

Liver AST of cholesterol treated group was significantly lower (P<0.001, P<0.01 & P<0.001) in relation to C-gp, S-gp and HS-gp respectively, while that of HS treated group showed significant increases (P<0.001, P<0.001 & P<0.01) in relation to C-gp, H-gp and S-gp

respectively. Liver AST of simvastatin treated group showed a significant increase ($P<0.05$) compared to that of the control group (Table 9 & Figure 20b).

Liver ALT was non significantly lower ($P<0.05$) in cholesterol treated group compared to that of control group, and significantly lower ($P<0.05$ & $P<0.001$) in relation to those of simvastatin and HS groups respectively. Liver ALT of HS treated group showed significant increases ($P<0.001$) compared to those of control and cholesterol treated groups (Table 9 & Figure 20b).

V. Kidney function:

Table (10) and figure (21) summarized the effect of cholesterol, simvastatin or both of them on kidney function's parameters (urea, uric acid and creatinine).

Serum urea nitrogen was significantly lower ($P<0.001$ & $P<0.01$) in cholesterol and HS treated groups compared to that of the control group respectively, while that of simvastatin treated group showed significant increases ($P<0.05$, $P<0.001$ & $P<0.001$) compared to C-gp, H-gp and HS-gp respectively (Table 10 & Figure 21a).

Serum uric acid was recorded to be significantly higher ($P<0.001$, $P<0.01$ and $P<0.001$) in all treated groups compared to the control group with % differences of 71.43, 75.33 and 83.12 for cholesterol, simvastatin and HS treated groups, respectively (Table 10 & Figure 21b).

Finally, serum creatinine was significantly decreased ($P<0.05$, $P<0.01$ & $P<0.01$) in H-gp, S-gp and HS-gp respectively in relation to control group (Table 10 & Figure 21c).

✓ Hormonal assays:

I. Serum levels of triiodothyronine (T_3) and thyroxin (T_4):

Table (11) and figures (22 and 23) showed that the levels of serum triiodothyronine showed non significant decreases ($P> 0.05$) in all treated groups in comparison to that of the control group (Table 11 & Figure 22).

The levels of thyroxin were decreased non significantly ($P> 0.05$) in cholesterol and simvastatin treated groups in comparison to that of the control group, while serum T_4 of HS treated group showed non significant increases ($P> 0.05$) in comparison to those of all other groups (Table 11 & Figure 23).

II. Serum testosterone:

Table (12) and figure (24) showed the effect of administration of cholesterol, simvastatin or both of them on serum testosterone of male rats. Cholesterol and HS treated groups showed non significant increases in serum testosterone in comparison to control group, while that of simvastatin treated group showed significant increases compared to those of all other groups.

✓ DNA fragmentation %:

Table (13) and figure (25) illustrated the effect of administration of cholesterol, simvastatin or both of them on the % of DNA fragmentation.

Cholesterol treated group showed a significant increase compared to other groups with % differences of 148.28, 334.03 and 299.08 for control, simvastatin and HS treated groups, respectively. The % DNA fragmentation of simvastatin and HS treated groups were significantly ($P<0.05$) reduced compared to that of the control group.