In the present study, the effects of simvastatin, $CaNa_2EDTA$, DMSA and vitamin E were investigated on several parameters related to hypercholesterolemia. Hypercholesterolemia was induced by feeding rats with cholesterol-rich diet for six weeks. All drugs were given concomitantly with cholesterol-rich diet for six weeks. The effects of the test drugs and their combinations on lipid profile markers including serum total cholesterol (TC), triglycerides (TG), low density lipoproteins cholesterol (LDL-c), very low density lipoproteins cholesterol (VLDL-c) and high density lipoproteins cholesterol (HDL-c) were estimated. Also their effects on some oxidative stress markers including serum malondialdehyde (MDA), blood superoxide dismutase (SOD) and reduced glutathione (GSH) as well as serum total nitrate/nitrite (NO_x), aortic endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) were determined. Furthermore, aortic calcium and wall thickness as well as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, creatinine and glucose were determined. In addition, the effects of the test drugs on body weight gain were estimated.

The main findings of the current study could be summarized as follows:

1. Diet-induced hypercholesterolemia resulted in alterations in the lipid profile, a state of oxidative stress and hyperglycemia coupled by decreased body weight gain and compensatory increase in serum NO_x level of rats.
2. In addition, decreased aortic eNOS activity as well as increased aortic iNOS activity, calcium content and wall thickness were observed.

3. Simvastatin, $CaNa_2EDTA$, DMSA and vitamin E significantly reduced serum TC, TG and VLDL-c levels of hypercholesterolemic rats.

4. Simvastatin and DMSA significantly reduced serum LDL-c level while $CaNa_2EDTA$ and vitamin E did not significantly affect serum LDL-c level of hypercholesterolemic rats.

5. DMSA significantly increased serum HDL-c level of hypercholesterolemic rats while simvastatin, $CaNa_2EDTA$ and vitamin E did not significantly affect it.

6. Simvastatin, $CaNa_2EDTA$, DMSA and vitamin E significantly decreased atherogenic index of hypercholesterolemic rats.

7. DMSA significantly increased high density lipoproteins cholesterol/total cholesterol ratio (HTR) of hypercholesterolemic rats while simvastatin, $CaNa_2EDTA$ and vitamin E did not significantly change it.

8. No interaction was observed between simvastatin and $CaNa_2EDTA$, DMSA or vitamin E on serum TC or LDL-c levels when given concomitantly.

9. There was an additive interaction between simvastatin and $CaNa_2EDTA$ or vitamin E on serum TG and VLDL-c as well as serum HDL- c levels when co-administered together.

10. No interaction was observed between simvastatin and DMSA on serum TG level while an additive interaction was observed between them on serum VLDL-c and HDL-c levels when combined together.

11. No interaction was observed between simvastatin and $CaNa_2EDTA$, DMSA or vitamin E on atherogenic index while an

additive interaction was observed between simvastatin and the other drugs on HTR when co-administered together.

12. Simvastatin, $CaNa_2EDTA$, DMSA and vitamin E significantly decreased serum MDA level while increasing blood GSH level of hypercholesterolemic rats.

13. $CaNa_2EDTA$, DMSA and vitamin E significantly elevated blood SOD activity of hypercholesterolemic rats while simvastatin did not significantly affect it.

14. An additive interaction was observed by concurrent administration of simvastatin with $CaNa_2EDTA$ or vitamin E on serum MDA and blood GSH levels.

15. A potentiating effect was observed between simvastatin and $CaNa_2EDTA$ or vitamin E on blood SOD activity when combined together.

16. No interaction was observed between simvastatin and DMSA on serum MDA level or blood SOD activity; whereas there was an additive interaction between them on blood GSH level when co-administered together.

17. Simvastatin significantly increased serum NO_x level of hypercholesterolemic rats.

18. $CaNa_2EDTA$, DMSA and vitamin E did not significantly change serum NOx level of hypercholesterolemic rats.

19. Simvastatin, $CaNa_2EDTA$, DMSA and vitamin E significantly increased aortic eNOS activity while decreasing aortic iNOS activity, calcium content and wall thickness of hypercholesterolemic rats.

20. No interaction was observed between simvastatin and $CaNa_2EDTA$, DMSA or vitamin E on serum NOx level, aortic eNOS and iNOS activities, calcium content or wall thickness when given concomitantly.

21. $CaNa_2EDTA$ and vitamin E significantly lowered serum glucose level of hypercholesterolemic rats; whereas simvastatin and DMSA did not significantly affect it.

22. A potentiating effect was observed between simvastatin and $CaNa_2EDTA$ on serum glucose level when co-administered together.

23. Simvastatin, $CaNa_2EDTA$, DMSA and vitamin E did not significantly affect body weight gain of hypercholesterolemic rats.

According to the previous findings, it could be concluded that:

- Feeding rats with cholesterol-rich diet for six weeks caused hypercholesterolemia associated with oxidative stress.
- Treatment of hypercholesterolemic rats with simvastatin, $CaNa_2EDTA$, DMSA or vitamin E as well as their combinations markedly improved hypercholesterolemia and its associated oxidative stress.
- The hypolipidemic actions of $CaNa_2EDTA$, DMSA and vitamin E are probably due to their antioxidant properties.
- Simvastatin, $CaNa_2EDTA$, DMSA and vitamin E improved endothelial function by increasing aortic eNOS and decreasing aortic calcification and wall thickening.
- Chelating agents such as $CaNa_2EDTA$ and DMSA could be used in the treatment of some cardiovascular diseases associated with

hypercholesterolemia by removing lipid/calcium plaque from blood vessels.

- Further clinical trials are needed to support the previous findings.