Introduction and Aim of work

Hypercholesterolemia represents a high risk factor for coronary heart disease (CAD) as it may predispose to cardiac ischemia, myocardial infarction and atherosclerosis. Atherosclerosis is a major cause of morbidity and mortality in developing countries, accounting for 50% of all deaths in 1997 **(Liao, 2002).**

Recently, dietary patterns in many countries have become westernized after the rapid growth of their economies. Therefore, numbers of people with hyperlipidemia, cardiovascular disease (CVD), and large intestinal cancer have increased rapidly **(Chen *et al.*, 2003).**

Cholesterol in the atherosclerotic plaques is mainly derived from circulating lipoprotein especially low density lipoprotein (LDL). The high levels of LDL cholesterol in blood are strongly associated with CAD **(Martin *et al.*, 1986).**

The pathology of atherosclerosis is due to deposition of lipids, especially cholesterol, in the arterial wall intimal layer both intracellulary and extracellulary. In hypercholesterolemia, the composition of the human diet plays an important role in the management of lipid and lipoprotein concentrations in the blood. Reduction in saturated fat and cholesterol intake has traditionally been the first goal of dietary therapy in lowering the risk for cardiovascular disease. This may reduce blood total cholesterol concentrations by ~ 3% (step 1 diet: <30% of total energy intake as fat, with 8-10% as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.0;

cholesterol intake <300 mg/day; and energy intake to achieve desirable body weight) or 6% (step 2 diet: <30% of total energy intake as fat, with 7% or less as saturated fat; ratio of polyunsaturated to saturated fatty acid >1.4; cholesterol intake <200 mg/day; and energy intake to achieve desirable body weight) in free-living subjects **(Kerckhoffs *et al.*, 2002).**

Medications are prescribed when diet cannot reduce the cholesterol to acceptable levels. The most effective and widely used medications to lower cholesterol are called statins. Simvastatin is a potent hypocholesterolemic and hypolipidemic drug of statin series (simvastatin, lovastatin, fluvastatin and pravastatin). It inhibits the de-novo synthesis of cholesterol in the liver via an inhibition of hydroxymethylglutarate Co enzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate which is the early step in the biosynthetic pathway of cholesterol. Simvastatin is commonly used nowadays for treatment of coronary heart disease, hypercholesterolemia and hyperlipidemia in human **(Shalaby *et al.*, 2004).**

The aim of the present work was to investigate the effect of cholesterol administration and the most potent hypolipidemic drug (simvastatin) on some physiological aspects in white rats, including:

1. Organ weights include heart, lungs, liver, spleen, kidneys and testes weights.
2. Blood parameters: red and white blood cell counts (RBCs and WBCs), hemoglobin content (Hb), hematocrit value (Hct %) and calculated blood indices (mean corpuscular volume, MCV; mean corpuscular

hemoglobin, MCH and mean corpuscular hemoglobin concentration, MCHC). Also, blood platelets were concerned.

3. Respiratory functions of blood:
   a) Arterial and venous blood gases include blood oxygen and carbon dioxide partial pressures, and percent blood oxygen saturation, oxygen carrying capacity and oxygen content.
   b) Blood acid-base status parameters include blood pH bicarbonate, total carbon dioxide and base excess in both arterial and venous blood.
   c) Blood oxygen equilibrium curve and half saturation pressure (P_{50}).
4. Biochemical assessment includes:
   a) Metabolites: serum glucose, total protein, albumin, globulin, uric acid, urea, creatinine, triglycerides and serum and liver total cholesterol. Also, serum HDL cholesterol, LDL cholesterol, VLDL cholesterol and atherosclerotic index were determined.
   b) Enzymes: serum and liver transaminase activities.
5. Hormone assay: serum triiodothyronine, thyroxin and testosterone were determined.
6. DNA fragmentation was also carried out to evaluate the DNA damage in liver of male rat.