CHAPTER VII

Summary and Conclusion
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Atherosclerotic cardiovascular disease, predominantly coronary artery disease is the single great cause of mortality, being responsible for about 1/3rd of all deaths annually. Our understanding of the cellular and molecular events that participate in the genesis of atherosclerosis has increased markedly in the past few years. This has lead to the recognition of major risk factors and identification of specific events in the disease process, which eventually provides numerous entry points for selective interference and inhibition of the process of atherogenesis.

The knowledge of the importance of inflammation, oxidative stress mediated endothelial dysfunction, oxidative modification of low-density lipoproteins, have provided the basis of antioxidant drug development. Moreover recognition of the final thrombotic event as a result of lesion rupture and the role of coagulation factors and platelets have opened another line of approach to the prevention and treatment. The observation of hypercoagulability during hyperlipidaemia have also provided rationale that lipid lowering by diet or drug therapy appears to ameliorate these disturbances thus providing possible mechanisms in reducing the risk of coronary heart diseases.

The various side effects attributed to hypolipidaemic, hypocholesterolaemic and antithrombotic drugs currently in use are a major hindrance in the amelioration of the disease process. The use of supplements to augment dietary modifications may also help to reduce cholesterol. Hence newer
agents having potent antiatherogenic efficacy are well warranted. Present study is an attempt to evaluate the efficacy of a herbal formulation ‘Caps HT2’, in relation to the various aspects of atherosclerotic disease processes.

Since serum cholesterol has been linked to atherogenesis, it is speculated that treatment to reduce cholesterol levels may slow the progression or induce the regression of atherosclerotic lesions. Cholesterol modifying therapy may not only decrease the formation and progression of lipid-laden plaques but also reduce the cholesterol content in cholesterol rich lesions.

Thus although none of the drugs used in previous prevention trials can be considered ideal in the amelioration of cardiovascular diseases, the recent experience with the herbal formulation, ‘Caps HT2’ supported the concept that lowering of plasma cholesterol levels and antioxidant defence will retard coronary atherosclerosis and thereby reduce the incidence of cardiovascular diseases.

In the present study, the assessment of the various therapeutic potentials of the formulation, ‘Caps HT2’ revealed its efficacy in the amelioration of atherosclerosis and related disease conditions. It was found effective in scavenging free radicals (superoxide, hydroxyl radical and hydrogen peroxide), there by playing it’s role in the protection of arterial intima against free radical mediated injury. The platelets play an important role in the process of atherogenesis by adhering to the damaged regions of the endothelial surface. The antiplatelet therapy constitutes the best available tool in ameliorating the mechanisms related to atherogenesis and this formulation has interestingly inhibited the ADP induced platelet aggregation.
The various coagulation factors associated with platelet aggregation and adhesion were seen elevated in the case of atherosclerosis. The coagulation of blood was found delayed to a greater extent after the intravenous administration of the formulation in rabbits, even for a shorter duration of 15 min, and was comparable to that of heparin. Hence, this formulation, ‘Caps HT2’ was found effective in preventing thrombogenesis by delaying the mechanisms associated with blood coagulation and clotting.

Considering the role of LPL in the metabolism of VLDL and chylomicrons, it could be assumed that the agent that can enhance the liberation of enzyme from the endothelial surface can play a major role in reducing hypertriglyceridemia. The glycerol liberated by the action of lipoprotein lipase enzyme in the formulation administered rabbits was found effectively higher than the normal rabbits. This herbal formulation exhibited an enhancing role in activating and releasing the enzyme, effecting in the metabolic degradation of lipids, mainly triglycerides.

The efficacy in the anti-inflammatory action of the formulation was significant with acute as well as chronic inflammations, induced by carrageenan and formalin in rats. The anti-inflammatory effect of the formulation was noteworthy, as inflammation being the initial step towards endothelial dysfunction.

Experimental hyperlipidaemia in rats was associated with an increase in all the serum lipid parameters. The administration of the herbal formulation, ‘Caps HT2’ resulted a highly significant reduction in total cholesterol,
LDL cholesterol, triglycerides and phospholipids with a concomitant rise in HDL cholesterol. Changes in the concentrations of LDL cholesterol and HDL cholesterol induced by therapy retard or reverse the flow of cholesterol in atheromatous lesions, thereby improving the stability of plaques and lowering the risk of plaque disruption. The efficacy of the formulation was found greater than that of the standard drug lovastatin and also evident in relation to weight increase and atherogenic index.

It is possible that the beneficial cardiovascular effects of the formulation may be related to its antioxidant, anticoagulant, anti-inflammatory, platelet aggregation inhibition and lipoprotein lipase enzyme releasing and hypolipidaemic properties.

As the formulation was found effective with the various therapeutic potentials associated with atherosclerosis, the formulation was evaluated for the non-toxic safe dose. The body weight and the various serum biochemical parameters studied authenticated the efficacy of this formulation in the treatment of atherosclerosis without any toxic effects in the vital organs, the heart, liver and kidney.

The present study has also revealed the in vivo antiatherogenicity of the formulation, 'Caps HT2' in the experimental model of rabbits. The results support that the formulation administration decreased the percentage increase in body weight, indicating the efficacy against obesity.

In the study in rabbits, the formulation exerted its beneficial effect partially by reducing the atherogenic properties of cholesterol. The administration
increased HDL cholesterol and decreased the LDL cholesterol. The decrease in plasma TG and phospholipid concentrations may also contribute to the suppression of the development of atherosclerosis in rabbits.

The increased storage of cholesterol, phospholipids and triglycerides observed in the liver, heart muscles, aorta and kidney by the administration of high fat/high cholesterol diet was highly reduced and found reduced to that of the standard drugs, probucol and lovastatin. It has assumed that the administration of the formulation, ‘Caps HT2’ might have helped in the mobilisation of fat, especially cholesterol from liver and prevented its deposition in the heart muscles, kidney and aorta.

The decrease in the rate of lipid peroxidation was noteworthy with the administration of the herbal formulation, ‘Caps HT2’, as peroxidation of lipids being a major event in the processes of atherogenesis. Lipoprotein lipase enhanced the clearance of chylomicron remnants, effectively reducing the LDL and VLDL cholesterol concentrations in the blood, another effect noticed by the administration of the formulation. The HMG CoA reductase activity was also found decreased in the formulation treated animals resulting in the decreased synthesis of cholesterol.

The imbalance between oxidant and antioxidant generating systems leading to oxidative stress has been reported in the pathogenesis of atherosclerosis. The antioxidant enzyme activities (SOD, CAT, GPx) were greatly enhanced in the high fat/high cholesterol fed group and reached to the normal rate by the administration of the formulation. The increase in antioxidant enzyme
activity observed in the present study may be a step to counteract ROS injury and to overcome oxidative stress.

The results also support that the atherogenic diet administered provoked atheromatous lesions in the arterial intima and the formulation administration effected the regression of atherosclerotic plaque. The plaque regression and the amelioration of sclerosis observed in the present study might be the collective effect of the antioxidant and hypolipidaemic efficacy of the ingredients of the formulation and plaque regression was highly noticeable in the formulation treated rabbits. Furthermore it could be proposed that antioxidant enzymes reduce endothelial dysfunction, and HMG CoA reductase and lipoprotein lipase with resultant decrease in the synthesis of lipids ameliorate the risk towards cardiovascular diseases.

It has been reported that in young healthy men that constantly low HDL cholesterol concentration is directly associated with vascular endothelial dysfunction, as well as the increased *in vivo* LDL oxidation. These findings are in line with experimental studies showing that HDL may protect endothelium and decrease lipoprotein oxidation, and may therefore; provide insight into epidemiological observations indicating that high HDL cholesterol levels operate as protective factor against cardiovascular disease. Low HDL levels are associated with increased oxidative stress, consistent with the idea that HDL cholesterol may act as an antioxidant.291

Feeding of the formulation, ‘Caps HT2’ significantly reduced the lipid content, and the greater decrease noticed in the formulation treated groups
compared to standard drugs might be a possible reason for the most effective plaque regression efficacy noticed.

The present study concluded that the formulation, 'Caps HT2' possessed antioxidant, anticoagulant, anti-inflammatory, platelet antiaggregatory, lipoprotein lipase releasing, HMG CoA reductase inhibiting, and lipid peroxidation reducing, hypolipidaemic/hypocholesterolaemic and plaque regressing activities. The dietary control of limiting fat and cholesterol intake alone is not enough to reduce serum cholesterol to safe levels because of the ability of the liver to synthesise cholesterol.

The formulation, 'Caps HT2', was found to possess greater efficacy compared to that of the commercially available herbal formulation, liposem. Liposem significantly ameliorated obesity in experimental animals. On the other hand the formulation, 'Caps HT2' was effective in reducing sclerosis rather than obesity. The regression of plaque noticed was greater by the administration of the formulation, 'Caps HT2' compared to that of the standard drugs lovastatin and probucol.

The formulation was found non-toxic, effective, safe and economical for long-term administration and could be used for the treatment of cardiovascular and related diseases. Further clinical studies may help to prove the functional efficacy in humans.