Introduction
Cholesterol is one of the several types of fats (lipids) that are essential to good health. Cholesterol is an important component of cell membranes and vital to the structure and function of all cells. Cholesterol also is a building block in the formation of certain types of hormones (Fayad, et al., 2001).

When the levels of cholesterol and triacylglycerols, another blood fat, in the bloodstream become too high, the likelihood of developing cholesterol-containing fatty deposits (plaques) in the blood vessels increases (Small, 1988). Over time, plaques narrow arteries, impeding blood flow and creating a condition called atherosclerosis. Narrowing of the arteries around the heart (coronary artery disease) can prevent the heart from getting as much oxygen-rich blood as it needs. This means an increased risk of a heart attack. Likewise, decreased blood flow to the brain can cause a stroke, and less blood flowing to the lower limbs may result in gangrene (Vogel, et al., 1998).

Cholesterol, like oil, cannot dissolve in the blood unless it is combined with special proteins called lipoproteins (without combining with lipoproteins, cholesterol in the blood will turn into a solid substance) (Mendis, et al., 1990). The cholesterol that is secreted by the liver into the blood is combined either with very low-density lipoproteins (VLDL) or high-density lipoproteins (HDL). VLDL cholesterol is then metabolized in the bloodstream to produce LDL cholesterol. The cholesterol combined with low-density lipoproteins is called LDL cholesterol, and the cholesterol combined with high-density lipoproteins is called HDL cholesterol.
**LDL cholesterol**

LDL cholesterol is called "bad" cholesterol, because elevated LDL cholesterol is associated with an increased risk of coronary heart disease (News item, 1993). LDL lipoprotein deposits cholesterol on the artery walls, causing the formation of a hard, thick substance called cholesterol plaque. Arteries that supply blood and oxygen to the heart muscles are called coronary arteries. When coronary arteries are narrowed by atherosclerosis, they are incapable of supplying enough blood and oxygen to the heart muscle during exertion. Lack of oxygen (ischemia) to the heart muscle causes chest pain, also formation of a blood clot in the artery can cause complete blockage of the artery, leading to death of the heart muscle (heart attack). Atherosclerotic disease of coronary arteries (coronary heart disease) is the most common cause of death throughout the world, (Ulbricht, *et al.*, 1991).

The liver not only manufactures and secretes LDL cholesterol into the blood, it also removes LDL cholesterol from the blood (Abbey, *et al.*, 1994). To remove LDL cholesterol from the blood, the liver relies on special proteins called LDL receptors that are normally present on the surface of liver cells. LDL receptors snatch LDL cholesterol particles from the blood and transport them inside the liver. A high number of active LDL receptors on the liver surfaces is associated with the rapid removal of LDL cholesterol from the blood and low blood LDL cholesterol levels. A deficiency of LDL receptors is associated with high LDL cholesterol blood levels (Grundy, *et al.*, 1969).
HDL cholesterol

HDL is the good cholesterol because it protects the arteries from the atherosclerotic process. HDL cholesterol extracts cholesterol particles from the artery walls and transports them to the liver to be disposed through the bile. It also interferes with the accumulation of cholesterol in the artery walls by the LDL cholesterol particles.

The risk of atherosclerosis and heart attack in both men and women is strongly related to HDL cholesterol levels. Low levels of HDL cholesterol are linked to a higher risk, whereas high HDL cholesterol levels are associated with a lower risk (Mendis, 1990).

Very low and very high HDL cholesterol levels can run in families. Families with low HDL cholesterol levels have a higher incidence of heart attacks than the general population, while families with high HDL cholesterol levels tend to live longer with a lower frequency of heart attacks.

Like LDL cholesterol, life style factors and other conditions influence HDL cholesterol levels. HDL cholesterol levels are lower in persons who smoke cigarettes, eat a lot of sweets, are overweight and inactive, and in patients with type II diabetes mellitus (Dreon, et al., 1999).

HDL cholesterol is higher in people who are lean, exercise regularly, and do not smoke cigarettes. Estrogen increases a person’s HDL cholesterol, which explains why women generally have higher HDL levels than men do (de Roos et al., 1999).
For individuals with low HDL cholesterol levels, a high total or LDL cholesterol blood level further increases the incidence of atherosclerosis and heart attacks. Therefore, the combination of high levels of total and LDL cholesterol with low levels of HDL cholesterol is undesirable whereas the combination of low levels of total and LDL cholesterol and high levels of HDL cholesterol is favourable.

**LDL cholesterol/HDL cholesterol and total cholesterol/HDL cholesterol ratios**

The total cholesterol to HDL cholesterol ratio (total/HDL) is a number that is helpful in predicting atherosclerosis. The number is obtained by dividing total cholesterol by HDL cholesterol. (High ratios indicate higher risks of heart attacks, low ratios indicate lower risk) (Tasaka, 1996).

High total cholesterol and low HDL cholesterol increase the ratio, and is undesirable. Conversely, high HDL cholesterol and low total cholesterol lowers the ratio, and is desirable. An average ratio would be about 4.5. Ideally we want to be better than average if we can. Thus the best ratio would be 2 or 3 or less than 4.

Another ratio is LDL/HDL. The LDL/HDL ratio is actually a more pure ratio than total cholesterol/HDL. Because LDL is a measure of bad cholesterol and HDL is a measure of good cholesterol, whereas the total cholesterol is the sum of HDL, LDL and the VLDL. Adding up the HDL, LDL and VLDL makes up the total cholesterol measurement (Behall, *et al.*, 1984).
Even though total cholesterol/HDLc ratio is not as accurate or pure as the LDLc/HDLc ratio, the former is more commonly obtained because the total cholesterol is easier and cheaper to obtain than the LDL cholesterol levels.

**Lipoprotein (a), Lp(a) cholesterol**

Lipoprotein (a), Lp(a), is a LDL cholesterol particle that is attached to a special protein called apo(a). In large part, a person's level of Lp(a) in the blood is genetically inherited. Elevated levels of Lp(a) (higher than 20 mg/dl to 30 mg/dl) in the blood are linked to a greater likelihood of atherosclerosis and heart attacks in both men and women. The risk is even more significant if the Lp(a) cholesterol elevation is accompanied by high LDLc/HDLc ratios (Reder, *et al.*, 1992).

Certain diseases are associated with elevated Lp(a) levels. Patients on chronic kidney dialysis and those with nephrotic syndrome (kidney diseases that cause leakage of blood proteins into the urine) tend to have high levels of Lp(a) (Marconima, *et al.*, 1997).

There are many theories as to how Lp(a) causes atherosclerosis although exactly how Lp(a) accumulates cholesterol plaques on the artery walls has not been well defined. Clinical trials that conclusively prove lowering Lp(a) reduces atherosclerosis and the risk of heart attacks. Currently, there is no international standard for determining Lp(a) cholesterol levels, and commercial sources of Lp(a) testing may not have the same accuracy as research laboratories. Therefore, specifically measuring and treating elevated Lp(a)
cholesterol levels are not widely performed in \textit{specimen} (Krohenberg, \textit{et al.}, 1996).

Most lipid-lowering medications such as statins, Lipid, and cholestyramine have a limited effect in lowering Lp(a) cholesterol levels. Estrogen has been shown to lower Lp(a) cholesterol levels by approximately 20\% in women with elevated Lp(a) cholesterol. Estrogen can also increase HDL cholesterol levels when given to postmenopausal women. Additionally, nicotinic acid (Niacin or Niaspan) in high doses has been found to be effective in lowering Lp(a) cholesterol levels by approximately 30\% (Scanu, 1992; Stein \textit{et al.}, 1997).

**Triacylglycerols, chylomicrons and VLDL**

Triacylglycerols is a fatty substance that is composed of three fatty acids each of which is attached to a glycerol molecule. Like cholesterol, triacylglycerols in the blood either comes from the diet or the liver. Also, the cholesterol, triacylglycerols cannot dissolve and circulate in the blood without combining with a lipoprotein. Thus, after a meal, the triacylglycerols and cholesterol that are absorbed into the intestines are packaged into round particles called chylomicrons before they are released into the blood circulation (Van Vlijmen \textit{et al.}, 1994).

A chylomicron is a collection of cholesterol and triacylglycerols that is surrounded by a lipoprotein outer coat (Chylomicrons contain 90\% triacylglycerols and 10\% cholesterol). There are special enzymes on the blood
vessels that break up the triacylglycerols inside the chylomicrons, releasing fatty acids in the process. The fatty acids can either be used by the muscles as energy, or absorbed by fat cells where they are incorporated again into triacylglycerols that can be stored in the fat cells for future energy needs. The chylomicrons are then removed from the circulation by the liver (Van Vlijmen et al., 1998).

The liver not only removes triacylglycerols and chylomicrons from the blood, it also synthesizes and packages triacylglycerols into VLDL (very low-density lipoprotein) particles and releases them back into the blood circulation. Therefore, before breakfast after an overnight fast, most of the triacylglycerols in the blood comes from the liver in the form of VLDL particles. Like chylomicrons, VLDL particles contain mostly triacylglycerols. Some of the VLDL particles lose triacylglycerols in the blood and become cholesterol-rich LDL particles (Motwani JG and Topol, 1998).

**RISK FACTORS FOR HYPERCHOLESTEROLEMIA**

The way of lifestyle can cause or contribute to high total cholesterol levels (Jialal, 1996).

**Inactivity**

Lack of exercise may lower the level of high-density lipoprotein (HDL) cholesterol, "good" cholesterol (Reaven, et al., 1990).
Obesity

Excess weight increases triacylglycerol. It also lowers HDL cholesterol and increases very-low-density lipoprotein cholesterol (Kris, *et al.*, 1999).

Diet

Cholesterol occurs naturally in animal food such as meat, eggs and cheese. Eating a high-fat, high-cholesterol diet contributes to an increased blood cholesterol level. Saturated fats raise blood cholesterol levels. Polyunsaturated fats lower blood cholesterol but also seem susceptible to oxidation. Over time, oxidation speeds buildup of plaques inside the arteries. Monounsaturated fats may help lower blood cholesterol and are resistant to oxidation (Hu, *et al.*, 1999).

These factors increase the likelihood that high total cholesterol levels will lead to atherosclerosis (Knopp, *et al.*, 1999).

Smoking

Cigarette smoking damages the walls of the blood vessels, making them prone to accumulation of fatty deposits (Khosla, 1994). Smoking also may lower the level of HDL cholesterol by as much as 15 percent (Dwyer, 1988).
High blood pressure

By damaging the walls of the arteries, high blood pressure can accelerate the accumulation of fatty deposits on the walls of the arteries (Mansell, 1991).

Type 2 diabetes

This type of diabetes generally develops after the age of 40. The condition results in a buildup of sugar levels in the blood. Chronic high blood sugar may lead to narrowing of the arteries (Reiser, 1985).

Family history of atherosclerosis

If a close family member (parent or sibling) has developed atherosclerosis before age 45, high cholesterol levels develop a greater risk than average of developing atherosclerosis.

Many factors help determine whether the LDL-cholesterol level is high or low. The following factors are the most important:

- Heredity
- Diet
- Weight
- Physical activity/exercise
- Age and sex
- Alcohol
- Stress
Heredity

Genes influence the levels of LDL ("bad") cholesterol. One specific form of inherited high cholesterol that affects 1 in 500 people is familial hypercholesterolemia, which often leads to early heart disease. But even if you do not have a specific genetic form of high cholesterol, genes play a role in influencing the LDL-cholesterol level. *(Shoenfeld et al., 2001)*

Diet

Two main nutrients in the foods make the LDL ("bad") cholesterol level go up: saturated fat, a type of fat found mostly in foods that come from animals; and cholesterol, which comes only from animal products. Saturated fat raises LDL-cholesterol level more than anything else in the diet *(Kromhout, 1999)*. Eating too much saturated fat and cholesterol is the main reason for high levels of cholesterol and a high rate of heart attacks worldwide. Reducing the amount of saturated fat and cholesterol is a very important step in reducing the blood cholesterol levels *(Denke, et al., 1993)*.

Weight

Excess weight tends to increase LDL ("bad") cholesterol level. Weight loss helps to lower high LDL-cholesterol level and overweight. Weight loss also helps to lower triacylglycerol and raise HDL ("good") cholesterol levels *(DiBuono, 1999)*.
**Physical activity/exercise**

Regular physical activity may lower LDL ("bad") cholesterol and raise HDL ("good") cholesterol levels (Willich, 1993).

**Age and sex**

Before the age of menopause, women usually have total cholesterol levels that are lower than those of men of the same age. As women and men get older, their blood cholesterol levels rise until about 60 to 65 years of age. After the age of about 50, women often have higher total cholesterol levels than men of the same age (Pekkamen, 1987).

**Alcohol**

Alcohol intake increases HDL ("good") cholesterol but does not lower LDL ("bad") cholesterol (Hein, 1996). It is not certain whether alcohol reduces the risk of heart disease. Drinking too much alcohol can damage the liver and heart muscles, lead to high blood pressure, and raise serum triacylglycerol levels. Because of the risks, involved alcoholic beverages should not be used as a way to prevent heart disease (Marques, 1996).

**Stress**

Stress over a long term has been shown in several studies to raise blood cholesterol levels (Jiang, 1996). When some people are under stress, they...
console themselves by eating fatty foods. The saturated fat and cholesterol in these foods contribute to higher levels of blood cholesterol (McCann, 1990).

**COMPLICATIONS OF HIGH CHOLESTEROL IN THE BLOOD STREAM**

A high cholesterol level in conjunction with other adverse factors increases the risk of developing atherosclerosis and cardiovascular disease.

Atherosclerosis results in narrowing of the arteries. This does not occur suddenly, but builds up over several years during which cholesterol and fat have been deposited in the artery walls. The result is that the arteries become constricted and hardened, their elasticity disappears and the volume of blood able to travel through them is reduced (Ornish et al., 1990).

The symptoms are therefore the consequences of cardiovascular disease. They depend on the degree of narrowing, the likelihood that the plaque is going to rupture (vulnerability) and the organ supplied by the affected arteries.

- In the brain, an atherosclerotic carotid or cerebral (brain) artery might block with clotted blood (thrombus) or a smaller intracerebral vessel may rupture causing a local haemorrhage. Both these circumstances result in a stroke (cerebrovascular accident or CVA).

- In the heart, narrowed coronary arteries cause angina, and ruptured plaques cause coronary thrombosis (myocardial infarct)
Stages in the development of Atherosclerosis

Mild Plaque

Moderate Plaque

Severe Plaque

Regular Fatty Streak

Adapted from Paul et al., Princen from connective tissue disease at TNO pharma, the Netherlands (2000)
which may lead to reduced heart function (heart failure) if a significant amount of heart muscle is damaged.

- Carotid arteries in the neck can become narrowed and may lead to clots forming in the neck and floating downstream into the brain, causing a stroke (CVA) or recurrent temporary strokes (transient ischaemic attacks, also known as TIAs).

- Leg pain on exertion can be experienced due to atherosclerosis in the arteries that supply the lower limbs (intermittent claudication). If a major peripheral vessel to a lower limb blocks suddenly, an acutely ischaemic leg will occur which may be limb-threatening. In the worst cases of chronic lower limb atherosclerosis, this can lead to a leg so starved of blood that it cannot survive and requires amputation.

- It is common in those people most affected to have the disease in several arteries throughout their circulation including the aorta (the main artery in the chest and abdomen, the renal (kidney) arteries and the mesenteric (intestinal) vessels (Hein et al., 1996).

Hyperlipidemia is generally recognized as a major risk factor in the development of atherosclerosis. The lipid hypothesis states that reduction in the serum lipid levels may be accompanied by a proportional reduction in the incidence of atherosclerotic disease. Although this theory has not been proved,
several drugs are being used to reduce serum lipid levels and research continues in this area (Lutgens et al., 1999).

Hypolipidemic drugs may lower serum triacylglycerols, cholesterol or both. Since triacylglycerol cholesterol circulate in the form of lipoproteins, hypolipidemic drugs will also have a pronounced effect on serum lipoproteins.

**Hypolipidemic drugs**

The most effective means of lowering blood cholesterol is to reduce dietary saturated fat intake (Raonskov, 2000). Treatment of elevated cholesterol includes diet, weight loss, regular exercise and occasionally medications. Studies have suggested that the use of hypolipidemic medications, that is, drugs that lower cholesterol and/or triacylglycerol often slow down progression of atherosclerosis and by this means reduce the incidence and deaths from CHD.

Currently available hypolipidemic drugs are (Gotto, 1995):

a. HMG-COA reductase inhibitors
b. Drugs that lower the concentration of plasma lipoprotein
c. Bile acid sequestrants

**Statins**

The statins are the most widely used medications today in lowering LDL cholesterol. Most of the clinical trials that showed heart attack reduction and
HMG-COA Reductase inhibitors

Mevastatin

Simvastatin

Lovastatin
improved longevity used one of the statins as the cholesterol lowering medication. Statins are well tolerated with low side effect rates when used long term. Statins not only lower blood LDL cholesterol levels, they also help increase HDL cholesterol levels.

The statin medicines are marketed as:

- Lescol (fluvastatin sodium) made by Novartis
- Lipitor (atorvastatin calcium) made by Parke-Davis and Pfizer
- Mevacor (lovastatin) made by Merck
- Pravachol (pravastatin sodium) made by Bristol-Myers Squibb
- Zocor (simvastatin) made by Merck

The statins act by repressing or inhibiting an enzyme called HMG-CoA reductase. The role of this enzyme is the promotion of a chemical reaction early in the synthesis of cholesterol. By inhibiting HMG-CoA reductase, the statins hinder the production (synthesis) of cholesterol by the liver. Diminished synthesis of cholesterol in the liver in turn stimulates (increases) the activity of LDL receptors on the surface of liver cells. Increasing LDL receptor activity decreases LDL cholesterol levels in blood.

Studies have conclusively established that lowering LDL cholesterol with diet and statins reduces the risk of a second heart attack. The prevention of recurrent heart attacks in patients who have already suffered a heart attack is called secondary prevention.

Studies have also demonstrated that reducing LDL cholesterol with diet and stains reduces the risk of having the first heart attack. Prevention of heart
attacks in those who have never had a heart attack is called primary prevention. Studies have also confirmed that reducing LDL cholesterol benefits both men and women.

Statins are currently the most important class of medications in lowering LDL cholesterol, which is now the most important first step in preventing atherosclerosis and heart attacks. But statins are not the only answer. Other cholesterol-altering medications can also be important in the fight against atherosclerosis in certain patients with familial hypercholesterolemia (FH), a statin alone may not be enough when LDL cholesterol levels are very high. A statin may need to be combined with another medication such as cholestyramine or nicotinic acid in order to lower the LDL cholesterol to acceptable levels.

Statins may also not be as effective as other medications in treating elevated Lp(a) cholesterol levels and in enlarging small LDL cholesterol particle sizes. For example, estrogen and niacin are more effective than statins in decreasing the blood Lp(a) cholesterol levels. Gemfibrozil and Niacin are more effective than statins in raising blood HDL levels and in increasing the size of the LDL cholesterol particle. Diets rich in B vitamins or vitamin supplements, such as folic acid and vitamin B6, help lower blood homocysteine levels. Elevated homocysteine levels also aggravate atherosclerosis (Shu-Long Jen, 1997).
Nicotinic acid

Nicotinic acid (niacin) is a B vitamin. An average American diet contains 15-30 mg of niacin per day. However, in treating blood cholesterol and triacylglycerol disorders, high doses (1-3 grams a day) of nicotinic acid are necessary. Nicotinic acid increases HDL cholesterol, lowers LDL cholesterol, and improves the LDL/HDL ratio. Nicotinic acid also increases LDL cholesterol particle sizes while lowering Lp(a) cholesterol and triacylglycerol levels. Nicotinic acid is most suited for individuals whose only problem is low HDL cholesterol. Nicotinic acid used alone can raise HDL cholesterol levels by 30% or more.

Nicotinic acid not as effective as a stain in lowering LDL cholesterol levels. The most common side effect of nicotinic acid is a flushing sensation of the face and a general sense of itching, which occur about half an hour after taking the drug. Another side effect is upset stomach. Another side effect is irritation of the liver with an abnormal elevation of liver enzymes in the blood. This liver irritation is usually reversible upon discontinuing nicotinic acid. Other side effects of nicotinic acid include aggravating blood sugar levels in patients with diabetes mellitus and precipitating painful arthritis attacks in patients with gout (Gotto, 1995).

Gemfibrozil

Gemfibrozil (Lipid) is a fibric acid derivative that has been reported to raise HDL levels by about 15%. Gemfibrozil can also lower triacylglycerol
levels and increase the size of LDL cholesterol particle sizes. Therefore, gemfibrozil is best suited for patients with elevated triacylglycerol levels, LDL cholesterol pattern B, and low HDL cholesterol (Tasaka, 1995). Gemfibrozil is not as effective as the statins in lowering LDL cholesterol and is insufficient for this purpose when used alone.

Gemfibrozil (Iopid)

The side effects of gemfibrozil include nausea, stomach upset, and sometimes diarrhea. Like the statins and nicotinic acid, it can also cause liver irritation. The liver irritation is usually mild and reversible, but it occasionally can be severe enough to require stopping the drug. Gemfibrozil can cause gallstones when used over several years. The drug can also intensify the effectiveness of blood thinners such as Coumadin when both medications are used together. Thus, the dose of Coumadin should be adjusted to avoid over-thinning of the blood, which can lead to excessive bleeding (Tasaka, 1995).

Cholestyramine

Cholestyramine (Questran) and colestipol (Colestid) are sand-like materials which bind bile salts in the intestine and allow fat and cholesterol to be eliminated in the stool. Cholestyramine is a resin that increases LDL
receptor activity and lowers LDL cholesterol. Cholestyramine has been used effectively in combination with gemfibrozil to help lower LDL cholesterol levels. With these drugs, cholesterol can be reduced by 20%, but triacylglycerol levels may increase. These drugs can have the side effects of bloating, nausea, indigestion, and constipation. They also interfere with the absorption of many other drugs from the stomach and intestine (Murray M, 1995).

\[
\text{Cholestyramine (questran)}
\]

\[
\text{Resin} - \text{N}^+\text{R}_3\text{Cl}^- + \text{R}^+\text{CO}_2^- \\
\text{Resin} - \text{N}^+\text{R}_3\text{CO}_2^- \text{ R}^+ + \text{Cl}^-
\]

**CLOFIBRATE (ANTICHOLESTEROL) (ATROMID-S)**

Clofibrate the ester of an aryl-oxyalkanoic acid, reduces plasma TG (and VLDL). The ester is absorbed from the intestinal tract, hydrolysed, and the acid form is the metabolite which appears in the plasma. Clofibrate acts by depression of hepatic lipoproteins, perhaps as a result of reduced freefatty acid flux to the liver, and by enhancing the degradation of VLDL by increasing lipoprotein lipase activity. Clofibrate is usually well tolerated but side effects have included dyspepsia, nausea, allergic entaneous reactions, decreased libido and impotence, weight gain, alopecia, myalgia and leukopenia. It is completely
absorbed from the intestine and the acid has a mean half life of 15 hrs. The major fraction is albumin bound. Essentially all is excreted in the urine-60% as glucuronide. Clofibrate is mainly indicated in hyperlipidemias of types IIb, III, IV & V.

Clofibrate (Atromid-s)  
Chemical Name: ethyl-2-(4-chlorophenoxy) 2-methyl propionate isobutyric ester

Mechanism of action

- Increases the clearance of the triacylglycerol-rich lipoproteins by increasing the activity of lipoprotein lipase (Segal, 1972).

- In patients with hypercholesterolemia, the body cholesterol pools are decreased as faecal and biliary cholesterol excretions are increased.

- Due to the decrease in VLDL concentrations, the content of triacylglycerol in HDL is decreased, the total HDL is slightly increased, cholesterol biosynthesis in the liver is inhibited, fatty acid oxidation by the liver may be increased (Decoopman, 1977).

Clofibrate treatment is beneficial in patients with familial dysbetalipoproteinaemia, to produce VLDL reductions in patients with
moderately endogenous hypertriglyceridemia and brings about variable effects in patients with severe mixed lipemia. Clofibrate has been reported to have no effect on the lipemia of patients with primary chylomicronemia due to congenital deficiency of lipoproteinlipase and it has no value in the treatment of familial hypercholesterolemia.

The side-effects of clofibrate include (Gotto, 1995),

- Nausea, gastrointestinal tract discomfort.
- Myalgia associated with increased levels of creatinine phosphokinase. This occurs more often in patients with low serum albumin levels and should thus not be given to patients with nephritis.
- Rare reports of a weak association with GIT carcinoma, and a modest increase in the incidence of cholelithiasis (gallstones).
- Rare toxic effects are dermatitis, hepatic dysfunction and bone marrow depression.
- Incidence of decreased libido, breast tenderness, alopecia and brittle hair have been reported.

**ECLIPTA ALBA**

More recently, attention on more natural methods of cholesterol lowering are coming into vogue. Today, all over the world a search is on for a new drug
which could control hypolipidemia with little or no side effects. In this era of molecular thinking, the biological value of a drug, and evidence for the total absence of undesirable side effects and/or toxicities play an important role.

Of the many plants having hypolipidemic effect, the most commonly used herbal drugs are the crude gum of guggulu (Nair, et al., 1994), garcinia (Haymsfield, et al., 1998) cambogia fruit extract and tree backs of terminalia arjuna (Ram, et al., 1997). One among these traditional herbs, *Eclipta alba*, is chosen for the present study as a hypolipidemic agent.

*Eclipta alba* is a traditional Ayurvedic herb which grow and abundantly in the tropical and sub-tropical parts of the world (Dhar, et al., 1968). In Ayurvedic medicine *Eclipta alba* is said to be the best drug for the treatment of liver cirrhosis (Chandra, et al., 1987) and infective hepatitis (Dixit, et al.,
1979). It is widely used in India for liver enlargement, jaundice (Dixit, et al., 1981) and other ailments of the liver and gall bladder (Mogri, et al., 1981).

*Eclipta alba* is commonly called as eclipta, bhringaraj, and false daisy and it belongs to the family compositae (Chopra, et al., 1986).

This annual is a creeping and moisture-loving herb; it has a short, flat or round stem and small white flowers on a long stalk. The leaves are opposite and lance-shaped. Eclipta grows abundantly in the tropics and is used with success in Ayurvedic medicine. In India it is used in the treatment of liver cirrhosis and infective hepatitis. Also for liver enlargement, jaundice and other ailments of the liver and gall bladder. In scientific studies eclipta alba also shows good antifungal activity. Eclipta and mineral oil (USP) keeps the hair black and lustrous (The Wealth of India, 1952).

In Suriname’s traditional medicine, eclipta is used against anaemia, dysentery, eye diseases, asthma (Leal, et al., 2000) and liver cirrhosis. The juice of Eclipta together with honey, is used to treat upper respiratory congestion in children.

**Traditional Uses**

Bhringaraj is commonly used as a deobstruent to promote bile flow and to protect the liver parenchymal tissue in viral hepatitis and other conditions involving hepatic enlargement. The fresh juice of the leaves is given in the treatment of edema, fevers, liver disorders, and rheumatic joint pains; it is also used to improve the appetite and to stimulate digestion (Second supplement
to Glossary of India 1965-81). The juice is given with honey to treat upper respiratory congestion in children. A hair oil prepared from boiling the fresh leaves with either coconut or sesame oil renders the hair black and lustrous. It is popularly used to enhance the memory and has a reputation as an antiaging agent in Ayurveda. A herbal preparation is made with sesame oil and used over glandular swellings and various skin conditions. The leaf juice is also effective when applied externally to treat minor cuts, abrasions, and burns (Dube, et al., 1978).

_Eclipta alba_ is used in treating Viral hepatitis, hepatic enlargement with biliary stasis, hair hygiene, impaired memory, minor cuts, abrasions and burns.

**Clinical Research**

_Eclipta alba_ protected guinea pigs against mortality from carbon tetrachloride-induced liver damage. In the control group there was a 77.7% mortality rate after 24 hours versus 22.3% in the _Eclipta alba_-treated group. Serum transaminases were also significantly lower in the treated group (Mogri, et al., 1981). Histopathological examination of the liver revealed a reduction of parenchymal damage in the _Eclipta alba_-treated animals. Similar hepatoprotective effects have also been reported in rabbits. Gupta _et al._, (1976) reported _Eclipta alba_ to possess myocardial depressant and hypotensive effects. There are also reports of clinical improvement in the treatment of infective hepatitis. The alcoholic extract has shown antiviral activity against Ranikhet disease virus (Sankaran, 1980).
Table 1: System-wise Pharmacological Action and Therapeutic uses of *Eclipta alba* (Ashwini Kumar *et al.*, 1986)

<table>
<thead>
<tr>
<th>System</th>
<th>Pharmacological actions</th>
<th>Therapeutic uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Externally</td>
<td>Anti-inflammatory, Analgesic Astringent action on wound, Wound healing promoter</td>
<td>Elephantiasis, wounds, headache Migraine, white hairs.</td>
</tr>
<tr>
<td>Skin</td>
<td>-</td>
<td>Leprosy, Leucoderma, Urticaria and other minor skin diseases.</td>
</tr>
<tr>
<td>Eye</td>
<td>Improves vision</td>
<td>Night blindness</td>
</tr>
<tr>
<td>N.S.</td>
<td>Analgesic</td>
<td>Headache, Vertigo</td>
</tr>
<tr>
<td>D.S.</td>
<td>Appetizer, Digestive, Liver tonic increases bile flow, anthelminthic</td>
<td>Loss of appetite, Indigestion hepatomegaly, Splenomegaly, Jaundice, piles. castor oils in worms.</td>
</tr>
<tr>
<td>G.U.S.</td>
<td>Diuretic, Aphrodisiac (Seeds)</td>
<td>Burning Micturition</td>
</tr>
<tr>
<td>C.V.S.</td>
<td>Hypotensive</td>
<td>Hypertension, Anaemia, Oedema.</td>
</tr>
<tr>
<td>R.S.</td>
<td>Palliative of kapha dosha</td>
<td>Cough, Bronchial Asthma.</td>
</tr>
</tbody>
</table>

N.S Nervous System;
G.U.S Genito Urinary System
R.S. Respiratory System
D.S. Digestive System;
C.V.S.: Cardio Vascular System,

Although modern drugs are effective in the symptomatic control of disease their use is often associated with a number of undesirable side effects. Results of World Health Organisation study, in patients who used clofibrate, suggested that clofibrate might increase the patient's risk of cancer, liver disease and pancreatitis, although it might also decrease the risk of heart attack.
In order to overcome these adverse effects, search is on for a traditional ayurvedic herbal drug with no side effects. One such drug is *Eclipta alba*, which offers significant protection against liver damage, cancer and other diseases in addition to its action on the lipids. Hence, *Eclipta alba* is chosen for our present study as a hypolipidemic agent against high fat diet induced hypercholesterolemia in rats.

**Experimental induction of hypercholesterolemia and hyperlipidemia**

The history of induction of experimental hyperlipidemia had been reviewed by Katz and Stamles (1953) and by Myasnikow (1960) and Schettler (1961).

Early pioneers Saltykow (1908) were able to induce hyperlipidemia in rabbits by feeding cholesterol rich diet. The famous experiments by Anitschkow (1914) and (1913) established that pure cholesterol can induce hyperlipidemia in rabbits and in his later studies he confirmed the atherogenic stimulus by this sterol beyond doubt and opened the flood gates for a stream of investigation involving cholesterol feeding.

The albino rat has long been believed to be refractory to the development of hyperlipemia by various workers. In 1968, Wissler *et al.*, experimentally evoked a non reactive type of coronary arterial lipidosis with heavy infiltration of tunica intima and associated with a high degree of hypercholesterolemia and were successful in producing proliferative vascular lesions by prolonged feeding of fat enriched diet, containing cholesterol and choline to hypothyroid rats.
Hypercholesterolemia and hypertriglyceridemia have been defined as risk factors for hyperlipidemia. Animal studies with induction of hyperlipidemia produce arterial lesions resembling atherosclerosis.

Metabolic alterations due to hyperlipidemia in general and hypercholesterolemia in particular are not confined to the blood vessels but occur in other tissues or organs which are bathed by the blood plasma. Popjak, 1946 has observed that feeding of excess cholesterol and choloic acid in experimental animals expands bile acid, alters carbohydrate metabolism and elevates concentration of liver cholesterol. These response patterns of bile acid metabolism to dietary cholesterol are consistent with changes in blood cholesterol levels in various species.

Cholesterol feeding in experimental animals induces a marked change in the structure, composition, electrophoretic mobility and atherogenicity of plasma lipoproteins changes in different lipoprotein classes following cholesterol diet have been well documented by the extensive work done by (Tararak and Adgamova, 1973) on various animal species.

Though rabbits are probably the best established model for atherosclerosis, atherogenesis in rats are more akin to the humans and with a proper atherogenic diet they are susceptible to development of atherosclerosis. The rats are easy to handle and their low cost is suitable for mass studies. Despite certain morphologic differences between man and rat, lipid metabolism of the artery wall is very similar at comparable stages of the disease and justifies the use of rats as an experimental model for atherosclerosis.