EMACER MONOGRAPH

Hyperlipoproteinemias cause atherosclerosis which is a major cause of death in the developed world and is also now becoming a major cause of morbidity and mortality in India, especially with changing lifestyles and increasing stress and food habits shifting towards the 'fast food' era. If is extremely important to understand the risk factors, the criteria for starting treatment, the efficacy and safety profile of drugs for hyperlipoproteinemia and the drugs which are available for pharmacotherapy especially in the Indian perspective. The significant contributions of Central Drug Research Institute, Lucknow has developed potent lipid lowering drugs like Gugulipid an already marketed product. At present it is recommended that for mild to moderate hyperlipoproteinemia Guggul extracts would be an extremely cost effective indigenous choice for mild to moderate hyperlimia would be manageable. The other alternatives like Gemfibrozil though highly effective for moderate to severe hyperlipoproteinemia are extremely expensive and have other side effects and only very few can afford to take it on long term basis in India.

Levels of lipoproteins (and therefore lipids, particularly LDL cholesterol) increase slightly as people age. Levels are normally slightly higher in men than in women, but levels increase in women after menopause. The increase in levels of lipoproteins that occurs with age can result in hyperlipoproteinemia and increase the risk of atherosclerosis. Factors that increase the risk of hyperlipoproteinemia include having close relatives who have had hyperlipoproteinemia (having a family history of the disorder), being overweight, consuming a diet high in saturated fats and cholesterol, being physically inactive, and consuming a moderate to excessive amount of alcohol.

Some people are more sensitive to the effects of diet than others, but most people are affected to some degree. One person can eat large amounts of animal fat, and the total cholesterol level does not rise above 200 mg/ml. Another person can follow a strict low-fat diet, and the total cholesterol does not fall below 260 mg/ml. This difference seems to be mostly genetically determined. A person's genetic makeup influences the rate at which the body makes, uses, and disposes of these fats. Eating excess calories can result in high triglyceride levels, as can excessive consumption of alcohol.

Some disorders, including some hereditary disorders (cause lipid levels to increase. Diabetes that is poorly controlled or kidney failure can cause total cholesterol levels or triglyceride levels to increase. Obstructive liver disease and an underactive thyroid gland (hypothyroidism) can cause the total cholesterol level to increase .Oral contraceptives, corticosteroids, and thiazide diuretics (to some extent) can cause triglyceride levels to increase

High lipid levels in the blood usually cause no symptoms. Occasionally, when levels are particularly high, fat is deposited in the skin and tendons and forms bumps called xanthomas. Very high triglyceride levels can cause the liver or spleen to enlarge and may increase the risk of developing pancreatitis. Pancreatitis can cause severe abdominal pain and is occasionally fatal.

The risk of developing atherosclerosis increases as the total cholesterol level increases. Atherosclerosis can affect the arteries that supply blood to the heart (causing coronary artery disease), those that supply blood to the brain (causing cerebrovascular disease), and those that supply the rest of the body (causing peripheral arterial disease). Therefore, having a high total cholesterol level also increases the risk of having a heart attack or stroke. Having a low total cholesterol level is generally considered better than having a high one. However, having a very low cholesterol level may not be healthy either .For adults, a total cholesterol level of less than 200 mg/ml is desirable. In parts of the world (such as China and Japan) where the average cholesterol level is 150 mg/ml, coronary artery disease is less common than it is in countries such as the United States. The risk of a heart attack more than doubles when the total cholesterol level approaches 300 mg/ml.

The total cholesterol level is only a general guide to the risk of atherosclerosis. Levels of the components of total cholesterol—particularly LDL and HDL cholesterol—are more important. A high level of LDL (bad) cholesterol increases the risk. A high level of HDL (good) cholesterol decreases the risk, and a low level of HDL cholesterol (defined as less than 40 mg/ml) increases the risk. Experts consider an LDL cholesterol level of less than 100 mg/ml optimal.

Whether high triglyceride levels increase the risk of a heart attack or stroke is uncertain. Triglyceride levels higher than 150 mg/ml are considered abnormal, but high levels do not appear to increase risk for everyone. For people with high triglyceride levels, the risk of heart attack or stroke is increased if they also have a low HDL cholesterol level, diabetes, kidney disease, or many close relatives who have had atherosclerosis (family history).

Cholesterol is an extremely important biological molecule that has roles in membrane structure as well as being a precursor for the synthesis of the steroid hormones and bile acids. Both dietary cholesterol and that synthesized *de novo* are transported through the circulation in lipoprotein particles. The same is true of cholesteryl esters, the form in which cholesterol is stored in cells.
The synthesis and utilization of cholesterol must be tightly regulated in order to prevent over-accumulation and abnormal deposition within the body. Of particular importance clinically is the abnormal deposition of cholesterol and cholesterol-rich lipoproteins in the coronary arteries. Such deposition, eventually leading to atherosclerosis, is the leading contributory factor in diseases of the coronary arteries.

The process of cholesterol synthesis has five major steps:

- 1. Acetyl-CoAs are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
- 2. HMG-CoA is converted to mevalonate
- 3. Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP), with the concomitant loss of CO_2
- 4. IPP is converted to squalene
- 5. Squalene is converted to cholesterol.

The process begins with acetyl-CoA, a two-carbon molecule sometimes referred to as the "building block of life." Three acetyl-CoA molecules combine to form six-carbon hydroxymethyl glutaric acid (HMG). The step from HMG to mevalonate requires an enzyme, HMG-CoA reductase. Statin drugs work by inhibiting this enzyme—hence the formal name of HMG-CoA reductase inhibitors. Herein lies the potential for numerous side effects, because statin drugs inhibit not just the production of cholesterol, but a whole family of intermediary substances, many if not all of which have important biochemical functions in their own right.

Cholesterol is one of three end products in the mevalonate chain. The two others are ubiquinone and dilochol. Ubiquinone or Co-Enzyme Q10 is a critical cellular nutrient biosynthesized in the mitochondria. It plays a role in ATP production in the cells and functions as an electron carrier to cytochrome oxidase, our main respiratory enzyme. The heart requires high levels of Co-Q10. A form of Co-Q10 called ubiquinone is found in all cell membranes where it plays a role in maintaining membrane integrity so critical to nerve conduction and muscle integrity. Co-Q10 is also vital to the formation of elastin and collagen. Side effects of Co-Q10 deficiency include muscle wasting leading to weakness and severe back pain, heart failure (the heart is a muscle!), neuropathy and inflammation of the tendons and ligaments, often leading to rupture

Normal healthy adults synthesize cholesterol at a rate of approximately 1g/day and consume approximately 0.3g/day. A relatively constant level of cholesterol in the body (150 - 200 mg/ml) is maintained primarily by controlling the level of *de novo* synthesis. The level of cholesterol synthesis is regulated in part by the dietary intake of cholesterol. Cholesterol from both diet and synthesis is utilized in the formation of membranes and in the synthesis of the steroid hormones and bile acids. The greatest proportion of cholesterol is used in bile acid synthesis.

Fenugreek seed

Fenugreek is a food and a spice commonly eaten in many parts of the world, and has been used for centuries by practitioners of Ayurvedic and Traditional Chinese Medicine. Research in the past two decades has shown that fenugreek seeds help balance blood sugar in diabetics. Fenugreek may also have beneficial effects on triglycerides.

Studies in rodents indicate that fenugreek has immune stimulating, anti-oxidant and anti-tumor properties, and protects the liver against alcohol toxicity. Administration of fenugreek seed extract with ethanol to rats prevented the enzymatic leakage and the rise in lipid peroxidation. The seeds exhibited appreciable antioxidant property in vitro which was comparable with that of reduced glutathione and vitamin E. Further, examination of liver and brain revealed that, extract of fenugreek seeds could offer a significant protection against ethanol toxicity. Fenugreek also has anti-ulcer properties.

Supplementation of fenugreek leaves lower lipid profile in streptozotocin-induced diabetic rats.
J Med Food. 2004 Summer;7(2):153-6.
Many studies have shown the lipid-lowering effect of fenugreek leaves in diabetes mellitus. Albino Wistar rats were randomly divided into six groups: normal untreated rats; streptozotocin (STZ)-induced diabetic rats; STZ-induced rats + fenugreek leaves; STZ-induced rats + fenugreek leaves; STZ-induced rats + glibenclamide; and STZ-induced rats + insulin. Rats were made diabetic by STZ injected intraperitoneally. Fenugreek leaves were supplemented in the diet daily to diabetic rats for 45 days, and food intake was recorded daily. Blood glucose, total cholesterol, triglycerides, and free fatty acids were determined in serum, liver, heart, and kidney. Our results show that blood glucose and serum and tissue lipids were elevated in STZ-induced diabetic rats. Supplementation of fenugreek leaves lowered the lipid profile in STZ-induced diabetic rats.

Enhancement of circulatory antioxidants by fenugreek during 1,2-dimethylhydrazine-induced rat colon carcinogenesis.
J Biochem Mol Biol Biophys. 2002 Aug;6(4):289-92.
Some studyhave shown the modulatory effect of fenugreek seeds (a spice) on circulatory lipid peroxidation (LPO) and antioxidant status during 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in male Wistar rats. Inclusion of fenugreek in the diet significantly decreased LPO with simultaneous enhancement of circulating antioxidants. We report that fenugreek exert its chemopreventive effect by decreasing circulatory LPO and enhancing antioxidant levels.

Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Eur J Clin Nutr. 1990 Apr;44(4):301-6.
In one of the studies effect of fenugreek seeds (Trigonella foenum graecum) on blood glucose and the serum lipid profile was evaluated in insulin-dependent (Type I) diabetic patients. Isocaloric diets with and without fenugreek were each given randomly for 10 d. Defatted fenugreek seed powder (100 g), divided into two equal doses, was incorporated into the diet and served during lunch and dinner. The fenugreek diet significantly reduced fasting blood sugar and improved the glucose tolerance test. There was a 54 per cent reduction in 24-h urinary glucose excretion. Serum total cholesterol, LDL and VLDL cholesterol and triglycerides were also significantly reduced. The HDL cholesterol fraction, however, remained unchanged. These results indicate the usefulness of fenugreek seeds in the management of diabetes.

The saponins are thought to inhibit cholesterol absorption and synthesis, and may also have a positive effect on blood sugar control in people who suffer from diabetes. In terms of weight control, the soluble fibre in fenugreek seeds can reduce dietary fat absorption by binding to fatty acids as well as create a sensation of "fullness" and reduced appetite. Thus it is a good agent for reducing serum cholesterol.

The herb affects cholesterol levels in the same fashion as Pectin. Fenugreek also contains saponins. The saponin-containing plant fibres could inhibit the intestinal absorption of cholesterol much the same as Alfalfa saponins do (i.e. by absorbing bile acids and increasing the loss of bile acids by fecal excretion, which then leads to an increased conversion of cholesterol into bile acid by the liver).

Safety of Fenugreek

As a commonly eaten food, fenugreek is generally regarded as safe. The only common side effect is mild gastrointestinal distress when it is taken in high doses. Animal studies have found fenugreek essentially non-toxic.

Curcuma longa

Curcuma longa, a perennial herb, is a member of the Zingiberaceae (ginger) family. The plant grows to a height of three to five feet, and is cultivated extensively in Asia, India, China, and other countries with a tropical climate. It has oblong, pointed leaves and bears funnel-shaped yellow flowers. (1) The rhizome is the portion of the plant used edicinally; it is usually boiled, cleaned, and dried, yielding a yellow powder. Dried Curcuma longa is the source of the spice turmeric, the ingredient that gives curry powder its characteristic yellow color. Turmeric is used extensively in foods for both its flavor and color. urmeric has a long tradition of use in the Chinese and Ayurvedic systems of medicine, particularly as an anti-inflammatory agent, and for the treatment of flatulence, jaundice, menstrual difficulties, hematuria, hemorrhage, and colic. Turmeric can also be applied

topically in poultices to relieve pain and inflammation. (2) Current research has focused on turmeric's antioxidant, hepatoprotective, anti-inflammatory, anticarcinogenic, and antimicrobial properties, in addition to its use in cardiovascular disease and astrointestinal disorders.Turmeric's protective effects on the cardiovascular system include lowering cholesterol and triglyceride levels, decreasing susceptibility of low density lipoprotein (LDL) to lipid peroxidation, (32) and inhibiting platelet aggregation. (33) These effects have been noted even with low doses of turmeric.

Chemistry
Curcuma longa rhizomes yield about 8% essential oils and 10% fatty oil.
Three major constituents have been identified:

(1.) Curcumin (diferuloyl methane)
(2.) Curcumin methane.
(3.) Di-hydroxy cinnamoyl methane.

The volatile oils contain cineol, camphor and linalool and are probably responsible for the antispasmodic activity. Borneol is present in the essential oil fraction and is largely responsible for the digestion-improving properties.

A study of 18 atherosclerotic rabbits given low-dose (1.6-3.2 mg/kg body weight daily) turmeric extract demonstrated decreased susceptibility of LDL to lipid peroxidation, in addition to lower plasma cholesterol and triglyceride levels. The higher dose did not decrease lipid peroxidation of LDL, but cholesterol and triglyceride level decreases were noted, although to a lesser degree than with the lower dose. (32) Turmeric extract's effect on cholesterol levels may be due to decreased cholesterol uptake in the intestines and increased conversion of cholesterol to bile acids in the liver. (14) The inhibition of platelet aggregation by C. longa constituents is thought to be via its potentiation of prostacyclin synthesis and inhibition of thromboxane synthesis.

Turmeric is known to reduce elevated levels of triglycerides and lipids. Turmeric when feeded to rats shows elevation in the activity of hepatic cholesterol –7 alpha-hydroxylase which is the rate-limiting enzyme of bile acid synthesis. This suggests that turmeric can stimulate the conversion of cholesterol bile acid, an important pathway of elimination of cholesterol from the body. However, simultaneous stimulation of cholesterol synthesis by turmeric suggests that there may not be any significant contribution of stimulation of bile acid biosynthesis to the hypoglycemia cholesterolemic action of turmeric and the latter action may be said due to interference with exogenous cholesterol absorption.
Turmeric used in the doses of 4mg/kg/day or curcumin 0.4mg/kg/day decrease serum lipid peroxides, which play an important role in pathogenesis of age related disease like atherosclerosis. Turmeric /curcumin inhibits the proliferation of vascular smooth muscles, increases fibrinolytic activity and have anti platelet activity, these properties of

curcumin may also contribute to the hypolipidimic action of turmeric. In clinical trial conducted turmeric 50gm/day was found to be as effective as clofibrate.

Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats

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Molecular and Cellular Biochemistry (Netherlands), 1997, 166/1-2 (169-175)

Streptozotocin-induced diabetic rats were maintained on 0.5% curcumin containing diet for 8 weeks. Blood cholesterol was lowered significantly by dietary curcumin in these diabetic animals. Cholesterol decrease was exclusively from LDL-VLDL fraction. Significant decrease in blood triglyceride and phospholipids was also brought about by dietary curcumin in diabetic rats. In a parallel study, wherein diabetic animals were maintained on a high cholesterol diet, the extents of hypercholesterolemia and phospholipidemia were still higher compared to those maintained on control diet. Curcumin exhibited lowering of cholesterol and phospholipid in these animals also. Liver cholesterol, triglyceride and phospholipid contents were emin showed a distinct tendency to counter these changes in lipid fractions of liver. This effect of curcumin was also seen in diabetic animals maintained on high cholesterol diet. Dietary curcumin also showed significant countering of renal cholesterol and triglycerides elevated in diabetic rats. In order to understand the mechanism of hypocholesterolemic action of dietary curcumin, activities of hepatic cholesterol-7a-hydroxylase and HMG CoA reductase were measured. Hepatic cholesterol-7a-hydroxylase activity was markedly higher in curcumin fed diabetic animals suggesting a higher rate of cholesterol catabolism.

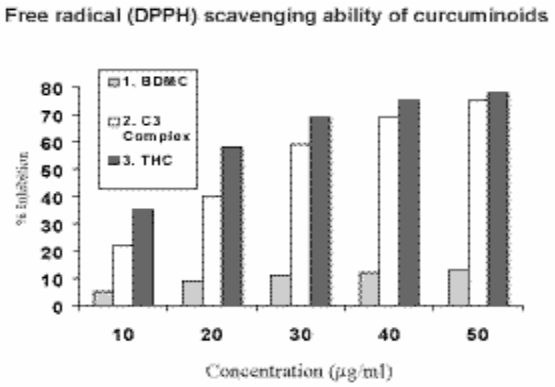
There are several studies on the beneficial effects of oral curcumin intake and cholesterol reduction. According to the Indian J Physiology Pharmacology [Oct 1992, 36 (4) p239-43], administration of curcumin was found to significantly lower serum and tissue cholesterol levels. Also, oral administration of curcumin decreased lipid peroxidation, indicating the use of curcumin helps in conditions associated with peroxide induced injury such as liver damage and arterial diseases. In the journal of Molecular and Cellular Biochemistry (Netherlands) [1997, 166/1-2 (169-175)], rats were fed a diet of 0.5% curcumin for eight weeks. Cholesterol, specifically the LDL-VLDL fraction, was lowered. There was also a decrease in blood triglycerides and phospholipids. In a parallel study, diabetic animals were fed a high cholesterol diet; in this case curcumin still lowered cholesterol blood levels. These studies and many others can be found on this web site.

Antioxidant Effects
Water- and fat-soluble extracts of turmeric and its curcumin component exhibit strong antioxidant activity, comparable to vitamins C and E. A study of ischemia in the feline heart demonstrated that curcumin pretreatment decreased ischemia-induced changes in the heart. (6) An in vitro study measuring the effect of curcumin on endothelial heme

oxygenase-1, an inducible stress protein, was conducted utilizing bovine aortic endothelial cells. Incubation (18 hours) with curcumin resulted in enhanced cellular resistance to oxidative damage Another in vitro study demonstrated that low concentrations of curcumin incubated with activated macrophages resulted in a decrease in mRNA levels and nitric oxide synthase activity. This study demonstrates curcumin's antioxidant role in down-regulating nitric oxide formation, a key element in inflammation and possibly in the process of carcinogenesis.

The unique composition of curcuminoids and their demonstrated capabilities to not only scavenge and neutralize harmful existing free radicals, but also to prevent their formation merits their description as "bioprotectant". This bioprotective action of curcuminoids validates their potential role as antioxidants for oral administration as well as for topical application to retard the progression of free radical mediated disease processes.

Curcuminoids thus represent a class of valuable phytonutrients with unique bioprotective properties. If regularly administered as nutritional supplement, these natural compounds would potentially help in maintaining good health and in slowing down the progression of various disease conditions. Topical application would help in neutralizing damaging free radicals on the surface of the skin, thereby retarding aging and damage due to ultraviolet radiation.



Safety and Dosage

No significant toxicity has been reported following either acute or chronic administration of turmeric extracts at standard doses. At very high doses (100 mg/kg body weight), curcumin may be ulcerogenic in animals, as evidenced by one rat study. Because of its numerous protective benefits, regular addition of turmeric to animal feed may be beneficial. For a specific therapeutic effect, the typical canine dosage of curcumin is 50-250 mg three times daily, depending on the size of the animal. If using whole turmeric, the average canine dosage is one-half teaspoon twice daily. Feline dosages are in the range of 50-100 mg daily of curcumin and approximately one-quarter teaspoon daily if using whole turmeric. Equine dosages of curcumin are much higher due to the size of the animal, and range between 1,200 and 2,400 mg daily. Curcumin and turmeric research in these animals is limited and the dosages stated above are estimates only.

The fruits of *Emblica officinalis* (Amla) are widely used in the Indian System of Medicine and are believed to increase defense against disease. In the present study, the effects of chronic oral administration of fresh fruit homogenate of Amla on: (i) myocardial antioxidant system and (ii) oxidative stress induced by ischemic-reperfusion injury (IRI) in rat heart were investigated. Fresh amla fruit homogenate, in three different doses (250, 500 and 750 mg/kg) and normal saline (C) were administered orally to Wistar albino rats (120-150 gms) of either sex daily for 30 days. There was reduction in basal myocardial lipid peroxidation, as evidenced by decreased thiobarbituric acid reactive substances (TBARS) level, and augmentation of myocardial endogenous antioxidants, like superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) in the treated rats. Hearts were also subjected to *in vitro* IRI (9 min of global ischemia, followed by 12 min of reperfusion, Langendorff's mode). Significant myocyte injury and rise in myocardial TBARS along with depletion of SOD, catalase, GSH (reduced glutathione) and GPx occurred in the control group. No significant increase in myocardial TBARS and depletion of antioxidant enzymes were observed in the treated groups. Myocyte injury was evident only in 250 mg/kg group. The results indicate that chronic *Emblica officinalis* administration causes myocardial adaptation by augmenting endogenous antioxidants and protects rat hearts from oxidative stress associated with ischemic-reperfusion injury.

Ezetimibe reduces cholesterol absorption. This decreases the content of cholesterol in chylomicrons. In the circulation, chylomicrons deliver triglycerides to muscle and fat tissue, but return to the liver with a full complement of cholesterol that was absorbed by the intestine. Therefore, ezetimibe reduces the flux of cholesterol from the intestine to the liver. Because this cholesterol is packaged and resecreted by the liver into the blood as VLDL particles, containing apo B-100, and because VLDL particles are the precursor particles of LDL in plasma, reduced flux of cholesterol to VLDL particles will lower LDL cholesterol. This mechanism is distinct from that of statins, which promote the clearance of LDL principally in the liver. Evidence that ezetimibe reduces LDL

production may be inferred from a study in which patients with homozygous familial hypercholesterolemia were treated with ezetimibe plus statin therapy. The efficacy of statins is reduced in these individuals, in whom the LDL receptor is functionally absent. However, the efficacy of ezetimibe is largely unaffected. It is important to consider that ezetimibe therapy may lead to increased LDL receptor expression in individuals with functional LDL receptors, and that this may comprise a component of the mechanism by which ezetimibe lowers plasma LDL cholesterol and triglyceride concentrations.

Macrophage-mediated oxidation of LDL is probably a hallmark in early atherosclerosis. The LDL oxidative state is elevated by increased ratio of poly/mono unsaturated fatty acids, and it is reduced by elevation of LDL-associated antioxidants such as vitamin E, beta-carotene, lycopene, and polyphenolic flavonoids. The macrophage oxidative state depends on the balance between cellular NADPH-oxidase and glutathione (a potent antioxidant.) LDL-associated polyphenolic flavonoids which inhibit its oxidation, can also reduce the macrophage oxidative state, and subsequently the cell-mediated oxidation of LDL. So what all of this complex sounding terminology means to you is that cholesterol is not all bad. Take a close look at your HDL:LDL ratio and make sure you get enough dietary antioxidants

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