Introduction to Hyperlipidemia and Its Management: A Review

[1]Priyanka Phogat, [2]Aakash Deep, [3]Prabodh Chander Sharma, [4]Sanjeev K. Mittal, [5]Saloni Kakkar, [1]Ruchi Goyal, [6]Kapil Thakral

[1]Department of Pharmaceutical Sciences, Hindu College of Pharmacy, Sonepat-131001
[2]Department of Pharmaceutical Sciences, G.V.M. College of Pharmacy, Sonepat-131001
[3]Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119
[4]Department of Pharmaceutical Sciences, Goenka College of Pharmacy, Sikar-332301
[5]Department of Pharmaceutical Sciences,Maharishi Dayanand University,Rohtak-124001
[6]Department of Pharmaceutical Sciences, Keshav College of Pharmacy, Assand-132046

Summary

Hyperlipidemia is caused by overabundance of lipids or fatty substances in the blood and is an important risk factor in development of atherosclerosis and heart disease. Hyperlipidemia may be caused by genetic factors or by generalized metabolic disorders like diabetes mellitus, excessive alcohol intake, hypothyroidism, or primary biliary cirrhosis. Alteration in Cholesterol, trigyceride and very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and intermediate-density lipoproteins (IDL), which are different forms of lipids, responsible for possible complications in human body such as acute pancreatitis, occlusion of blood vessels and reduced elasticity of the lumen of the artery. Moreover risk increases with diabetes mellitus, hypothyroidism, nephrosis, alcoholism, use of oral contraceptives, family history of hyperlipidemia and improper diet that is high in fat and cholesterol. Though drugs therapies available for the treatment of hyperlipidemia includes use of drugs like Niacin, Fibrates (clofibrate, gemfibrozil), HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin and fluvastatin), Bile acid binding resins (cholestyramine and cholestipol) and Probucol but associated with lots of side effects. Therefore, herbal treatment for hyperlipidemia has been appreciated because of no side effects, economic and easy availablility. Herbal drugs involved in the treatment of hyperlipidemia are Allium sativum, Allium cepa, Bosswellia serrata, Brassicavercapitata, Commiphora mukul, Garcinia cambogia, Glycine max, Phyllanthus niruri, Moringa olifera, Saururus chinensis, Curcuma loga, Terminalia arjuna, Acorus calamus, Liriope platyphylla, Citrus, Hibiscus sabdariffa, Schisandrin B, ShanZha, Ulva Pertusa, Picrorrhiza rhizoma.

***For Correspondence**
Faculty, Department of Pharmaceutical Sciences,
G.V.M. College of Pharmacy, Sonepat-131001
Mobile: +919896096727
E.mail: aakashdeep82@gmail.com

Introduction

The hyperlipidemias are a complex group of diseases that can be designated either primary or secondary, depending on their causes. Primary hyperlipidemias can result from a single inherited gene defect, or more commonly, are caused by a combination of genetic and environmental factors. Secondary hyperlipidemias are the result of a more generalized metabolic disorder such as diabetes mellitus, excessive alcohol intake, hypothyroidism, or primary biliary cirrhosis.[2]Hyperlipidemia is also known by other names such as acquired hyperlipoproteinemia; high blood cholesterol; high blood triglycerides; high cholesterol; high triglycerides; hyperlipidemia.[1]

Hyperlipidemia is caused by excess lipids or fatty substances in the blood and is an important risk factor in developing atherosclerosis and heart disease. Forms of lipids in the blood are cholesterol, triglycerides, and lipoproteins, which are molecules of fat and cholesterol linked to protein. Types of lipoproteins are: very low-density lipoproteins VLDL, low-density lipoproteins LDL and intermediate-density lipoproteins (IDL). Chylomicrons are also classified as lipoproteins and are composed of triglycerides, cholesterol and protein. There are also high-density lipoproteins HDL that are inversely related to heart disease risk and are therefore known as "antirisk" factors.[1]There are six types of hyperlipidemia that are differentiated by the type(s) of lipids that are elevated in the blood.

Type of Hyperlipoproteinemias

(i) Primary hyperlipoproteinemias can be due to: (a) A single gene defect, is familial, and called 'monogenic' or genetic. (b) Multiple genetic, dietary and physical activity related causes: 'polygenic' or multifactorial.

On the whole, LDL is the primary carrier of plasma CHE, and VLDL that of TGs.[3] The important features of major types of hyperlipoproteinemias are given in tables below,

Table 1: Types of Primary Hyperlipoproteinemias

Type	Disorder	Cause	Occurrence	Elevated Plasma Level	Plasma Lipids	
					CH	TG
I	Familial lipoprotein lipase deficiency.	G	Very rare	Chylomicron	↑↑	↑↑↑↑
IIa	Familial Hypercholesterolemia.	G	Less common	LDL	↑↑	N
IIb	Polygenic Hypercholesterolemia.	MF	Commonest	LDL	↑	N
III	Familial dysbetalipoproteinemia.	G	Rare	IDL, Chy.rem.	↑	↑
IV	Hypertriglyceridemia.	MF, G	Common	VLDL	N	↑↑
V	Familial combined hyperlipidemia	G	Less common	VLDL, LDL	↑	↑

CH-Cholesterol; TG-Triglycerides; G-Genetic; MF-Multifactorial;
Chy.rem.-Chylomicron remnants; VLDL-Verylow-density lipoproteins;
IDL-intermediate density lipoprotein; LDL-low density lipoprotein.

ii) Secondary hyperlipoproteinemias can be due to: Diabetes, Myxoedema, Nephritic Syndrome, Chronic Alcoholism, Drugs (Corticosteroids, oral contraceptives, β and blockers) Treatment with oral contraceptives may provoke an iatrogenic endocrine disorder, occasionally resulting in increased triglyceridemia, stimulated by the estrogen content of the pill. Similarly, beta-blockers may be associated with Hypertriglyceridemia and at times also with reduced HDL-cholesterol.

Table 2: Secondary Form of Hyperlipoproteinemia[40]

S.No.	Disorder	Plasma lipid/Lipoprotein changes.	Mechanism/s
1.	Diabetes Mellitus.	Raised VLDL, occasionally LDL.	Increased VLDL secretion, reduced catabolism.
2.	Alcoholic Hyperlipidemia.	Raised VLDL.	Increased VLDL secretion.
3.	Uremia.	Raised VLDL.	Impaired VLDL catabolism.
4.	Oral contraceptives.	Raised VLDL, occasionally reduced HDL.	Impaired VLDL catabolism.
5.	Beta-blockers.	Raised VLDL, reduced HDL.	Impaired activation of lipoprotein lipase.
6.	Nephrotic syndrome.	Raised VLDL & LDL.	Compensatory for urinary albumin loss; partial inhibition of lipoprotein lipase.
7.	Corticosteroids.	Raised VLDL & LDL.	Inhibited lipoprotein lipase.
8.	Hypothyroidism.	Raised LDL, occasionally VLDL.	Reduced LDL receptors.
9.	Primary biliary cirrhosis.	Increased lipoprotein X.	Interaction of bile acids with LDL in the circulation.

Nutritional Supplements

Many double-blind trials have demonstrated that fish oils[4] (also called fish-oil concentrates) lower TG levels. The amount of fish oil used in much of the research was an amount that provided 3,000 mg per day of omega-3 fatty acids. Cod liver oil, another source of omega-3 fatty acids, has also been found to lower TGs.[5] Omega-3 fatty acids from fish oil and cod liver oil have been reported to affect blood in many other ways that might lower the risk of heart disease.[6] However, these supplements sometimes increase LDL cholesterol—the bad form of cholesterol. Research shows that when 900 mg of garlic extract is added to fish oil, the combination still dramatically lowers TG levels but no longer increases LDL cholesterol.[7] People who take fish oil may also need to take vitamin E to prevent the oil from undergoing potentially damaging oxidation in the body.[8] In one clinical trial, 300 IU of vitamin E per day prevented oxidation damage in individuals taking 6 grams of fish oil per day.[9] Pantethine is a byproduct of pantothenic acid (vitamin B5). Several clinical trials have shown that 300 mg of pantethine taken three times per day will lower TG levels. Pantothenic acid, which is found in most B vitamins, does not have this effect.[10] The niacin form of vitamin B3 is used by doctors to lower cholesterol levels, but niacin also lowers TG levels. Some doctors recommend inositol

hexaniacinate (a special form of vitamin B3) as an alternative to niacin. This form of vitamin B3 does not typically cause a skin flush and is said to be safer for the liver than niacin. In a preliminary trial, supplementation with 800 mg of calcium per day for one year resulted in a statistically significant 35% reduction in the average TG level among people with elevated cholesterol and triglycerides. However, in another trial, calcium supplementation had no effect on TG levels.[11] One of the differences between these two trials was that more people in the former trial had initially elevated TG levels. In a double-blind trial, 30 people with type 2 (non-insulin-dependent) diabetes received 200 mcg of chromium per day (as chromium picolinate) for two months and a placebo for an additional two months. The average TG level was significantly lower (by an average of 17.4%) during chromium supplementation than during the placebo period. Some, but not all, trials support these findings. It is not clear whether chromium supplementation affects TG levels in non-diabetics, but some evidence suggests that it does not.[12] L-carnitine is another supplement that has lowered TGs in several clinical trials. Some doctors recommend 1–3 grams of carnitine per day, in the form known as L-carnitine.[13] A double-blind trial found that a supplement of 5 grams of creatine plus 1 gram of glucose taken four times per day for five days followed by twice a day for 51 days significantly lowered serum total triglycerides in both men and women. However, another double-blind trial found no change in any of these blood levels in trained athletes using creatine during a 12-week strength training program. Creatine supplementation in this negative trial was lower—only five grams per day was taken for the last 11 weeks of the study.[14]

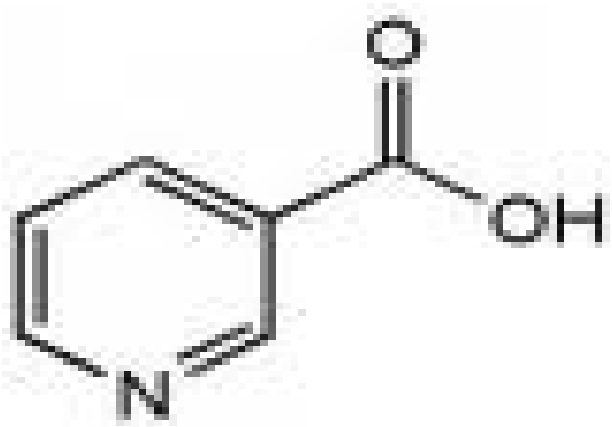
Chemotherapeutic Agents

Antihyperlipidemic drugs target the problem of elevated serum lipids (in both primary and secondary hyperlipidemias) with complementary strategies. These drugs may be used singly or in combination, but are always accompanied by the requirement that dietary lipids intake be significantly low, especially cholesterol and saturated fats, and the caloric content of the diet must be closely monitored.

A) Niacin (Nicotinic Acid)

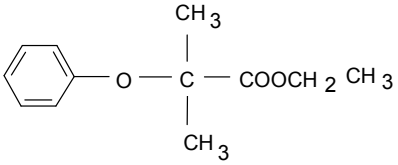
Nicotinic acid has a broad lipid lowering ability, but its clinical use is limited due to its unpleasant side effects. The structure[15] is shown below:

Nicotinic Acid

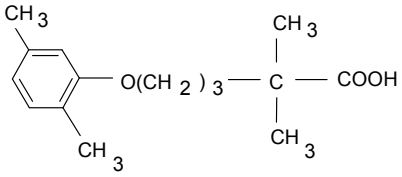


B) The Fibrates

Important Drugs among Fibrates are Clofibrate and Gemfibrozil. However, gemfibrozil has largely replaced clofibrate clinically because of the higher incidence of mortality with the latter agent. The deaths were not associated with cardiovascular causes, but rather with malignancy or complications due postcholecystectomy and pancreatitis.



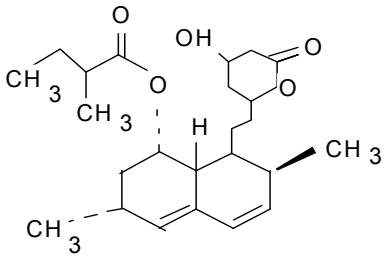
Clofibrate



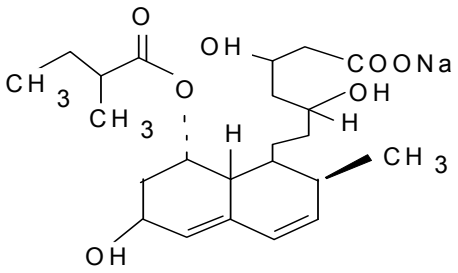
Gemfibrozi

C) HMG-CoA Reductase Inhibitors

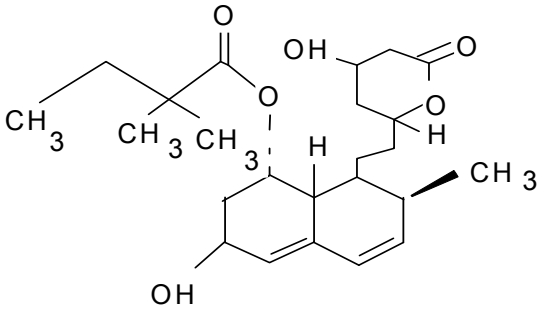
Important Drugs included are- Lovastatin, Pravastatin, simvastatin, Fluvastatin. This novel group of Antihyperlipidemic agents inhibits the first committed enzymatic step of sterol synthesis. As structural analogs of the natural substrate, 3-hydroxy-3-methylglutaric acid (HMG), all members of this group compete to block hydroxymethylglutaryl Coenzyme A reductase (HMG-CoA reductase). Except for fluvastatin, the other HMG reductase inhibitors are chemical modifications of compounds occurring naturally in fungi. The structures[15] are shown below:



Lovastatin



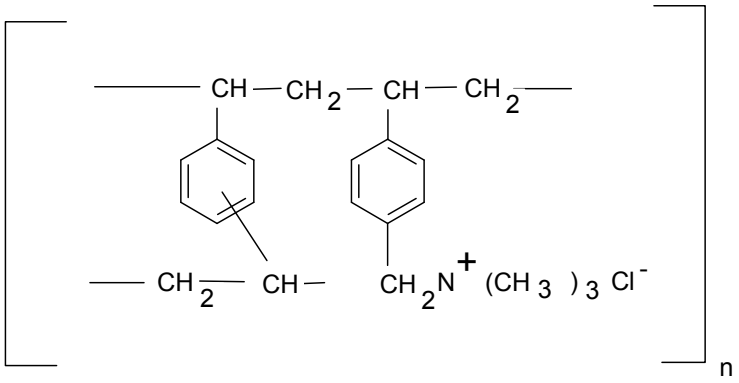
Pravastatin Sodium



Simvastatin

D) Bile acid binding resins.

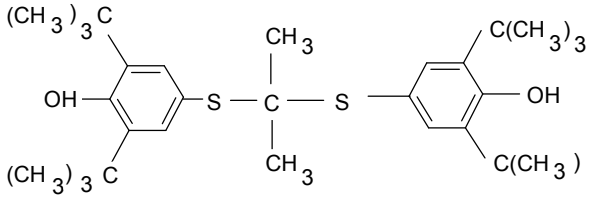
Important dugs included are- cholestyramine and cholestipol. Though safe, the resins are unpalatable, inconvenient and acute nausea flatulence heart burn, constipation, steatorrhoea and deficiency of fat soluble vitamin. Patient acceptability is poor.[2]



Cholestyramine

E) Probucol

Probucol was introduced in the 1970s, but because it reduced HDL levels to a greater extent than those of LDLs, it fell into disfavor. Newer information indicating that its antioxidant properties may be important in blocking atherosclerosis resulted in renewed interest. The structure[15] is shown below:

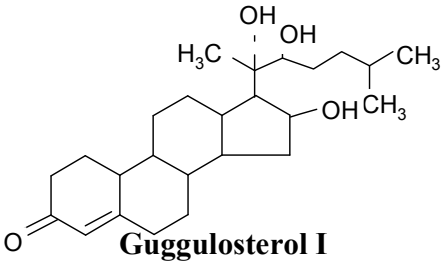


Probucol

Herbal Drugs Therapy

1) *Commiphora mukul (Gum guggul, Myrrh Extract) (Burseraceae)*

Guggul plant is native to Africa. In India, guggul plant is mainly found in Rajasthan and Gujarat states. Ajmer and Jaisalmer districts of Rajasthan are the prominent habitats.[41] The resin of the *Commiphora mukul* tree has been used in Ayurvedic medicine for more than 2000 years to treat a variety of ailments. Studies in both animal models and humans have shown that this resin, termed gum guggul, can decrease elevated lipid levels. The stereoisomers E- and Z-guggulsterone have been identified as the active agents in this resin. Guggul also contains three new sterols viz. guggulosterol I, guggulosterol II, guggulosterol III. Recent studies have shown that these compounds are antagonist ligands for the bile acid receptor farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis. It is likely that this effect accounts for the hypolipidemic activity of these phytosteroids.

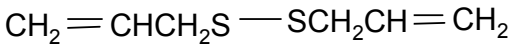


Guggulosterol I

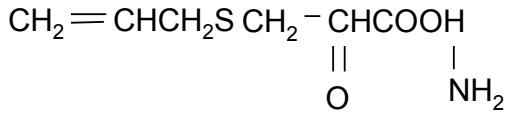
In clinical trials of standardized guggul extract, no significant side effects other than occasional mild gastrointestinal distress have been seen. Laboratory tests conducted in the course of these trials did not reveal any alterations in liver or kidney function, blood cell numbers and appearance, heart function, or blood chemistry.[16-19]

2) *Allium sativum (Garlic) (Liliaceae)*

Garlic is cultivated in Central Asia, southern Europe, U.S.A, and India. In India, it is found in almost all states and cultivated as a spice or a condiment crop. [41]The hypocholesterolemic activity of garlic is mainly due to allicin, a compound that is protective effect of garlic *(Allium sativum)* on circulatory lipid peroxidation and antioxidants was investigated during 7,12-dimethylbenz{a}anthracene(DMBA)-induced hamster buccal pouch carcinogenesis in male Syrian hamsters. Administration of garlic extract significant decreased lipid peroxidation with simultaneous depletion of antioxidants. Garlic exerted its protective effects by decreasing circulatory lipid peroxides and enhancing antioxidants.[20] Volatile oil of the drug is the chief active constituent, and contains allyl propyl disulphide, diallyl disulphide, alliin and allicin. Alliin by action of enzyme allinylase is converted into allicin. Garlic oil is yellow in color.[41]

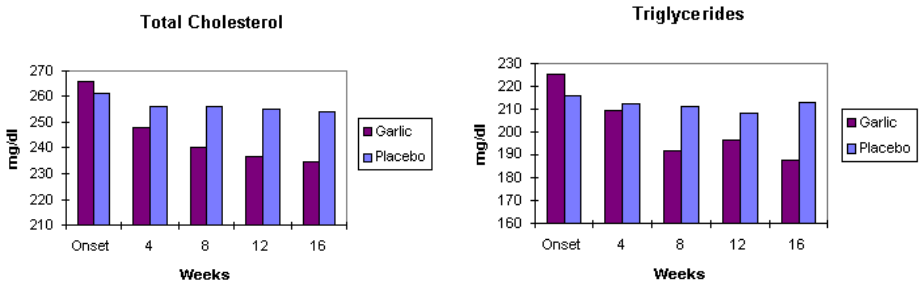


Allicin



Alliin

Overall a 12% reduction in total cholesterol was shown over a placebo and that this reduction was normally evident after only 4 weeks treatment and that this was likely to persist for as long as the study was in progress.



The largest study so far was conducted in Germany where 261 patients from 30 general practices were given either garlic powder tablets or a placebo. After a 12 week treatment period mean serum cholesterol levels dropped by 12% in the garlic treated group and triglycerides dropped by 17% compared to the placebo group

It has been known for several decades that high blood cholesterol is a major risk factor for heart attacks and strokes and that lowering of cholesterol, particularly the low density type called LDL, can significantly reduce the risk for these diseases. However, in the past decade it has been recognized that the real culprit is the oxidized LDL. Oxidized LDL, but not native or un-oxidized LDL, damages the lining of the blood vessels, causes growth of cells that form the wall of the blood vessel, and causes thickening and narrowing of blood vessels; all these events are recognized to contribute to heart attacks and strokes.

Short-term supplementation of garlic in human subjects has demonstrated an increased resistance of LDL to oxidation. These data indicate that suppressed LDL oxidation is one of the powerful mechanisms accounted for the benefits of garlic to protect hearts and blood vessels.[20]

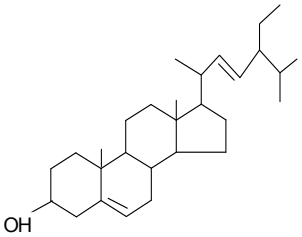
3) *Garcinia cambogia (Garcinia Extract) (Guttiferae)*

Extract of *Garcinia cambogia* fruit was used as a potential antiobesity agent. *Garcinia* extract inhibits lipid droplet accumulation in fat cells without affecting adipose conversion.[21]

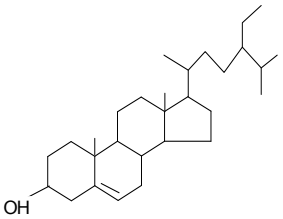
4) *Glycine max (Soy, Soja) (Leguminosae)*

Postmenopausal women have an increased risk of coronary heart disease. Oxidation of low-density lipoprotein (LDL) has been implicated in atherogenesis, and the presence of modified LDL in plasma appears to represent LDL oxidation *in vivo*. Because previous studies have demonstrated a strong antiatherogenic effect of estrogen due to its antioxidant activity and similar antioxidant activity was found for specific isoflavones derived from soy extract, the antioxidant activity of a phytoesterogen extract derived from soy and alfalfa was studied. Copper mediated LDL oxidation was inhibited in the presence of soy and alfalfa extracts, and this effect was further enhanced in the presence of acerola cherry extract, which is rich in ascorbic acid. In the presence of acerola cherry extract, both soy and alfalfa extracts potentially inhibited the formation of LDL. Acerola cherry extract can enhance the antioxidant activity of soy and alfalfa extracts in a variety of LDL oxidation systems. The protective effect of extracts is attributed to the presence of flavonoids in soy and alfalfa extracts and ascorbic acid in acerola extract, which may act synergistically as antioxidants.[22]

It contains appreciable amounts of the phytosterols stigmasterol and sitosterol.[41]



Stigmasterol



Sitosterol

5) *Phyllanthus niruri (Euphorbiaceae)*

Lipid lowering activity of *Phyllanthus niruri* alcoholic extracts in triton-induced hyperlipaemia was examined in rat. It was observed that administration of triton in rat caused increase in serum cholesterol by 3.5 fold, Phospholipid 2 fold and triglyceride 1.8 fold, respectively. Administration of *P.niruri* at the dose of 200mg/kg simultaneously with triton lowered the level of total cholesterol, Phospholipid and triglyceride by 27, 25 and 24 percent, respectively. In an experiment with cholesterol fed rats, P.niruri at a dose of 100mg/kg lowered the elevated level of very low density and low-density lipoprotein lipids in hyperlipidemic and drug fed animals.[23]

6) *Ocimum sanctum (Tulsi, sacred basil) (Labiatae)*

It is herbaceous, much branched annual plant found throughout India. [41] Effect of administration of 200mg/kg body weight of the aqueous extract of tulsi mixed with diet for eight weeks to diabetic rats was studied. There was significant reduction in fasting blood glucose, serum lipid profile, lipid peroxidation products (LPO), and improvement in glucose tolerance. The aqueous extract also decreased LPO formation {thiobarbituric acid reactive substances (TBARS)} and increased antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) in plasma and rat liver, lung, kidney and brain. The decrease in TBARS and increase in GSH, SOD, CAT, GPX, and GT clearly shows an antioxidative property of Ocimum sanctum.[24]

7) *Daewhang-Whangryunhaedok-Tank*

Herbal drug, Daewhang-whangryunhaedok-Tank (DWK) has been evaluated for its effects on experimental hyperlipidemic rats and mice induced by corn oil and high cholesterol diet. Oral administration of DWT significantly inhibited the increase of serum triglyceride and LDL-cholesterol levels in rats. Also, oral administration of DWT significantly prevented the increase of serum total cholesterol triglyceride and LDL-cholesterol, and liver total cholesterol and triglyceride in 1 percent cholesterol-diet fed mice. These results suggest that DWT is effective for the treatment of hyperlipidemia.[25]

8) ***Liposem***

The methanolic extract of Liposem was found to scavenge hydroxyl and superoxide free radicals, the IC50 required being 70.5 and 45.0 microgram respectively. The lipid peroxidation in rat liver homogenate induced by Fe2+ ascorbate system was also found inhibited by 273.5 microg of the extract. The hypolipidaemic effect was assessed by serum lipid profile in dietary hyperlipidaemic rats and found to have decreased dose dependently in all the four different concentrations of administration (100,200,300 and 400 mg/kg body wt.). Liposem significantly raised HDL cholesterol and the HDL/LDL+VLDL ratio. The atherogenic index and the reduction in body weight were significant, indicating the effectiveness against hyperlipidemia and obesity.[26]

9) *Saururus chinensis*

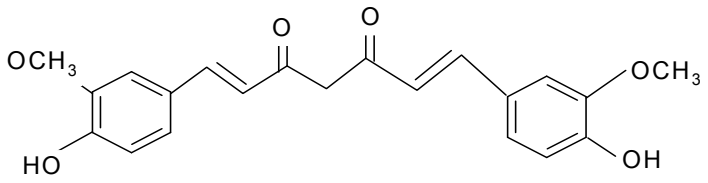
A new diarylbutane lignan, saururin A, and a known 8-O-4'-type neolignan, machilin D, were isolated from a total methanol extract of the underground parts of *Saururus chinensis*. The structures were elucidated by spectroscopic data analysis. Saururin A, machilin D and virolin exhibited significant LDL antioxidant activity in the thiobarbituric acid-reactive substance (TBARS) assay with IC50 values of 8.5,2.9, and 4.3 microM, respectively.[27]

10) *Moringa olifera (Sahjina) (Moringaceae)*

Rabbits were fed *Moringa olifera* (200 mg/kg/day, p.o) or lovastatin (6mg/kg/day, p.o.) in banana pulp along with standard laboratory diet and hypercholesterolaemic diet for 120 days. Moringa olifera and lovastatin were found to lower the serum cholesterol, Phospholipid, triglyceride, VLDL, LDL, cholesterol to phospholipid ratio and atherogenic index, but were found to increase the HDL ratio (HDL/HDL-total cholesterol) as compared to the corresponding control groups. Treatment with *M. olifera* or lovastatin in normal rabbits decreased the HDL levels. However, HDL levels were significantly increased or decreased in *M.olifera* or lovastatin treated hypercholesterolaemic rabbits, respectively. Lovastatin-*M.olifera* treated hypercholesterolaemic rabbits showed decrease in lipid profile of liver, heart and aorta while similar treatment of normal animals did not produce significant reduction in heart.[28]

11) *Curcuma longa (Turmeric) (Zingiberaceae)*

Curcuma is a genus of about 70 species of rhizomatous herbs distributed in South East Asia and especially India, China, Thailand, Italy, Malaysia, Archipelago and N. Australia.[41] Curcumin (diferuloylmethane), a major component of turmeric, is a yellow pigment obtained from rhizomes of *Curcuma longa,* is commonly used in Indian cuisine as a spice and food-coloring agent. Curcumin is reported to have hypolipidaemic effect in cholesterol fed rabbits, hypercholesterolemic rats and streptozotocin diabetic rats. This could be due to an increase in HDL cholesterol, indicating that curcumin may be mobilizing cholesterol from extra hepatic tissues to liver where it is catabolised. Curcumin is reported to activate the rate-limiting step in cholesterol catabolism, that is, cholesterol 7-α-hydroxylase thereby stimulating the conversion of cholesterol to bile acid, an important pathway in the degradation of cholesterol. The present study shows that the reduction in total cholesterol and triglycerides by curcumin is not attributed to a decrease in absorption of lipids from diet, as lipids (diet) were not administered during the study. Hence, the hypolipidemic effect of curcumin administration could be due to an increased catabolism of cholesterol into bile acids.[29] Curcumin species contain volatile oil, starch and curcumin. The structure of curcumin is shown on the next page:



Curumin

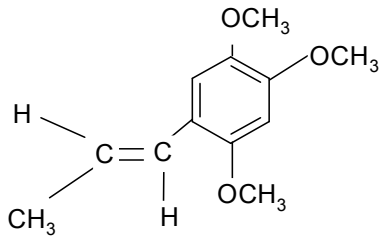
12) ***Terminalia arjuna (Arjun bark) (Combretaceae)***

The tree is common in Indian peninsula.[41] *Terminalia arjuna* bark powder fractionated by solvents viz., petroleum ether, solvent ether ands alcohol has lipids lowering and antioxidant activity. Feeding of the above fractions at the dose of 100 mg/kg in triton induced hyperlipidemic rats caused lowering of plasma lipids and these effects are more pronounced for solvent ether fraction. On the other hand solvent ether and alcoholic fractions at the concentration of 500-micro/ml inhibited the formation of hydroxyl (OH) radicals (40-45 percent) as well as superoxide (O_2) radicals generation (38-62 percent) in non-enzymatic systems in vitro.[30]

13) ***Acorus calamus (Bach, Sweet flag) (Araceae)***

Calamus is native of Eastern Europe and is found wild in England. In India, it is cultivated, as well as, found in Himalayas and also in Sikkim.[41] *Acorus calamus* (family Araceae) commonly known as Vacha, has been indicated in the treatment of lipid disorders in the Indian system of medicine. The effects of the aqueous and hydroalcoholic (100 and 200 mg/kg) were studied by monitoring the serum total cholesterol, triglycerides and HDL cholesterol levels in hyperlipidemic rats. Gemfibrozil at a dose of 10 mg/kg was the reference drug used for comparison. The findings indicate better efficacy with the hydroalcoholic extract as compared to the aqueous extract. The hydroalcoholic extract at a dose of 200mg/kg was founds to bring the total cholesterol and triglyceride levels back to baseline values and the HSDL cholesterol levels were raised back to the baseline values. Saponins separated from the hydroalcoholic extract were also founds to statistically decrease the serum total cholesterol and triglyceride levels, but were unable to bring them back to baseline values. However, saponins were found to be statistically superior in raising the levels of HDL cholesterol, thus indicating their contribution as one of the phytoconstituents of *Acorus calamus*, towards hypolipidemic activity.[31]

It contains 1.5% to 3.5% of volatile oil, starch, resin (2.5%) and tannin (1.5%). Volatile oil contains asaraldehyde. The other contents of the oil are asarone and eugenol.[41]



Asarone

14) ***Liriope platyphylla (Liriopis tuber extract)***

The effects of Liriopis Tuber (*Liriope platyphylla*) extracts to high cholesterol diet was examined on lipid metabolism in rats. Male Sprague-Dawley rats of 90+-10 g were divided into 6 groups; basal diet (normal group), 1% cholesterol diet (control group), high cholesterol diet supplemented with 3,5 % water extracts (C3W, 5CW group) and high cholesterol diet supplemented with 3,5% MeOH extracts (C3M, C5M group). These experimental diets were fed for 4 weeks. The lipid contents on serum, liver, feces were lower in Liriopis Tuber extracts groups than control group. Especially, the effect of water extract was better than MeOH extract.[32]

15) ***Retama raetam***

In normal and diabetic rats, the aqueous extract of *Retama raetam* RR (20 mg/kg) induced a significant decrease of the plasma triglycerides concentrations one week after repeated oral administration. This reduction was maintained two weeks after once daily repeated oral administration. A significant decrease of plasma cholesterol levels was also observed one week and two weeks after repeated oral administration. The aqueous extract of RR exhibits lipid and body weight lowering activities in both normal and severe hyperglycemic rats after repeated oral administration of RR aqueous extract at a dose of 20 mg/kg.[33]

16) ***Arachis hypogaea***

The hypolipidemic effect of aqueous extract of *Arachis hypogaea* was investigated in normal and alloxan-induced diabetic rats. The extract caused a significant decrease of fasting blood glucose of both normal and alloxan-induced diabetic rats from 102.60+-1.65 mg/dl to 88.79+-0.94 mg/dl for normal and 189.0+-30.79 mg/dl to 107.55+-1.54 mg/dl for alloxan-induced diabetic rats. The extract also caused a significant decrease in serum triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol in both normal and alloxan-induced diabetic rats.[34]

17) ***Cyclocarya paliurus (Batal)***

The inhibitory effect of *Cyclocarya paliurus* extract were examined on post-prandial hyperlipidemia in mice. A single oral administration of extract (250 mg/kg) suppressed an increase in plasma triacylglycerol (TG) levels when fed with 5 ml/kg of lard and olive oil. The inhibition rates were 28.6% and 24.1% respectively, but free fatty acid (FFA) levels in plasma were not significantly affected as compared with control group mice. In addition, with an IC50 of 9.1 microg/ml in vitro. These suggested that the hypolipemic action was probably interrelated with suppression of the activity of digestive lipase and as a result, the blood lipid level was reduced.[35]

18) ***Trichilia connaroides***

Hypercholesterolemic activity was studied on normal rats for hexane, chloroform and methanol extracts of *Trichilia connaroides*. The parameters studied include free cholesterol, triglycerides and high-density lipoprotein levels in blood. Only hexane and methanol extracts produced a rise in high-density lipoprotein level and did not show any fall in cholesterol and triglyceride level when compared to control group. On Triton-induced hypercholesterolemia, only cholesterol and triglyceride levels were studied for all the three extracts. Chloroform and methanol extracts produced a significant fall in cholesterol level within 24 h of induction when compared to control group.[36]

19) ***Cynara scolymus***

The methanolic extract from the leaves of artichoke (*Cynara scolymus*) was found to suppress serum triglyceride elevation in olive oil-loaded mice. Through bioassay-guided separation, sesquiterpenes (cynaropicrin, aguerin B, and grosneimin) were isolated as the active components together with new sesquiterpene glycosides (cynarascolosides A, B, and C). The oxygen functional groups at the 3- and 8- positions and exo-methylene moiety in alpha-methylene-gamma-butyrolactone ring were found to be essential for the anti-hyperlipidaemic activity of guaiane-type sesquiterpene. In addition, inhibition of gastric emptying was shown to be partly involved in anti-hyperlipidaemic activity.[37]

20) *Amirkabiria osdorastissima*

Male rabbits were fed: (a) rabbit chow; (b) 1% cholesterol diet; (c) cholesterol diet supplemented with the plant; (d) normal diet supplemented with the plant. After 12 weeks, biochemical factors were measured. The amounts of cholesterol, LDL, HDL, triglyceride and fasting blood sugar (FBS) were determined by enzymatic methods, quantitative CRP was determined by turbidimetric methods, malondialdehyde (MDA) & antioxidant capacity were determined by specterophotometrix methods. The results indicate that there is a significant difference between the groups supplemented with herbal medicine and others in the mean grade of fatty streak of right and left coronary artery and aorta. At the end of the 12-week period cholesterol, LDL & CRP were significantly reduced in groups, which received herbal medicine. The data suggests that *Amirkabiria odorastissima* Mozaffarian has beneficial effects to prevent development of fatty streak.[38]

21) *Citrus*

Formulations containing *citrus* polymethoxylated flavones (PMFs), mainly tangeretin, or citrus flavanone glucosides, hesperidin and naringin were evaluated for cholesterol-lowering potential in hamsters. Diets containing 1% PMFs significantly reduced serum total and very low-density lipoprotein (VLDL)+LDL cholesterol (by 19-27 and 32-40 percent respectively) and either reduced or tended to reduce serum triacylglycerols. Comparable reductions were achieved by feeding a 3% mixture of hesperidin and naringin (1:1,w/w), implying lower hypolipidemic potency of the hesperidin/naringin vs PMFs. HPLC-MS analysis identified high serum, liver, and urine concentrations of tangeretin metabolites including dihydroxytrimethoxyflavone and monohydroxytetramethoxyflavone glucuronides and aglycones. Total liver concentrations of tangeretin derivatives correspond to hypolipidemic concentrations of intact tangeretin *in vitro*.[39]

22) *Hibiscus sabdariffa*

The extract of leaves and calyces of *H. sabdariffa* was evaluated for antihyperlipidemic activities by studying there in vivo effects on cholesterol induced hyperlipidemia. In the study a group of rats treated with the calycis and leaves of H. *Sabdariffa* showed a significant decrease in serum TC, LDL-C, VLDL-C, TAG values alongwith an increase in serum HDL-C levels. The ethanolic extract of calyces showed a significant antihyperlipidemic activity followed by ethanolic extract of leaves.[42]

23) *Schisandrin B*

Schisandrin B is isolated from the fruit of Schisandra chinensis, a traditional Chinese herb which is clinically prescribed for the treatment of hepatitis. Increase in serum triglycerides level was observed with treatment with single oral doses of schisandrin B (in olive oil). In contrast, the LDL-C level was significantly lowered by 28%. However the treatment produced no detectable changes in serum total cholesterol and HDL-C levels in mice. While cholesterol/bile salt treatment did not change the serum triglyceride and total cholesterol level, it caused a significant increase in the LDL-C level but not the HDL-C level.[43]

24) *ShanZha*

Crataegus pimmatifida Bge. Var. *major* N.E. Br. (Rosaceae) is named ShanZha in Chinese, and is widely distributed in the northeast part of China. During the study dyslipidemia and obesity was induced in hamsters using a high fat diet. The group was then treated with ShanZha or vehicle for 7 days. The food intake, body weight and weights of both brown and white adipose tissues were found to decrease in hamsters receiving ShanZha in comparison with vehicle treated

treated control. Plasma levels of HDL-C was elevated whereas TC, TG and LDL-C decreased by this ShanZha treatment.[44]

25) *Ulva Pertusa*

Ulva pertusa is utilized by local inhabitants as a marine vegetable in Asia. Ulvan which is a sulfated polysaccharide from *Ulva pertusa* was degraded to yield two low molecular weight fractions U1 and U2. Rats on a hypercholesterolemic diet for were fed with the fractions for 21 days to evaluate and compare the antihyperlipidemic actions. The results exhibited that that ulvans with different molecular weights showed diverse effects on lipid metabolism. The high molecular weight ulvan was found to be effective in serum total and LDL-cholesterol, whereas low molecular weight fractions were in TG and HDL-cholesterol.[45]

26) *Picrorrhiza rhizome*

Picrorrhiza rhizome (PR), a traditional Korean herbal medicine, is a dried underground stem of *Picrorrhiza kurroa* Benth. (Family: *Scrophulariaceae*). The serum LDL, triglyceride and total cholesterol levels were dose-dependently lowered in PR extracts dosing groups in comparison to that of vehicle control group, respectively. The serum HDL levels were slightly but dose-dependently elevated in PR extracts dosing groups compared to that in vehicle control group, respectively. [46]

References

1. Tripathi, KD. "Hypolipidemic drugs and Plasma expanders". Essentials of Medical Pharmacology, 1994, 3rd edition, New Delhi: Medical Publishers (P) Ltd., 575-586.
2. Mycek, J. Mary; Harvey, A.; Richard; Champe, C. Pamela. "Antihyperlipidemic Drugs". Lippincott's Illustrated Reviews: Pharmacology. Editor: Winters Richard, 1997, 2nd edition, New York: Lippincott-Raven Publishers; 207-216.
3. Cutler, J.; Cocolas, H. George. "Antihyperlipidemic agents". Gisvold and Wilson, Block h. john, Beale M. John. Textbook of Organic Medicinal And Pharmaceutical Chemistry, 2004, 11th edition. London: Lippincott Williams & Wilkins; 667-692.
4. Prichard, BN; Smith, CCT; Ling, KLE; Betteridge, DJ. "Fish oils and cardiovascular disease". *BMJ* 1995; 310:819–820 [editorial/review].
5. Von Schacky, C; Fischer, S; Weber, PC. "Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans". *J Clin Invest* 1985; 76:1626–31.
6. Leaf, A; Weber, PC. "Cardiovascular effects of n-3 fatty acids". *N Engl J Med* 1988; 318: 549–57.
7. Adler, AJ; Holub, BJ. "Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men". *Am J Clin Nutr* 1997, 65, 445–450.
8. Haglund, O; Luostarinen, R; Wallin, R; et al. "The effects of fish oil on triglycerides, cholesterol, fibrinogen and malondialdehyde in humans supplemented with vitamin E". *J Nutr* 1991; 121:165–169.
9. Oostenbrug, GS; Mensink, RP; Hornstra, G. "A moderate *in vivo* vitamin E supplement counteracts the fish-oil-induced increase in in vitro oxidation of human low-density lipoprotein"s. *Am J Clin Nutr* 1993; 57:827S.
10. Arsenio, L; Bodria, P; Magnati, G; et al. "Effectiveness of long-term treatment with pantethine in patients with dyslipidemia". *Clin Ther* 1986; 8:537–545.
11. Carlson, LA; Olsson, AG; Oro, L; Rossner, S. "Effects of oral calcium upon serum cholesterol and triglycerides in patients with hyperlipidemia". *Atherosclerosis* 1971; 14:391–400.
12. Offenbacher, EG; Pi-Sunyer, FX. "Beneficial effect of chromium-rich yeast on glucose tolerance and blood lipids in elderly subjects". *Diabetes* 1980; 29:919–925.

13. Pola, P; Savi, L; Grilli, M; et al. "Carnitine in the therapy of dyslipidemic patients". *Curr Ther Res* 1980; 27:208–216.
14. Volek, JS; Duncan, ND; Mazzetti, SA; et al. "No effect of heavy resistance training and creatine supplementation on blood lipids". *Int J Sport Nutr Exerc Metab* 2000; 10:144–156.
15. S, Harkishan; Kapoor, VK. "Cardiovascular Agents". Medicinal and Pharmaceutical Chemistry, 1994, 1st edition. Delhi. Vallabh Prakashan, SU-221 Pitam Pura; 245-284.
16. Ackerknecht, E.H; 1973. Therapeutics: from the Primitives to the Twentieth Century. Hafner Press, New York.
17. Handbook of Domestic Medicine and Common Ayurvedic Remedies. 1979. Central Council for Research in Indian Medicine and Homeopathy, New Delhi, pp. 91-112.
18. Szapary, PO; Wolfe, ML; Bloedon, LT; et al. "Guggulipid for treatment of hypercholesterolemia: a randomized controlled trial". JAMA 2003; 290:765-772.
19. Malhotra, SC; Ahuja, MM; Sundaram, KR. "Long term clinical studies on the hypolipidaemic effect of Commiphora mukul (Guggulu) and clofibrate". Indian J Med Res 1977; 65:390-395.
20. Silagy, CS; Neil, HAW; 1994, *The Journal of the Royal College of Physicians*, Vol 28 No 1:39-45.
21. Hasegawa, N. " *Garcinia* extract inhibits lipid droplet accumulation without affecting adipose conversion in 3T3-L1 cells", *Phytotherapy Research*, 2001, v.15 (2): 172-173.
22. Hwang J, Hodis H.N., Sevanian A, " Soy and alfalfa phytoesterogen extracts become potent low-density lipoprotein antioxidants in the presence of acerola cherry extract", *Journal of Agricultural and Food Chemistry*, 2001, v.49 (1): 308-314.
23. Khanna A K, Chander R. " Lipid lowering activity of *Phyllanthus niruri*", *Journal of Medicinal & Aromatic Plant Sciences*, 2001, v.22 (Suppl.1): 29-30.
24. Halim EMA, Hussain KJ, Rao M. "Hypoglycemic, hypolipidemic and antioxidant properties of Tulsi", *Indian Journal of Clinical Biochemistry*, 2001, v.16 (2): 190-194.
25. Kim YS, Jung EA, Chang JC, Yang HK, Kim NJ. "Effect of Daewhang-whangryunhaedok-Tnk on hyperlipidemia", *Korean Journal of Pharmacognosy*, 2001, v.32 (2): 145-152.
26. Mary NK, Shylesh BS, Babu BH, Paddikala J. " Antioxidant and hypolipidaemic activity of herbal formulation Liposem", *Indian Journal of Experimental Biology*, 2001, v. 40(8): 901-904.
27. Ahn BT, Lee S, Kim JG, Bok SH, Jeong TS. "Low-density lipoprotein-antioxidant constituents of *Saururus chinensis*", *Journal of Natural Products*, 2001, v. 64 (12): 1562-1564.
28. Mehta K, Balaraman R, Amin AH, Bafna PA, Gulati OD. "Effect of fruits of *Moringa oleifera* on the lipid profile of normal and hypercholesterolaemic rats", *Journal of Ethnopharmacology*, 2004, v. 86(2-3): 191-195.
29. Majithiya JB, Parmar AN, Balaraman R. 2004. Research Letter. In: *Indian Journal of Pharmacology.* Editor: Raveendran R. Medknow Publications; p 382-383.
30. Puri A, Saxena R, Khanna AK, Chander R, Rastogi AK. "Lipid lowering activity of plant *Terminalia arjuna*", 2nd World Congress on " *Biotechnological Developments of Herbal Medicine*" NBRI, Lucknow, UP, 2003, 62.
31. Parab RS, Mengi SA. "Hypolipidemic activity of Acorus calamus in rats", *Fitoterapia*, 2003, v. 40 (1): 25-29.
32. Rhee IJ, Kim EJ, Jeong SW, Yang JH, Lee IS. "Effects of *Liriopis* Tuber extracts on lipid metabolism in rats fed high cholesterol diet", *Korean Journal of Pharmacognosy*, 2003, v.34 (1): 65-69.
33. Maghrani M, Lemhadri A, Zeggwagh NA, Amraoui AE, Haloui M, Jouad H, Eddouks M. 2004. *Journal of Ethnopharmacology*, v. 90(2-3): p.323-329. In: Indian Journal of Pharmacology. Editor: Raveendran R. Medknow Publications; p 170.
34. Bilbis LS, Shehu RA, Abubakar MG. "Hypoglycemic and hypolipidemic effects of aqueous extract of *Arachis hypogaea* in normal and alloxan-induced diabetic rats", *Phytomedicine*, 2003, v.9 (6): 553-555.

35. Kurihara H, Asami S, Shibata H, Fukami H, Tanaka H. "Hypolipemic effect of *Cyclocarya paliurus* Iljinskaja in lipid-loaded mice", *Biological & pharmaceutical* Bulletin, 2003, v. 26 (3): 383-385.
36. Purnima AL, Mathuram V. "Hypocholesterolemic and antihypercholesterolemic activity of extracts of *Trichila connaroids* on rats", *Indian Journal of Pharmaceutical Sciences*, 2003, v. 65 (5): 537-539.
37. Shimoda H, Ninomiya K, Nishida N, Yoshino T, Morikawa T, Matsuda H, Yoshikawa M. "Anti-hyperlipidemic sesquiterpenes and new sesquiterpene glycosides from the leaves of *Cynara scolymus*", Bioorganic & medicinal Chemistry Letters, 2003, v. 13 (2): 223-228.
38. Asgary S, Naderi G, Dashti G, Paknahad Z. "Effect of *Amirkabiria odorastissima* mozaffarin on the development and progression of fatty streaks in hypercholesterolemic rabbits", *Phytotherapy Research*, 2004, v. 18 (5): 370-372.
39. Kurowska EM, Manthey JA. "Hypolipidemic effects and absorption of Citrus polymethoxylated flavones in hamsters with diet-induced Hypercholesterolemia", *Journal of Agricultural & Food Chemistry*, 2004, v.52 (10): 2879-2886.
40. Paeletti, R., Ciseri, R. "Plasma lipid modifying agents". Principles of Pharmacology: Basic concepts and clinical applications. Munson, P. 1994, Chapman & Hall Publishing Inc., 1189-1207.
41. Kokate, CK., Purohit, AP., Gokhale, SB. Pharmacognosy. 2002, Nirali Prakashan, 270-310.
42. Gosain, S, Aakash Deep, et.al. "Hypolipidemic effect of ethanolic extract from the leaves of *hibiscus sabdariffa* in hyperlipidemic rats" Acta. Pol.Pharmaceutica Drug-Research.2010; 67:179-184.
43. Pan Si-Yuan, Dong Hang, Han Yi-Fan , Li Wen-Yuan, Zhao Xing-Ye , Ko Kam-Ming "A novel experimental model of acute hypertriglyceridemia induced by schisandrin B" *European Journal of Pharmacology*, 2006; 537: 200–204.
44. Kuo Daih-Huang, Yeh Ching-Hua, Shieh Po-Chuen, Cheng Kai-Chun, Chen Fu-An, Cheng Juei-Tang "Effect of ShanZha, a Chinese herbal product, on obesity and dyslipidemia in hamsters receiving high-fat diet" *Journal of Ethnopharmacology,* 2009; 124: 544–550.
45. Pengzhan Yu, Ning Li, Xiguang Liu, Gefei Zhou, Quanbin Zhang , Pengcheng Li "Antihyperlipidemic effects of different molecular weight sulfated polysaccharides from *Ulva pertusa* (Chlorophyta)" *Pharmacological Research* 2003; 48: 543–549.
46. Hyeung Sik Lee, Hyo Chan Ahn, Sae Kwang Ku "Hypolipemic effect of water extracts of *Picrorrhiza rhizoma* in PX-407 induced hyperlipemic ICR mouse model with hepatoprotective effects: A prevention study" *Journal of Ethnopharmacology* 2006;105: 380–386