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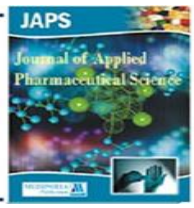

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Drug therapy for hyperlipidaemia (dyslipidaemia) – A review

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ABSTRACT

Lipids are transported in human plasma as complexes bound to proteins called lipoproteins. Elevation of plasma concentration of lipoproteins is called hyperlipoproteinaemia or hyperlipidaemia. Lipoproteins are divided into high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), intermediate density lipoprotein (IDH) chylomicrons and lipoprotein a [Lp(a)]. There is no therapeutic approach that will reduce chylomicron catabolism. HDL is the good lipoprotein. Hypolipidaemic drug therapy can reduce LDL-cholesterol (LDL-C) thus reducing the risk of coronary heart disease. A complete lipoprotein profile of the patient is required (total cholesterol, LDL-C, HDL-C and triglycerides) before commencing drug therapy. The cholesterol lowering drugs include statins, fibrates, bile acid sequestrants, inhibitors of intestinal sterol absorption, nicotinic acid derivatives and others like dextrothyroxine, omega H-3-marine triglycerides. The adverse effects of these drugs were also highlighted.

Key words: Hyperlipidaemia, Drug Therapy, Adverse Effects.

INTRODUCTION

Virtually all the lipids of human plasma are transported as complexes with proteins (apoproteins) because they are insoluble in plasma. Except for fatty acids which are visible in plasma, and bound chiefly to albumin, the lipids are carried in special macromolecular complexes termed lipoproteins. A number of metabolic disorders that involve elevations in plasma concentrations of any of the lipoprotein species are thus termed hyperlipoproteinaemias or hyperlipidaemias. However, the term hyperlipaemia is restricted to conditions that involve increased levels of triglycerides in plasma (Katzung, 2004). Lipoproteins are classified on the basis of their triglycerides, cholesterol (free and esterified), phospholipids and protein contents into chylomicron and remnants, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and lipoprotein a [Lp (a)].

Chylomicrons

They are the largest of the lipoproteins with small amounts of cholesterol, phospholipids and protein (Katzung, 2004). Chylomicrons are synthesised in the gastrointestinal tract (GIT) from the fatty acids of dietary triglycerides and cholesterol absorbed from the small intestine by epithelial cells. Triglyceride synthesis is regulated by diacylglycerol transferase, an enzyme that regulates triglyceride synthesis in many tissues (Hardman and Limbird, 2001). They transport

dietary tryglycerides from the intestinal mucosa via the thoracic duct into the plasma and finally to the tissues. The excess chylomicrons are eliminated by the liver. Chylomicrons are the only lipoproteins that float on the top of a tube of plasma that has been allowed to stand undisturbed for 12 hours. The buoyancy of chylomicrons reflects their 98 to 99% fat content of which 85% is dietary triglycerides. In normolipidaemic individuals, chylomicrons are present in plasma for 3 to 6 hours after a fat-containing meal has been ingested. After a fast of 10 to 12 hours no chylomicrons remains (Hardman and Limbird, 2001; Katzung, 2004). The concentration of chylomicrons can be controlled only by reducing dietary fat consumption. There is no current therapeutic approach that will reduce chylomicron catabolism, except for insulin replacement in patients with type I diabetes mellitus (because insulin prevents the hydrolysis of the enzyme, lipoprotein-lipase, thus it acts longer).

High-Density Lipoproteins (HDL)

These are the good lipoproteins. They contain more protein and less cholesterol and triglycerides. They transport cholesterol and triglycerides from the plasma to the tissues for utilisation. Thus increase in HDL is associated with a decreased risk of atherosclerosis.

Low-Density Lipoproteins (LDL)

They contain more cholesterol and triglycerides than protein. They are obtained from intervascular breakdown of VLDL. The high cholesterol content of LDL may be responsible for their higher atherogenic potential than other lipoproteins.

Very-Low Density Lipoproteins (VLDL)

They contain more triglycerides and less cholesterol, phospholipids and protein. They transport triglycerides from the liver to other tissues for utilisation or storage. Triglycerides are removed from VLDL and chylomicrons by lipoprotein-lipase. The activity of this enzyme is increased by insulin and thyroxine.

Intermediate-Density Lipoprotein (IDL)

Their major constituents are cholesteryl esters and "endogenous" triglycerides. 50% of IDL is converted to LDL, mediated by hepatic lipase. The two major pathological consequences of hyperlipidaemia are acute pancreatitis and atherosclerosis. Acute pancreatitis occurs in patients with marked hyperlipaemia. In such persons, control of triglyceride levels can prevent recurrent attacks of this life-threatening disease. Atherosclerosis however, occurs in persons with hypercholesterolaemia. This gave rise to the almost universally accepted "cholesterol-diet-Coronary Heart Disease (CHD)-hypothesis" that, "elevated plasma cholesterol levels cause CHD which is mostly a consequence of diets rich in saturated fats. Studies have shown that hypolipidaemic drug Therapy reduces the risk of CHD by reducing LDL-Cholesterol (LDL-C) to less than 100mg/dl (Hardman and Limbird, 2001).

The major risk factors for CHD include elevated LDL-C, reduced HDL-C, cigarette smoking, hypertension, type 2 diabetes mellitus, advancing age and a family history of premature CHD events in a first-degree relative.

Management of Hyperlipidaemia

A complete lipoprotein profile of the patient is required (Total Cholesterol, LDL-C, HDL-C and triglycerides) rather than screening for total cholesterol and HDL-C alone. The classification of lipid levels is shown in Table 1. If the values for total cholesterol, LDL-C and triglycerides are in the lowest category and the HDL-C level is not low, lifestyle recommendations (diet and exercise) are made to ensure maintenance of a normal lipid profile. Before drug therapy is initiated, secondary causes of hyperlipidaemia should be excluded. Most secondary causes can be excluded by ascertaining the patient's medication history and by measuring serum creatinine, liver function tests, fasting glucose and thyroid-stimulating hormone levels (Hardman and Limbird, 2001).

Cholesterol Lowering Drugs

The commonest and most important hyperlipidaemia is hyper-cholesterolaemia (Lawrence *et al*., 1997). Most treatment work by reducing the intracellular concentration of cholesterol in hepatocytes, leading to compensatory over expression of low density lipoprotein (LDL) receptors on their surface and increased uptake of cholesterol-rich LDL particles from the bloodstream (Okenwa, 1997; Lawrence *et al*., 1997; Katzung, 2004).

The drugs reduce blood cholesterol levels by 25-35% and cause a 35-45% reduction in risk of ischaemic heart disease (Lawrence *et al*., 1997). The main indications for their use are in patients with even slight elevations of cholesterol after myocardial infarction and in patients with gross excess of cholesterol and a family history of ischaemic heart disease (Lawrence *et al*., 1997). Drugs that lower cholesterol level are shown in Fig. 1 to 20 and they include:

Table 1: Classification of Plasma Lipid Levels.

Total Cholesterol	
<200 mg/dl	Desirable
200 – 239 mg/dl	Borderline high
≥240 mg/dl	High
HDL-C	
<40 mg/dl	Low (consider <50 mg/dl as low for women)
>60 mg/dl	High
LDL-C	
<100 mg/dl	Optimal
100 – 129 mg/dl	Near optimal
130 – 159 mg/dl	Borderline high
160 – 189 mg/dl	High
≥190 mg/dl	Very high
Triglycerides	
<150 mg/dl	Normal
150 – 190 mg/dl	Borderline high
200 – 499 mg/dl	High
≥500 mg/dl	Very high

Abbreviations: HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.
2001 National Cholesterol Education Programme guidelines.
Source: Hardman and Limbird (2001)

Statins or competitive inhibitors of 3-hydroxyl-3-methyl glutaryl coenzyme (HMG CoA Reductase)

They are the most effective drugs which inhibit the rate limiting step in cholesterol synthesis (Hardman and Limbird, 2001). They are structural analogues of HMG-CoA which is formed by HMG-CoA reductase in the synthesis of mevalonate (Fig.1).

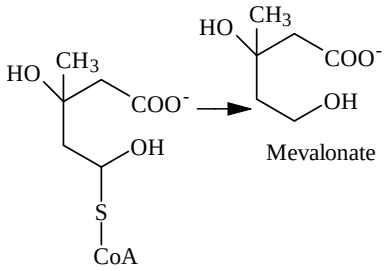


Fig. 1: HMG-CoA reduced intermediate. **Source:** Katzung (2004)

Mevalonate in turn is a critical compound in the synthesis of cholesterol (Katzung, 2004). Examples of statins include simvastatin (Zocor or Zimvor), lovastatin (or Mevachor), mevastatin, pravastatin (or Pravachol), fluvastatin (or Leschol), cervastatin (or Baycol), atorvastatin (or Lipitor), rosuvastatin (or Crestor) (Figs. 2 to 8) and ZD 4522, which is still in developmental clinical trials (Olson *et al*., 2000).

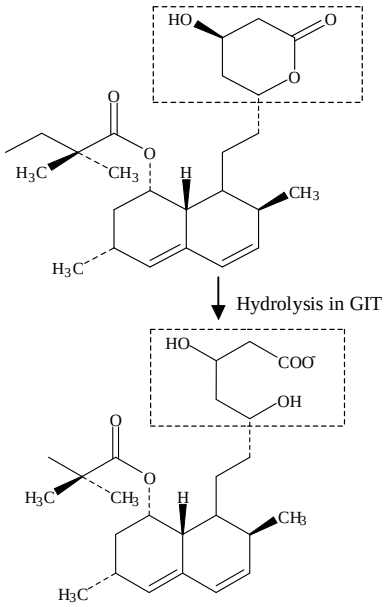


Fig. 2: Simvastatin. **Source:** Hardman and Limbird (2001)

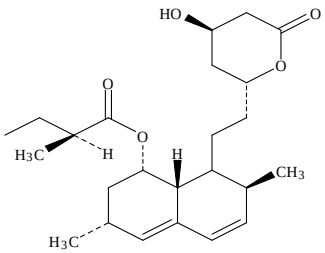


Fig. 3 Lovastatin. **Source:** Hardman and Limbird (2001).

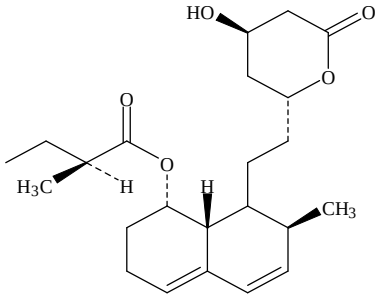


Fig. 4: Mevastatin. **Source:** Hardman and Limbird (2001).

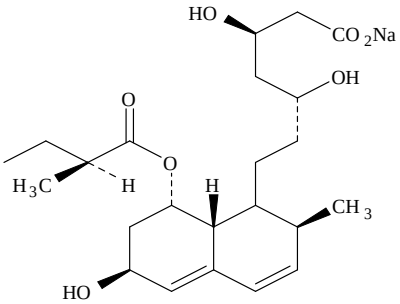


Fig. 5: Pravastatin. **Source:** Hardman and Limbird (2001)

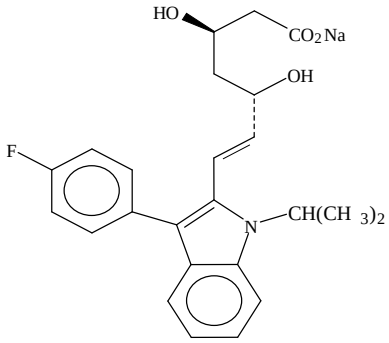


Fig. 6: Fluvastatin. **Source:** Hardman and Limbird (2001)

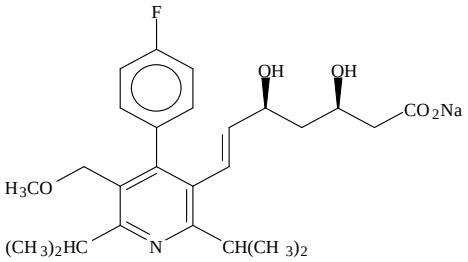


Fig. 7: Cervistatin. **Source:** Hardman and Limbird (2001).

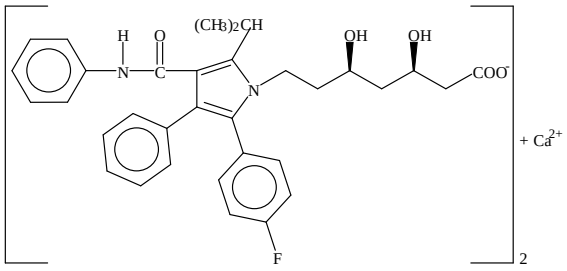


Fig. 8: Atorvastatin. **Source:** Hardman and Limbird (2001).

The safety of statins during pregnancy has not been established. Women wishing to conceive should not take statins. Nursing mothers are also advised to avoid taking statins (Hardman and Limbird, 2001).

The side effects of statins are numerous. They increase the activity of aminotransferase (up to 3 times the normal), which portends more severe hepatic toxicity. Thus the patients may present with malaise, anorexia and precipitous decrease in LDL. So, they should be used with caution in patients with underlying liver disease or a history of alcohol abuse. Rarely, there is a marked elevation in creatinine phosphorus kinase activity leading to generalised pain or weakness in skeletal muscles. Myopathy may occur with monotherapy (Lawrence *et al*., 1997; Katzung, 2004). Concomitant use with amiodarone or verapamil (calcium channel blocker) causes an increased risk of myopathy. Rarely, hypersensitivity syndromes like lupus-like disorder occur. Peripheral neuropathy can occur. In this case, drugs should be temporarily discontinued in the event of serious illness, trauma or major surgery. Myostis (inflammation of the muscle) occurs rarely, most reports being in transplant patients receiving cyclosporine. Plasma level of drug may be elevated in patients ingesting more than 1 litre of grapefruit juice daily (Lawrence *et al*., 1997; Katzung, 2004).

Fibric Acid Derivatives (Fibrates)

They inhibit hepatic lipid synthesis causing plasma cholesterol to decline by 10-20% and triglycerides by 20-30%. Associated with this is a risk in the "protective" HDL-cholesterol which may have contributed to the reduction in non-fatal myocardial infarction (Hardman and Limbird, 2001). They are the drugs of choice for mixed hyperlipidaemia (elevated cholesterol plus triglycerides) but may be used in hypercholesterolaemia alone or with anion exchange resins (Lawrence *et al*., 1997). Examples include clofibrate (or Atromid-S), gemfibrozil (or Lopoid), fenofibrate (or Tricor), bezafibrate (or Bezalip) and ciprofibrate (Figs. 9 to 13).

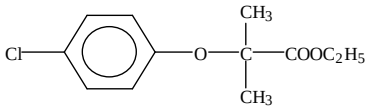


Fig. 9: Clofibrate. **Source:** Hardman and Limbird (2001).

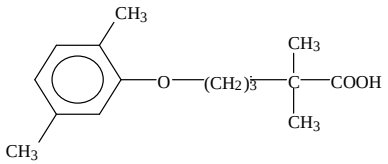


Fig. 10: Gemfibrozil. **Source:** Hardman and Limbird (2001); Katzung (2004).

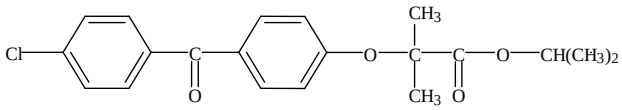


Fig. 11: Fenofibrate. **Source:** Hardman and Limbird (2001); Katzung (2004).

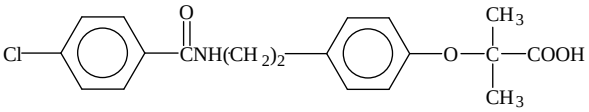


Fig. 12: Bezafibrate. **Source:** Hardman and Limbird (2001)

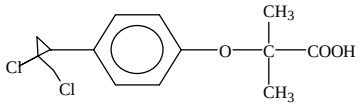


Fig. 13: Ciprofibrate. **Source:** Hardman and Limbird (2001).

The side effects of these drugs include aggravating deterioration in kidney function, thus are contraindicated where hepatic or renal function is severely impaired (except gemfibrozil), inducing a myostis-like syndrome particularly in patients with poor renal function and displacing oral anticoagulants (e.g. warfarin) and oral antidiabetic agents from their plasma proteins, thus enhancing their effect (Lawrence *et al*; 1997). Others include gastrointestinal (GIT) disturbance, nausea, diarrhoea, vomiting, indigestion, allergic reactions (urticaria, pruritus), increased activities of alkaline phosphatase or amine transferase in the blood, loss of hair and increased risk of gall bladder stone (cholelithiasis). Thus, they should be used with caution in patients who have had a cholecystectomy (Lawrence *et al*; 1997). Gemfibrozil can cause arrhythmia, hypokalaemia (potentiating the toxicity of cardiac glycosides) and myopathy increases if given with reductase inhibitors.

Anion Exchange Resins (Bile-Acid Sequestrants)

These resins are the only hypocholesterol drugs currently recommended for children 11 to 20 years of age (Hardman and Limbird, 2001), although data now are emerging that document the safety of statin therapy of children of this age range (National Cholesterol Education Programme, 1991). These drugs, being negatively charged, bind positively charged bile acids. Because of the large size, resins are not absorbed and the bound bile acids are excreted in the stool. They are quite safe as they are not systemically absorbed. Examples include cholestyramine (or Questran), colestipol (or Colestid) and colesevelam (or Welchol) (Figs. 14 to 16).

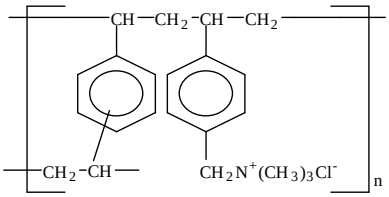


Fig.14: Cholestyramine. **Source:** Hardman and Limbird (2001).

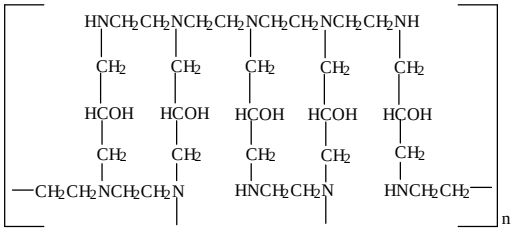
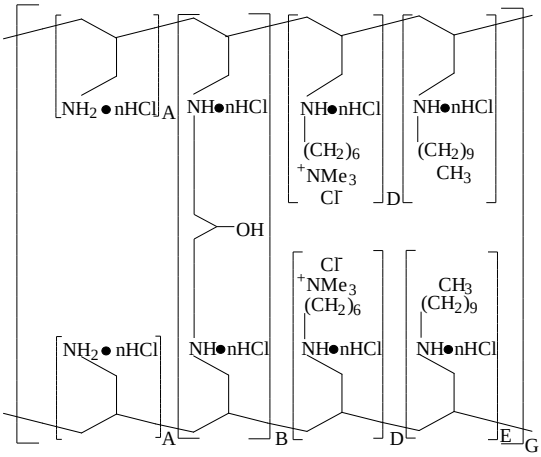


Fig. 15: Colestipol. **Source:** Hardman and Limbird (2001).



KEY
A = Primary Amines
B = Cross-linked Amines
D = Quaternary Ammonium Alkylated Amines
E = Decyalkylated Amines
n = Fraction of Protonated Amines
G = Extended Polymeric Network

Fig. 16: Colesevelam. **Source:** Hardman and Limbird (2001).

Some of the side effects include constipation and bloating (can be relieved by increasing dietary fibre or mixing psyllium seed with the resin); heartburn and diarrhoea are occasionally reported and any additional medication (except statin) should be given 1 hour before or at least 2 hours after the resin to ensure adequate absorption. Cholestyramine impairs absorption of lipid soluble vitamins (ADEK), folic acid and drugs absorbed in conjunction with lipids e.g. griseofulvin and acid drugs e.g. tetracycline, warfarin, thiazide-diuretics and barbiturates. In large doses it may cause stearrhoetora (fatty stool) and hyperchloremic acidosis. It can also cause dry flaking skin. Colestipol can lead to a transient increase in the activities of alanine and aspartate amino-transferase and alkaline phosphatase in the blood.

Inhibitors of Intestinal Sterol Absorption

Ezetimibe (or Zetia) (Fig. 17) is the only drug in this category. It is an azetidione-based cholesterol absorption inhibitor which blocks the intestinal absorption of cholesterol resulting in lowered plasma total cholesterol and LDL-C levels (Hardman and Limbird, 2001).

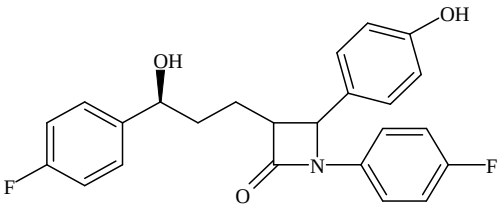


Fig. 17: Ezetimbe. **Source:** Katzung (2004).

It undergoes glucuronidation in the intestine and the absorbed glucoronide, an active metabolite is excreted into the bile by the liver. The half life of the active metabolite is 22 hours, so the drug can be given once daily (Katzung, 2004). The side effects include a low incidence of reversible, impaired hepatic function with a small increase in incidence when given with a reductase inhibitor. Liver function tests should be done before starting the drug and then at intervals of 2-4 months (Katzung, 2004).

Nicotinic Acid Derivatives

These include nicotinic acid (Pyridine-3-carboxylic acid or Vitamin B_3 or niacin, Fig. 18), nicofuranose and acipimox.

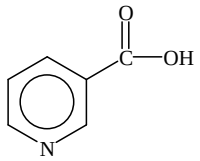


Fig. 18: Nicotinic acid. **Source:** Hardman and Limbird (2001).

Nicotinic acid lowers plasma triglyceride and cholesterol concentration. It acts as an antilipolytic agent in adipose tissue, reducing the supply of non-esterified free fatty acids and hence the availability of substrate for hepatic triglyceride synthesis. There are two commonly available forms of niacin-crystalline niacin (immediate release or regular, i.e. it dissolves quickly after ingestion) and sustained-release, which continuously releases niacin, 6 to 8 hours after ingestion up to a total daily dose of 2 g per day. Crystalline niacin is available in a variety of strengths from 50 mg to 500 mg tablet. It is best to start with a low dose (e.g. 100 mg twice daily taken after breakfast and supper), to minimise flushing and pruritis. The dose may be increased stepwise every 7 days up by 100 to 200 mg to a total daily dose of 1.5 to 2.0 g. After 2 to 4 weeks at this dose, transaminases, serum albumin, fasting glucose and uric acid levels should be measured. Lipid levels should be checked and the dose increased further until the desired effect on plasma lipids is achieved. After a stable dose is attained, blood should be drawn every 3 to 6 months to monitor for the various toxicities.

The side effects of nicotinic acid include hepatotoxicity which causes elevated serum transaminases and hyperglycaemia (Hardman and Limbird, 2001), flushing of the skin (preventable by low dose aspirin), GIT upset e.g. dyspepsia, commonly occurs. It can be diminished by gradually building up the oral dose over 6 weeks and in time clearance develops (Lawrence *et al*., 1997). There can also be pruritus of face and upper trunk, reactivation of ulcer diseases and tachyarrhythmia, especially in the elderly. The adverse effects of nicofuranose are the same as for nicotinic acid, but the prostaglandin-mediated symptoms are less (BNF, 2003). Acipimox is better tolerated than nicotinic acid, but unlike nicotinic acid, it does not reduce circulating levels of the prothrombotic protein, lipoprotein a.

Other Drugs

Other drugs used in the management of hypercholesterolaemia are dextrothyroxine (or Choloxin, Fig. 19) (Drug Bank, 2007) (no longer recommended because of the serious side effects like insomnia, restlessness, irritability, fever, tremor, loss of weight, menstrual disorder, visual disorder, loss of hair etc.) and probucol (or Lorelco or Lurselle, Figs. 20a and 20b) (Narsipur

et al., 2003). The probucol causes GIT disturbances (nausea, diarrhoea, vomiting, abdominal pain), rarely allergic reaction (skin rash, urticaria, pruritus and dizziness). It should be used with caution in patients with compensated myocardial insufficiency and cardiac arrhythmia because it potentiates arrhythmia.

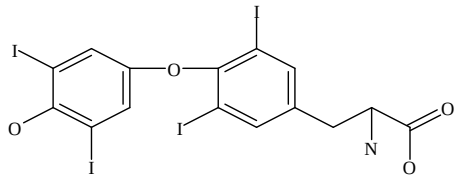


Fig. 19: Dextrothyroxin. (2-amino-3-(4-hydroxy-3, 5-diodo-phenoxy)-3, 5-diodo phenyl)-propanoic acid). $C_{15}H_{11}I_{14}NO_4$. **Source:** Drug Bank (2007)

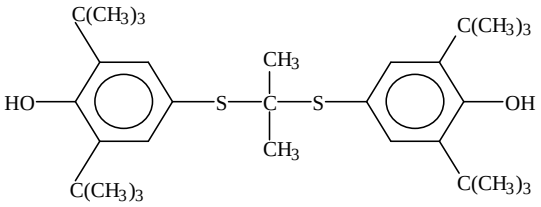


Fig. 20a: Probucol. **Source:** Narsipur *et al*., (2003).

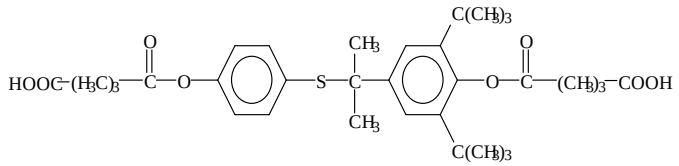


Fig. 20b: Water-soluble probucol. (An ester, probucol diglutamate. It achieves higher levels in plasma thereby facilitating loading of cells). **Source:** Narsipur *et al.*, (2003)

Other drugs that generally lower hyperlipidaemia are omega-3-Marine triglycerides (Maxepa) and alpha-tocopherol acetate (Vitamin E). In summary, suggested lipid lowering drugs for patients with different profiles of serum lipid concentrations is given in Table 2.

Table 2: Lipid lowering drugs for patients with different profiles of serum lipid concentration.

Increased Lipid	Drugs
Cholesterol alone	1. HMG CoA reductase inhibitor; 2. Fibrate; or 3. Bile acid sequestrants.
Cholesterol and triglyceride (e.g. in diabetes mellitus, hypothyroidism, nephrotic syndrome, renal transplantation)	1. Fibrate; 2. HMG CoA reductase inhibitors; or 3. Nicotinic acid derivatives.
Triglyceride alone (e.g. diabetes mellitus, obesity, alcoholism, chronic renal insufficiency, chronic liver disease, cholestasis, cholelithiasis, hepato-cellular disease, drugs like oestrogen	1. Fibrate; 2. Nicotinic acid derivative; or 3. Omega-3-Marine triglyceride (Maxepa).

Note: The bile acid sequestrants can be combined with the fibrates or with the HMGCoA reductase inhibitors, but the fibrates and the HMGCoA reductase inhibitors should only be combined with caution. Source: Graham Smith and Aranson (2002).

CONCLUSION

Hypolipidaemic drugs though effective, exhibit a wide range of side effects, with the exception of the bile and sequestrants which are quite safe as they are not systemically absorbed. It therefore behoves us to look inwards for plants as potentials in the management of hyperlipidaemia.

REFERENCE

BNF British National Formulary. A Compilation of the British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1987.

Drug Bank. http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/gelCARD = APRD00911. txt. 2007 *Access Date*: 11/06/2007.

Graham-Smith DG and Aronson JK. Oxford Textbook of Clinical Pharmacology and Drug Therapy. 3rd ed. Oxford University Press, Oxford, (2002).

Hardman JG and Limbird LE. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 10th ed. McGraw Hill. Co. Inc., USA. (2001) 971-1001.

Katzung BG. Basic and Clinical Pharmacology, 9th ed. A Lange Medical Pub. McGraw Hill Co., Singapore, (2004).

Lawrence DR, Bennet PN and Brown MJ. Clinical Pharmacology. 8th ed. Churchill Livingstone, New York, (1997).

Narsipur SS, Peterson OW, Smith RB et al: Mechanisms of Glomerular Immune Injury: Effects of Antioxidant Treatment. J Am Soc Nephrol 2003; 14: 1748-1755.

National Cholesterol Education Programme. Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. U.S. Department of Health and Human Services. NIH Publi. No. 91-2732, Bethesida, M.D. 1991.

Okenwa MC. Current Book of Medical Pharmacology and Therapeutics. Parkland Medical Publications, Benin City, Nigeria, (1997).

Olsson AG, Pears JS, Mckellar J, Caplan RJ and Raza A. Pharmacodynamics of new HMG-CoA reductase inhibitor ZD-4522 in patients with hypercholesterolaemia. Atheroselerosis, 2000; 151:39 (Abstract).