



# A Review Article On Herbal Medicine Used In Hyperlipidemia

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## Abstract

Hyperlipidemia has been ranked as one of the greatest risk factors contributing to prevalence and severity of coronary heart diseases. Coronary heart disease, stroke, atherosclerosis and hyperlipidemia are the primary cause of death. The elevation of serum total cholesterol and low density lipoprotein (LDL) cholesterol has been reported as a primary risk factor for cardiovascular disease. Hyperlipidemia is a condition when abnormally high levels of lipids i.e. the fatty substances are found in the blood. Hypolipidemic drugs are extensively used as prophylactic agents to prevent such atherosclerosis induced disorders. More than 70 medicinal plants have been documented to have significant hypolipidemic action. During the last decade, an increase in the use of medicinal plants has been observed in metropolitan areas of developed countries. Medicinal plants play a major role in hypolipidemic activity. The advantages of herbal medicines reported are effectiveness, safety, affordability and acceptability. Traditional herbal medicines are naturally occurring, plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices. Traditional herbal medicines are getting significant attention in global health debates. In China, traditional herbal medicine played a prominent role in the strategy to contain and treat severe acute respiratory syndrome.

## Introduction :

Many hope traditional herbal medicine research will play a critical role in global health. China, India, Nigeria, the United States of America (USA) and WHO have all made substantial research investments in traditional herbal medicines. Industry has also invested millions of US dollars looking for promising medicinal herbs and novel chemical compounds. Hyperlipidemia is a condition when abnormally high levels of lipids i.e. the fatty substance are found in the blood. This condition is also called hypercholesterolemia/hyperlipoproteinemia. Human body is complex machinery and for maintaining the homeostasis of various organ and organ system. Any undesirable change will disturb the balance resulting in diseased state. Lipids are fats in the blood stream, commonly divided into cholesterol and triglycerides. Cholesterol circulates in the bloodstream and is involved in the structure and function of cells. Triglycerides (TG) are best viewed as energy that is either used immediately or stored in fat cells. TG are manufactured in the liver from the foods or by being absorbed from

the intestine. Virchow in 19th century who identified cholesterol crystals in atherosclerotic lesion and stated that endothelial cell injury initiates atherogenesis.

Ayurveda (translated as “the science of life”) is one of the oldest medical systems in the world. Its origins date back to thousands of years ago in the Vedic era in the Indian subcontinent. Ayurveda defines life, “ayu”, as a union of mind, body, spirit, and senses and health as the balanced state of these factors. The wisdom of Ayurveda is based on three major classical texts, namely Charaka Samhita, Sushruta Samhita, and Ashtanga Hridaya, plus six minor texts. These ancient texts give detailed descriptions of over 700 herbs and 6000 formulations in addition to descriptions of various diseases, diagnostic methods, and dietary and lifestyle recommendations [18]. Ayurvedic treatment focuses on restoring the balance of the disturbed body–mind matrix through diet and behavioral modifications, administration of drugs, and detoxification and rejuvenation therapies. The branch of Ayurvedic science that deals with herbs and their qualities is called Dravyaguna vigyan. Ayurvedic formulations are prepared based on this knowledge and largely comprise herbs. Classical and proprietary Ayurvedic formulations may consist of a single herb or mixtures of many herbs in any form, viz., juice, extract, powder, tablet, or decoction.

### **CLASSIFICATION OF LIPID CONCENTRATIONS :**

The cholesterol along with some other types of fats cannot be dissolved in the blood. Moreover, in order to be transported to and from cells, they have to be specially carried by certain molecules called lipoproteins, which consist of an outer layer of protein with an inner core of cholesterol and triglycerides<sup>6,7</sup>. In addition, the lipoproteins have been found essential for cholesterol to move around the body. The lipids can be classified as TC, triglycerides, LDL, HDL and very low density lipoprotein (VLDL) cholesterol.

#### **Total cholesterol :**

According to guidelines of National Cholesterol Education Program (NCEP), TC concentrations below 200 mg/dL have been regarded as desirable, whereas, concentrations greater than 240 mg/dL are referred to as hyperlipidemic. However, epidemiological evidence suggests that the risk of cardiac events decreases as TC levels fall approximately to 150 mg/dL. Moreover, TC should be less than 180 mg/dL for children<sup>8-10</sup>.

#### **Triglyceride :**

Triglycerides are another type of fat that is carried in the blood by VLDL. The excess calories, alcohol or sugar in the body get converted into triglycerides and stored in fat cells throughout the body<sup>11</sup>. The triglyceride concentration less than 150 mg/dL is regarded as normal, whereas, concentrations of 200-499 mg/dL are considered as high. Moreover, concentrations of 500 mg/dL or higher are considered dangerous for the development and progression of various CVDs.

#### **LDL cholesterol :**

LDL is commonly known as the bad cholesterol, which is produced by the liver and carry cholesterol and other lipids from the liver to different areas of the body like muscles, tissues, organs and heart. The high levels of LDL indicate much more cholesterol in the blood stream than necessary and hence, increase the risk of heart disease<sup>8,12</sup>. According to NCEP guidelines, LDL cholesterol concentrations below 100mg/dL are considered optimal, whereas concentrations in the range of 160-189 mg/dL are considered to the higher side. However, increasing evidence supports that normal human LDL cholesterol concentration can be as low as 50 to 70 mg/dL<sup>9</sup>. Moreover, it has been comprehensively seen that the risk of CVDs decreases as LDL cholesterol concentration decreases.

## HDL cholesterol

HDL is commonly referred to as the good cholesterol, which is produced by the liver to carry cholesterol and other lipids from tissues back to the liver for degradation. High levels of HDL cholesterol have been considered as a good indicator of a healthy heart. The concentrations of 60 mg/dL or higher have been considered as optimal, whereas, HDL concentrations below 40 mg/dL are considered as major risk factor for CVDs. However, HDL is often interpreted in the context of TC and LDL concentrations, and hence may be regarded as less significant when LDL is low.

## VLDL Cholesterol :

VLDL is similar to LDL cholesterol in the sense that it contains mostly fat and not much protein. VLDL cholesterol is the lipoproteins that carry cholesterol from the liver to organs and tissues in the body. They are formed by a combination of cholesterol and triglycerides. Moreover, VLDLs are heavier than LDL, and are also associated with atherosclerosis and heart disease.

## MECHANISM OF LIPID TRANSPORT :

Lipids are insoluble in water. Hence, they are transported around the body as lipoproteins. Lipids originate from two sources: endogenous lipids, synthesized in the liver, and exogenous lipids, ingested and processed in the intestine. Approximately 7% of body's cholesterol circulates in plasma in the form of low density lipoproteins (LDL). The level of plasma cholesterol is influenced by its synthesis and catabolism in which liver plays a crucial role

## TYPES OF HYPERLIPIDEMIA

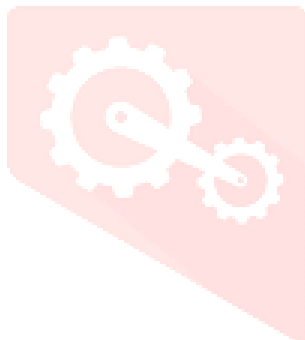
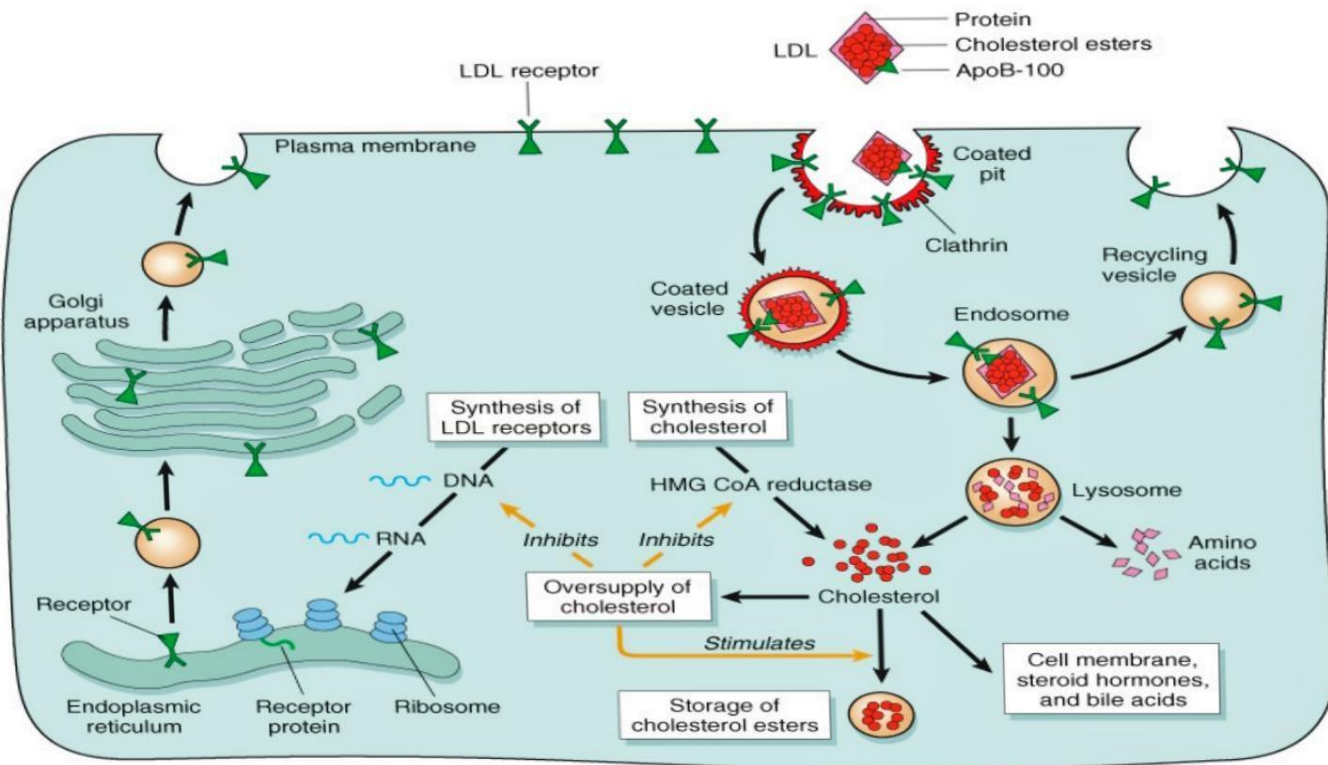
Hyperlipidemia can be broadly divided into:

**Primary hyperlipidemia** is due to Single gene defect:

It is familial and called as monogenic or genetic.

### Polygenic gene defect

Multiple genetic defect, dietary and physical activity are caused due to it.



TYPE	DISORDER	CAUSE	OCCURANCE	ELEVATED PLASMA LIPOPROTEIN
I.	Familial lipoprotein lipase deficiency	Genetic	Very rare	Chylomicrons
II <sub>a</sub>	Familial hypercholesterolemia	Genetic	Less common	LDL
II <sub>b</sub>	Polygenic hypercholesterolemia	Multifactorial	Commonest	LDL
III	Familial dysbetalipoproteinemia	Genetic	Rare	IDL,Chylomicrons Remnants
IV	Hypertriglyceridemia	Multifactorial Genetic	Common	VLDL
V	Familial combined hyperlipidemia	Genetic	Less common	VLDL,LDL

LDL-low density lipoprotein,VLDL-very low density lipoprotein,IDL-intermediate density lipoprotein<sup>16</sup>.

**Table 1. Types of primary hyperlipidemia.**

**SECONDARY HYPERLIPIDEMIA** It is associated with diabetes, myxoedema, nephritic syndrome, chronic alcoholism, with use of drugs like corticosteroids, oral contraceptives, Beta blockers.

TYPE	REASONS
Hypercholesterolemia	<ul style="list-style-type: none"> <li>• Hypothyroidism</li> <li>• Anorexia nervosa</li> <li>• Acute intermittent porphyria</li> <li>• Obstructive liver disease</li> <li>• Nephrotic syndrome</li> <li>• Drugs: Progestins, thiazide diuretics, glucocorticoids, betablockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus.</li> </ul>
Hypertriglyceridemia	<ul style="list-style-type: none"> <li>• Obesity</li> <li>• Pregnancy</li> <li>• Lipodystrophy</li> <li>• Acute hepatitis</li> <li>• Diabetes mellitus</li> <li>• Ileal bypass surgery</li> <li>• Glycogen storage disease</li> <li>• Systemic lupus erythematosus</li> <li>• Monoclonal gammopathy: multiple myeloma</li> <li>• Drugs: Alcohol, estrogens, isotretinoin, beta blockers, glucocorticoids, bile-acid resins, thiazides, asparaginase, interferons, azole antifungals, mirtazapine, anabolic steroids, sirolimus, bexarotene.</li> </ul>

**Table 2. Types of secondary hyperlipidemia**

## CAUSES OF HYPERLIPIDEMIA

The main causes of hyperlipidemia include lifestyle changes, and the main risk factor is a low-fat diet greater than 40 percent of total calories, saturated fat intake greater than 10 percent of total calories; and cholesterol intake of more than 300 milligrams per day or treatable medical condition<sup>18</sup>. Abnormal cholesterol levels a healthy lifestyle that includes a high-fat diet and other lifestyle factors such as obesity and heavy alcohol consumption use and non-training. Other factors include diabetes, kidney disease, pregnancy, and an underactive thyroid<sup>19</sup>. Other diseases that can increase cholesterol levels include polycystic ovary syndrome and kidney disease. high level Female hormones such as estrogen have been shown to increase or alter cholesterol levels. In addition, medications such as diuretics, Beta blockers and drugs used to treat depression also increase cholesterol levels<sup>20</sup>. One more Age and gender are modifiable factors in the development and progression of hyperlipidemia. Cholesterol levels have been shown to increase between the ages of 21 and 23. Heredity is also a factor that affects progression hyperlipidemia, because it has been noted that genes partially determine the amount of cholesterol in the body. Other factors that cause hyperlipidemia include:

### **Berardinelli-Seip congenital lipodystrophy-hyperlipidemia**

Rare genetic disorders with hepatomegaly, genetic disorders characterized by diabetes, loss of body fat, hepatomegaly, genital enlargement, skeletal growth and other abnormalities.

#### **Berardinelli-Seip congenital lipodystrophy, type 1 - hyperlipidemia**

A rare genetic disorder caused by a defect in the AGPAT2 gene on chromosome 9q34.326, characterized by early onset diabetes, loss of body fat, severe insulin resistance, high blood triglycerides, and fatty liver

#### **Berardinelli-Seip congenital lipodystrophy, type 2 - hyperlipidemia**

A rare genetic disorder that causes early-onset diabetes on chromosome 11q13 in the BSCL2 gene.loss of body fat, severe insulin resistance, high blood triglycerides and fatty liver.

### **Cholestasis**

This is a condition that prevents the passage from the liver to the duodenum. There are two types, which happens first Metabolic cholestasis is a mechanical obstruction in the duct system caused by gallstones or other forms of obstruction.Bladder disorders occur due to genetic defects or acquired as a side effect of many medications.

## **PATHOPHYSIOLOGY OF HYPERLIPIDEMIA**

The pathophysiology of hyperlipidemia can be studied under two headings, i.e., primary hyperlipidemia and secondary hyperlipidemia. The pathophysiology of primary hyperlipidemia involve that the idiopathic hyperchylomicronemia defect in lipid metabolism leads to hypertriglyceridemia and hyperchylomicronemia which is caused by a defect in lipoprotein lipase activity or the absence of the surface apoprotein CII<sup>31</sup>.Moreover, hyperchylomicronemia in cats with autosomal recessive defect in lipoprotein lipase (LPL) activity showed the occurrence of primary hyperlipidemia.

- In secondary hyperlipidemia, the postprandial absorption of chylomicrons from the gastrointestinal tract occurs 30-60 min after ingestion of a meal containing fat that may increase serum triglycerides for 3-10 hours<sup>33</sup>.The diabetes mellitus patients have been noted to possess low LPL activity which further caused high synthesis of VLDL cholesterol by the liver ultimately leading to hyperlipidemia. Moreover, hypothyroidism-induced low LPL activity and lipolytic activity has been noted to reduce hepatic degradation of cholesterol to bile acids. Furthermore, hyperadrenocorticism increased the synthesis of VLDL by the liver causing both hypercholesterolemia and hypertriglyceridemia<sup>34,35</sup>.Liverdisease hypercholesterolemia has been noted to

be caused by reduced excretion of cholesterol in bile. Furthermore, in nephrotic syndrome, the common synthetic pathway for albumin and cholesterol causes low oncotic pressure ultimately leading to enhanced cholesterol synthesis.

- The response-to-injury hypothesis states that risk factors such as oxidized LDL, mechanical injury to the endothelium, excessive homocysteine, immunologic attack, or infection-induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. The eventual clinical outcomes may include angina, myocardial infarction, arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death.
- Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL then recruits monocytes into the artery wall. These monocytes then become transformed into macrophages that accelerate LDL oxidation.
- Oxidized LDL provokes an inflammatory response mediated by a number of chemoattractants and cytokines (e.g., monocyte colony-stimulating factor, intercellular adhesion molecule, platelet-derived growth factor, transforming growth factors, interleukin-1, interleukin-6).
- Repeated injury and repair within an atherosclerotic plaque eventually leads to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T lymphocytes. Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis.
- The extent of oxidation and the inflammatory response are under genetic control, and primary or genetic lipoprotein disorders are classified into six categories for the phenotypic description of hyperlipidemia. The types and corresponding lipoprotein elevations include the following: I (chylomicrons), IIa (LDL), IIb (LDL + very low density lipoprotein, or VLDL), III (intermediate-density lipoprotein, or IDL); IV (VLDL), and V (VLDL + chylomicrons). Secondary forms of hyperlipidemia also exist, and several drug classes may elevate lipid levels (e.g., progestins, thiazide diuretics, glucocorticoids,  $\beta_2$  blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus).
- The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (LDL-R) or, rarely, a defect of internalizing the LDL-R complex into the cell after normal binding. This leads to lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL-C being inversely proportional to the deficit in LDL receptors.

## DIAGNOSIS OF HYPERLIPIDEMIA

- The National Cholesterol Education Program recommends a fasting lipoprotein profile (FLP). Total cholesterol, LDL, HDL, and triglycerides should be measured in all adults 20 and older at least once every 5 years.
- Measure plasma cholesterol (about 3% below serum determination), triglycerides and HDL levels are important after fasting for 12 hours or more because triglycerides can rise during fasting. individual; Total cholesterol is only affected by fasting.
- Two determinations, between 1-8 weeks, with the patient on a stable and heavy diet, in a non-acute setting Disease, it is recommended to reduce the variation and take a safe base. If total cholesterol is high If it is more than 200 mg/dL, a second determination is recommended, and if the value is more than 30 mg/dL, the average of three values should be used.



- Once a cleft palate is diagnosed, the main component of the evaluation is the history (age, gender, and women, menstruation, and estrogen replacement status), physical examination, and laboratory tests.
- A thorough history and physical examination should (1) assess the presence or absence of cardiovascular risk factors cardiovascular disease in individuals; (2) family history of premature cardiovascular disease or lipids malfunctions; (3) presence or absence of secondary causes of hyperlipidemia, including concomitant medications; and (4) presence or absence of xanthoma, abdominal pain or pancreatitis, kidney or liver disease, peripheral coronary artery disease, abdominal aortic aneurysm, or cerebrovascular disease (carotid artery, stroke, or temporal lobe) ischemic attack).
- Diabetes is now equal to the risk of CHD. That is, the presence of diabetes in the patient CHD is known to be associated with a higher risk of CHD in the absence of diabetes.
- Lipoprotein agarose-gel if physical examination and history are insufficient to diagnose a familial disorder Electrophoresis is useful for determining which lipoprotein classes are affected. If your triglyceride level is below 400 mg/dL and type III hyperlipidemia or chylomicrons not detected by electrophoresis can then be calculated. VLDL and LDL concentrations:  $VLDL = \text{triglycerides} / 5$ ;  $LDL = \text{total cholesterol} - (VLDL + HDL)$ . An initial test is used total cholesterol to detect cases, but subsequent management decisions should be based on LDL.
- Determination of HDL as total cholesterol consists of cholesterol derived from LDL, VLDL and HDL Useful for increasing total plasma cholesterol. HDL can be increased with moderate alcohol consumption (less than two drinks a day), exercise, smoking cessation, weight loss, oral contraceptives, phenytoin, and terbutaline. HDL can be lowered by smoking, obesity, sedentary lifestyle, and medications such as  $\beta$  blockers.
- Diagnosis of lipoprotein lipase deficiency is based on low or no enzyme activity in normal human plasma apolipoprotein C-II, which is a cofactor of the enzyme.

#### The Lipid Levels You Want to Lower Your Risk of Heart Disease 1

- LDL is less than 130 mg/dL or if you have been diagnosed with diabetes
- HDL greater than 40 mg/dL (men) or 50 mg/dL (women);
- Total cholesterol is less than 200 mg/dL; and
- Triglycerides less than 200 mg/dL or 150 if you have heart disease or diabetes.

#### TREATMENT

The National Cholesterol Education Program of the Adult Care Panel III (NCEP ATP III) recommends fasting Lipoprotein profiling and risk factor assessment are used in the initial classification of adults. There are three categories Risks that alter the goals and methods of LDL-lowering therapy. The highest risk category is known CHD or CHD equivalent risk; The risk of major coronary events is equal to or greater than that defined CHD (that is, greater than 20% over 10 years or 2% per year). The intermediate category includes two or more risk factors, The 10-year risk for CHD is 20% or less. The lowest risk category is a person with a risk factor of zero to one, usually associated with a 10-year CHD risk of less than 10% 39%. In recent years, guidelines for the use of lipid-lowering therapy have become more aggressive Results of large trials show mortality for statin use. Most guidelines recommend statin therapy for a CAD with a 10-year risk greater than 20% after a trial of dietary therapy (high risk) failed. However, with a 10% risk, treatment can be cost-effective. The goal of treatment is to reduce LDL cholesterol levels and therapeutic lifestyle changes (TLC) and appropriate drug therapy in adults and children. Although this goal is a summary point, the main reason for the creation of TLC

and drug therapy is to reduce Risk of first or recurrent events such as MI, angina, heart failure, ischemic stroke, or other types of peripheral arterial disease. Diseases such as carotid stenosis or abdominal aortic aneurysm

1. Medical treatment involves two approaches:

- Non-pharmacological treatment
- Pharmacological treatment

### **Non-pharmacological treatment**

The goal of dietary therapy is to reduce the intake of total fat and saturated fatty acids (eg, saturated fat) and cholesterol gradually to achieve the desired body weight.

- Saturated fat intake at 7 percent of daily calories;
- Reduce total fat intake by 25-35 percent of daily calories;
- Less than 200 mg of dietary cholesterol per day;
- Eat 20-30 g of soluble fiber per day, which is found in oats, peas, beans and some fruits; and
- Increase the intake of plant stanol or sterol, nuts, vegetable oil, corn, and rice to 2-3 g daily.

Other foods that can help control cholesterol include cold water fish such as salmon, sardines, and salmon. This is a fish contains omega-3 fatty acids that can lower triglycerides. Tofu and soybeans are substitutes for many meats. Contains powerful antioxidants that can lower LDL.

### **CLASSIFICATION OF DRUGS**

1. HMG-CoA reductase inhibitors (Statins): Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin.
2. Bile acid sequestrants (Resins): Cholestyramine, Colestipol.
3. Activate lipoprotein lipase (Fibric acid derivatives): Clofibrate, Gemfibrozil, Bezafibrate and Fenofibrate.
4. Inhibit lipolysis and triglyceride synthesis: Nicotinic acid.
5. Others: Ezetimibe, Gugulipid.

### **HERBAL MEDICINES**

Hyperlipidemia associated lipid disorders are considered to cause the atherosclerotic cardiovascular disease. The main aim of treatment in patients with hyperlipidemia is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular or cerebrovascular disease<sup>42</sup>. The consumption of synthetic drugs leads to hyperuricemia, diarrhoea, nausea, myositis, gastric irritation, flushing, dry skin and abnormal liver function. The medicinal plants play a major role in hypolipidemic activity<sup>43</sup>. The advantages of herbal medicines reported are effectiveness, safety, affordability and acceptability. Due to less communication means, poverty, ignorance and unavailability of modern health facilities, most people especially rural people are still forced to practice traditional medicines for their common day ailments. Most of these people form the poorest link in the trade of medicinal plants. Over the past decade, herbal medicine has become a topic of global importance, making an impact on both world health and international trade. Medicinal plants continue to play a central role in the healthcare system of large proportions of the world's population<sup>45</sup>. This is particularly true in developing countries, where herbal medicine has a long and uninterrupted history of use. Continuous usage of herbal medicine by a large proportion of the population in the developing countries is largely due to the high cost of Western Pharmaceuticals and Healthcare.

Herbal medicines have been main source of primary healthcare in all over the world. From ancient times, plants have been catering as rich source of effective and safe medicines. Today according to the WHO as many as 80 % of world populations are still dependent on traditional medicines. Herbal medicines are finished, labeled medicinal products that contain as active ingredients, aerial or under ground part of plants or other plant materials, or combination thereof, whether in the crude state or as plant preparations. Medicines containing plant materials combined with chemically defined active substances, including chemically defined isolated constituents of plants are not considered to be herbal medicines. Chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants<sup>48</sup>. The valuable medicinal properties of different plants are due to presence of several constituents i.e. saponins, tannins, alkaloids, alkenyl phenols, glycol-alkaloids, flavonoids, sesquiterpenes lactones, terpenoids and phorbol esters. Among them some are act as synergistic and enhance the bioactivity of other compounds. The Indian subcontinent is a vast repository of medicinal plants that are used in traditional medical treatments. In India, around 15000 medicinal plants have been recorded 51 however traditional communities are using only 7,000 - 7,500 plants for curing different diseases 52-54. The medicinal plants are listed in various indigenous systems such as Siddha (600), Ayurveda (700), Amchi (600), Unani (700) and Allopathy (30) plant species for different ailments<sup>55</sup>. According to another estimate 17,000 species of medicinal plants have been recorded out of which, nearly 3,000 species are used in medicinal field. The Indian Vedas also describes the widespread use of herbal products and aqueous extract of different plant parts for curing different diseases. Maximum 30% of root part of medicinal plant is used in different practices in comparison to other plant parts<sup>57</sup>. Medicinal plant based drug industries is progressing very fast in India but it is best with a number of problems. Currently used hypolipidemic drugs are associated with so many adverse effects and withdrawal is associated with rebound phenomenon which is not seen with herbal preparations. Plant parts or plant extract are sometimes even more potent than known hypolipidemic drugs. This indicates that the research has stopped with just reporting the effect of plant derivates and the findings are not translated into clinical research. Taking these finding forward is mandatory to develop new drugs in this area.

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