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Cardiovascular Risk Factors: Implications in Diabetes, Other Disease States and Herbal Drugs

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1. Introduction

The danger and the increasing prevalence of heart diseases world wide are now of a great concern and are attributed to the cardiovascular risk factors. Cardiovascular risk factors have been identified to be the underlying latent or potent causes of death in all heart diseases and also in many other disease states such as diabetes. Reduction in the risk factors with synthetic drugs or drugs of natural products origin in the course of treatment of some disease states where implicated has been found to improve tremendously the health of the patient.

Cardiovascular risk factors include triacylglycerols (triglycerides), cholesterol, cholesteryl esters, very low density lipoprotein–cholesterol (VLDL-c), low density lipoprotein-cholesterol (LDL-c), and anti-athrogenic high density lipoprotein–cholesterol (HDL-c) and are collectively referred to as plasma lipids. An increase in plasma lipids concentrations beyond certain level give rise to physiological condition known as "Hyperlipidemia". Hyperlipidemia is, therefore, characterized by abnormal elevation in plasma triglyceride, cholesterol and low density lipoprotein-cholesterol (LDL-c) and very low lipoprotein - cholesterol (VLDL-c) and has also been reported to be the most prevalent indicator for susceptibility to atherosclerotic heart disease (Maruthapan and Shree, 2010). Managing cardiovascular disease states, therefore, requires drugs that would be capable of lowering blood plasma lipids in order to reduce mortality and morbidity associated with the cardiovascular complications (Hasimun et al., 2011). It has been reported in epidemiological studies that a strong positive correlation exists between increase in the blood cholesterol level and incidence of cardiovascular heart disease (CHD) (Hamed et al., 2010; Imafidon 2010; Maruthapana and Shree 2010), and also increase in the incidence of atherosclerosis(Hasimun et al., 2011). A strong relationship between increase in C-reactive protein (CRP) and cardiovascular risk factors has also been reported as well as increase in myocardial infection and coronary artery disease among individuals with angina pectoris (Ghayour –Mobarhan et al. 2007).

Atherosclerosis arises from the deposition of fatty substances, cellular waste products, calcium and fibrin in the arteries, resulting in clotting (Lewis et al., 2002) and is considered

one of the major causes of coronary heart disease. It is recognized as a common threat to life, usually seen in individuals consuming high quantities of cholesterol and saturated fats in their diets. It has also been established in animal studies that raising dietary cholesterol alone could increase atherosclerosis susceptibility (Madhumathi et al., 2006). Atherosclerosis is characterized by endothelia dysfunction, muscular inflammation resulting from build up of plasma lipids which tantamount to vascular remodeling, acute and chronic luminal obstruction, abnormalities in the blood flow and diminished oxygen supplies to target organs (Madhumathi et al., 2006). The development of atherosclerosis could also be attributed to other factors such as oxidative stress which is responsible for the oxidation of low-density lipoprotein-cholesterol (LDL-c) and is considered as one of the first steps of atherosclerotic pathogenesis. Local inflammatory processes have also been identified to play a crucial role in the transition from reversible accumulation of cholesterol in the arterial wall to irreversible damage of the arteries (Brunner-La Rocca1, et al., 2005). Many factors contributing to etiology of atherosclerosis in addition to diet include diabetes mellitus, psychological factors and the presence of glucocorticoids.

Diabetes mellitus (DM) is a major degenerative disease in the world today afflicting many lives both in the developed and developing countries (Ogbonnia et al., 2011). It has been succinctly described as the common metabolic disorder of carbohydrate and fat metabolism, which is due to absolute or relative lack of insulin and is characterized by hyperglycaemia and hyperlipidemia (Sharon and Marvin, 1975; Walter, 1977). Diabetes is a multiple disease state and has been defined as "a state of premature cardiovascular death that is associated with chronic hyperglycemia and also associated with blindness and renal failure" (Fisher and Shaw, 2001). This assertion was to draw attention and to encourage multiple clinical approaches that would altogether help reduce cardiovascular risk factors in diabetic patients (Ogbonnia et al., 2011). Diabetes especially the type 2 model might be postulated to occur primarily due to underlying abnormality of insulin resistance - that is resistance of the body to the biological actions of insulin. The consequences of insulin resistance lead to hyperinsulinaemia and are associated with CRFs - dyslipidaemia including athrogenic lipid profile with increase in low and very-low density lipoprotein-cholesterols (LDL-c and VLDL-c) and reduction in the anti-athrogenic high density lipoprotein-cholesterol (HDL-c). Cardiovascular risk factors have been implicated and even occur at a frequency much higher than expected in some other disease states such as benign prostatic hyperplasia (BPH). Benign prostatic hyperplasia is a neoplastic enlargement of the prostate gland and is common in elderly men (Ejike and Ezeanyika, 2010). Epidemiological studies have demonstrated that many of the risk factors associated with cardiovascular diseases are the same as found in BPH (Dharmananda, 2011), and these risk factors include obesity, hypertension and diabetes. The diabetes connection may be considered very strong and the risk centers on the non-insulin dependent diabetes mellitus (NIDDM) which most often involves excessive insulin levels, a possible direct contributor to the growth of the prostrate (Hammarten and Hogstedt, 2011). The treatment of BPH became a medical issue mainly in 1970s at the same time that the cardiovascular disease therapy came to fore and the incidence of the disease has become higher (Dharmananda, 2011). Herbal or phytomedicines are now being investigated with some recorded successes for the management of cardiovascular risk factors with the accompanied disease states. Herbal remedies with active components understood to be sterols, such as beta-sitosterol has been used as a therapeutic agent for BPH (Bombardelli and Morazzoni, 1997).

2. Cardiovascular risk factors

Cardiovascular risk factors consisting mostly of plasma lipids including triacylglycerol (triglycerides), cholesteryl esters and cholesterol are synthesized by the liver and adipose tissues and may also be absorbed from the diet (Stryer, 1988). They are also efficiently synthesized from carbohydrate diets largely in the intestinal epithelia tissues in addition to the liver (Metzler, 1974), and are transported between various tissues and organs for utilization and storage. These plasma lipids like other lipids are generally insoluble in water and pose a transportation problem in aqueous blood plasma. This problem is overcome by associating the nonpolar lipids comprising triacylglycerol (triglycerides) and cholesteryl esters with amphipatic lipids such as phospholipids, cholesterol and proteins to produce water-miscible lipoproteins (Conn and Stumpf, 1976; Stryer, 1988). A lipoprotein is a particle consisting of core hydrophobic lipids surrounded by a shell of polar lipid and apoprotein and mediates the cycle by transporting lipids from the intestine as chylomicrons – and from the liver as very low density lipoproteins-cholesterol (VLDL-c) - to most tissues for oxidation and to adipose tissue for storage. Lipoproteins are grouped according to increasing densities by centrifugation as follow:

i.   Chylomicrons which incorporate intestinal absorbed triacylglycerol from intestinal absorption of triacylglycerol and other lipids.
ii. Very low density lipoprotein-cholesterol (VLDL-c, or pre – β- Lipoprotein), are derived from the combination of newly synthesized triacylglycerol together with small amounts of phospholipids and cholesterol and apolipoproteins all synthesized in the liver (Stryer, 1988).
iii. Intermediate density lipoprotein (IDL)
iv. Low density lipoprotein-cholesterol (LDL-c) (LDL-c or β-Lipoproteins), representing a final stage in the catabolism of VLDL-c, and

High density lipoproteins-cholesterol (HDL-c, or α-Lipoproteins), involved in cholesterol transport and also in VLDL-c and chylomicron metabolism.

Major groups of lipoproteins have been identified to be physiologically important and are used in clinical diagnosis. The primary role of LDL-c appears to be the transport of esterified cholesterol to tissue while that of the high density lipoproteins-cholesterol (HDL-c) is to carry excess cholesterol away from most tissues to the liver. The size of the lipoprotein particles also varies from a 200 – to 500 –nm diameter for chylomicrons to as little as 5 nm for the smallest HDL particles (Metzler, 1974).

Lipoprotein is made up of triacylglycerol (16%) which is the predominant lipid in chylomicrons and VLDL-c, while phosholipids (30%) and cholesterol (14%) are the predominant lipids of HDL-c and LDL-c respectively and cholesterol esters (36%) (Stryer, 1988). It also contains much smaller fraction of unesterified long chain fatty acids (free fatty acids) which are metabolically the most active of plasma lipids. These constitute what is collectively known as 'Cardiovascular Risk Factors' which are implicated in many disease states as potent or latent causes of death. Lipoproteins may be separated according to their electrophoretic properties into: α-, β-, and pre -β- Lipoproteins (Holme and Peck, 1998).

The protein moiety of a lipoprotein is known as apolipoprotein or apoprotein constituting nearly 70% of HDL-c and as little as 1% of chylomicrons. Some apolipoproteins are integral and can not be removed, whereas others are free to transfer to other lipoprotiens. Seven

principal apoprotein, A – 1, A – 2, A – 4, B – 48, B – 100, C and E have been isolated and characterized. They are synthesized and secreted by the liver and the intestine and generally have two principal roles: they solubilize highly hydrophobic lipid and also they contain signals that regulate the movement of particular lipid into and out of specific target cells and tissues.

Lipoprotein	Source/major core lipid	Diameter (nm)	Density (g/mL)	Composition	Main Lipid Components		Mechanism of lipid delivery
				Protein (%)	Lipid (%)	< 0.95	
Chylomicrons	Dietary triacylglycerol Intestine	90-1000	< 0.95	1-2	98-99	< 1.006	Hydrolysis by lipoprotein lipase
Chylomicrons remnants	Dietary cholesterol esters Chylomicrons	45-150	< 1.006	6-8	92-94	0.95-1.006	Receptor-mediated endocytosis by liver
VLDL	Endogenous triacylglycerols Liver (Intestine)	30-90	0.95-1.006	7-10	90-93	1.006-1.019	Hydrolysis by liproprotein lipase
IDL	Endogenous cholesterol esters VLDL	25-35	1.006-1.019	11	89	1.019-1.063	Receptor-mediated endocytosis by liver and conversion to LDL
LDL	Endogenous cholesterol esters VLDL	20-25	1.019-1.063	21	79		Receptor-mediated endocytosis by liver and other tissues
	Endogenous cholesterol esters						Transfer of cholesterol esters to IDL and LDL

Table 1. Composition of the Lipoproteins in plasma of humans.

Each apolipoproteins carry out one or more distinct roles.

i. The apo B, stabilizes lipoproteins micelles and as the sole protein of LDL-c serves the function of solubilizing cholesterol within LDL-c complex which in turn increases the transport capacity of LDL-c for subsequent deposit on arterial wall (Madhumathi et al., 2006).

ii. They are enzyme cofactors. The apoC-II has specific function of activating the lipoprotein lipase that hydrolyses triacylglycerols of chylomicrons and VLDL. Lack of either C-II or the lipase results in a very high level of triacylglycerol in the blood.

iii. They act as ligands for interaction with lipoprotein receptors in tissues, e.g apoB-100 and apo E for the LDL receptors, apo E for the LDL receptor– related protein (LRP) which has been identified as the remnant receptor, and apo A-1 for the HDL-c receptor. The function of Apo A-IV and apo D, however, are not yet clearly defined, although apo D, is believed to be an important factor in human neurodegenerative disorders.

2.1 Cholesterol

Cholesterol is physiologically very essential for all animal life, and is primarily synthesized from simpler substances within the body. It is an amphipathic waxy steroid of fat that is manufactured in the liver or intestines. It constitutes essentially structural component of membrane required in establishing proper membrane permeability and fluidity and is also a constituent of the outer layer of plasma lipoproteins. Cholesterol is the principal sterol synthesized by animals and transported in the blood plasma of all mammals (Leah, 2009). It is also an important component implicated in the manufacture of bile acids, steroid hormones, and vitamin D (Jain, 2005; Maxifield and Tabas, 2005; Hasimun, 2011). The hydroxyl group on cholesterol interacts with the polar head groups of the membrane phospholipids and sphingolipids, while the bulky steroid and the hydrocarbon chain are embedded in the membrane, alongside the nonpolar fatty acid chain of the other lipids. In this structural form, cholesterol reduces the permeability of the plasma membrane to protons (positive hydrogen ions) and sodium ions.
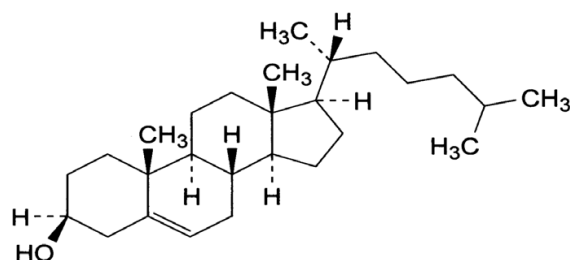

Fig. 1. Chemical structure of cholesterol

Most cholesterol is carried in the blood by low density lipoprotein (LDL), which delivers it directly to cells where it is needed. Both a 74-kDa cholesteryl ester transfer protein and a phospholipid transfer protein are also involved in this process. Cholesterol esterases, which release free cholesterol, may act both on lipoproteins and on pancreatic secretions. The LDL-cholesterol complex binds to LDL receptors on the cell surfaces. These receptors are specific for apolipoprotein B-100 present in the LDL. The occupied LDL-receptor complexes are taken up by endocytosis through coated pits; the apolipoproteins are degraded in lysosomes, while the cholesteryl esters are released and cleaved by a specific lysosomal acid lipase to form free cholesterol.

Animal fats are complex mixtures of triglycerides, with fewer amounts of phospholipids and cholesterol. As a consequence all food containing animal fats contain cholesterol to varying extent. Plasma cholesterol concentration elevation is, therefore ,one of the important CRFs as its transportation within lipoprotein is affected and is strongly associated with progression of atherosclerosis.

2.2 Triacylglycerols

Triacylglycerols (figure 2b see the figure below) serve as biochemical energy reserves in the cell and may be oxidized in the liver to provide energy or deposited as depot fat in characteristic regions of the animal where they act as a long-term food store and insulator (Plummer, 1998). They are the neutral and saponifiable lipids found in most organisms. Triacylglycerols (triglycerides) which are chemically fatty acid esters of the trihydroxy

alcohol, glycerol (Figure 2a), are compounds that usually make up the bulk of ingested lipids and are transported to the blood via the lymphatic system in the form of chylomicrons. Triacylglycerols synthesized endogenously as against those obtained from the diet, are carried by VLDL produced primarily by the liver (Styer, 1988). Studies have suggested that triacylgylcerol (TG)-rich lipoprotein(TRL) plays an important role in the development of atherosclerosis because both coronary artery disease and myocardial infarction have been associated with abnormal postprandial lipoprotein pattern (Moreno-Luna et al., 2007)

A triacylglycerol (Tristearin)
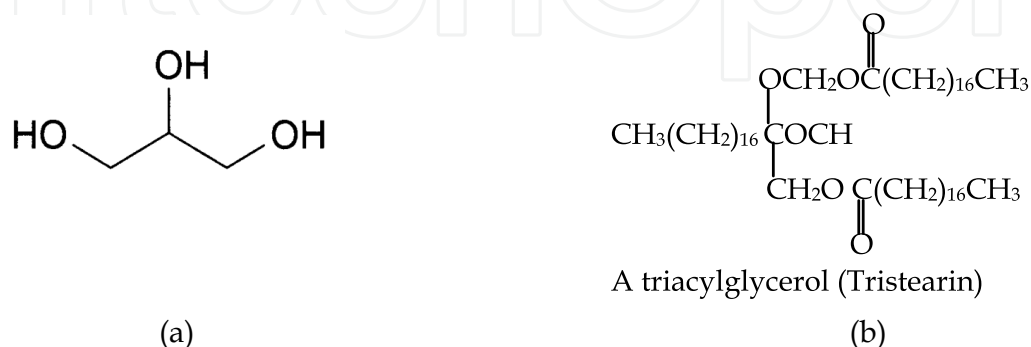
(a)   (b)

Fig. 2. (a) Chemical structure of cholesterol (b) chemical structure of triacylglycerol

Most of the fatty acids synthesized or ingested by an organism are either transformed into triacylgylcerols and stored for metabolism to give energy or incorporated into phospholipids components of the membrane. Triacylgylcerols have as precursor fatty acyl-CoAs and glycerol-β-phosphate but many enzymatic steps are involved in their biosynthesis in animal tissues. Although the triglycerides have been found to be important predictors of CVD in many studies, no clinical trial data has established that lowering triglycerides in individuals with or without diabetes independently leads to lowering of CVD occurring rates even after changes in HDL-cholesterol are adjusted for. From the foregoing, it is evident that elevated cholesterol, low HDL-c, high TG and high LDL-c are all risk factors for CVD. The pattern of occurrence of these abnormalities in type 2 DM especially has been severally reported in both developed and developing economies (Idogun et al., 2007; Williams et al., 2008).

2.3 Very Low Density Lipoprotein-cholesterol (VLDL-c or preβ- lipoproteins)

VLDL-c is synthesized in the liver and contains primarily triglycerides in their lipid cores for their export and also some cholesterol ester (Botham and Mayes, 2006). As their triglycerides are cleaved by endothelial lipoprotein lipase and transferred to hepatic tissues, the VLDL (very-low-density lipoprotein) particles lose most of their apolipoprotein C and become intermediate-density lipoproteins. VLDL is one of the five major groups of lipoproteins which functions to enable fats and cholesterol to move within the water-based solution of the bloodstream. VLDL-c particles have a diameter of 30-80 nm each and transports endogenous products such as triglycerides, phospholipids, cholesterol, and cholesteryl esters, whereas chylomicrons transport exogenous (dietary) products. It functions as the body's internal transport mechanism for lipids.

2.4 Low Density Lipoprotein-cholesterol (LDL-c)

The primary role of LDL-c appears to be the transport of esterified cholesterol to tissues (Guyton and Hall, 2006). Low density lipoprotein results when triacylglycerols are released from VLDL-c by the action of the same lipase that acts on chylomicrons and the remnants which are rich in cholesterol esters are called intermediate density lipoprotein (IDL). IDL particles have two fates as half of them are taken up by the liver and the other half converted into LDL which is the major carrier of cholesterol in blood (Styer, 1988). LDL-c or β- lipoprotein represent the final stage in the metabolism of VLDL. Originally, LDL-cholesterol was determined by a lengthy, laborious process called ultracentrifugation of serum. A much more rapid test became available based on the following Friedwald equation: Total cholesterol = LDL-cholesterol + HDL-cholesterol + VLDL-cholesterol (VLDL-cholesterol = triglycerides/5). One can rapidly and easily do a lipid profile by enzymatically measuring the important lipids — total cholesterol, HDL- cholesterol, and triglycerides. Dividing triglycerides by five gives the relatively unimportant, but hard to measure, VLDL-cholesterol, which is useful in then calculating the very important LDL cholesterol (Holme and Peck, 1998).

2.5 High Density Lipoprotein-cholesterol (HDL-c or ⟨-lipoprotein)

HDL-c is involved in the cholesterol transport and in VLDL and chylomicron metabolism. Unlike LDL which primary role appears to be the carriage of esterified cholesterol to the tissues, HDL functions to carry excess cholesterol away from most tissues to the liver. The apoA-I present in the HDL-c particle binds lipid and also activates lecithin cholesterol acyltransferase (LCAT), which catalyzes formation of cholesteryl esters which migrate into the interior of the HDL-c and are carried to the liver (Metzler, 1974). Recent studies on patients with LCAT deficiency have shown a modest but significant increase in incidence of cardiovascular disease consistent with a beneficial effect of LCAT on atherosclerosis (Rousset et al., 2009) HDL particles compared to other lipoproteins, are assembled outside of cells from lipids and proteins, some of which may be donated from chylomicrons or other lipoprotein particles. HDL has higher protein content than other lipoproteins and is more heterogeneous. The major HDL protein is apolipoprotein A-I, but many HDL particles also contain A-II, and apolipoproteins A-IV, D, and E may also be present. A low plasma level of HDL-cholesterol is associated with a high risk of atherosclerosis.

3. Implicated disease states

3.1 Diabetes

Diabetes mellitus is a major global health problem and is now recognized as one of the leading causes of death in the developing countries, where the high prevalence of the disease could be attributed to improved nutritional status coupled with a gross lack of modern facilities for the early diagnosis of the disease (Uebanso et al., 2007; Ogbonnia et al., 2008[a]). Diabetes mellitus (DM) is a complex disease characterized by abnormal pattern of fuel usage resulting from over production of glucose and its under utilization by other organs (Stryer, 1988). Diabetes has been succinctly described as the common metabolic disorder of carbohydrate and fat metabolism, which is due to absolute or relative lack of insulin and is characterized by hyperglycaemia (Walter, 1977; Shah et al., 2008 and Sharma et al., 2010; Dinesh et al., 2011).

Diabetes mellitus is therefore a multifactorial disease associated with hyperglycemia, (Shah et al., 2008; Sharma et al., 2010); lipoprotein abnormalities, raised basal metabolic rate and high oxidative stress inducing damage to beta cells. The abnormalities in carbohydrates and lipid metabolism in diabetes also result in excessive production of reactive oxygen species (ROS) and defect in ROS scavenging enzymes in addition to oxidative stress. The low level of insulin associated with diabetes has been found to increase the activity of anti-enzyme, fatty acyl Coenzyme A oxidase, which initiates the β-oxidation of the fatty acids, resulting in lipid peroxidation (Shah et al., 2008). Increased lipid peroxidation has also been found to impair membrane function by decreasing membrane fluidity and changing the activity of the membrane-bound enzyme and receptors. The resulting lipid radicals and lipid peroxides are harmful to the cell in the body and are associated with atherosclerosis and brain damage.

Chronic hyperglycemia which occurs in diabetes causes glycation of body proteins which in turn leads to secondary complications affecting eyes, kidneys, nerves and arteries (Mishra and Garg, 2011). These may be delayed, lessened or prevented by maintaining blood glucose values close to normal in modern medicine, though no satisfactory effective therapy is available for total cure of diabetes mellitus.

Diabetes mellitus is also associated with hyperlipidaemia with profound alteration in the concentrations and compositions of plasma lipid. Changes in the concentration of the lipids in diabetes contribute to the development of vascular disease. Excessive levels of blood cholesterol accelerate atherogenesis and lowering high blood cholesterol reduces the incidence of CHD (Grundy, 1986). One of the risk factors for coronary heart disease is elevated total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c) and lowered high density lipoprotein-cholesterol (HDL-c). The development of cardiovascular disease in DM is often predicted by several factors which include central obesity, hypertriglyceridemia and hypertension. Hypertriacylglyceridemia and low high-density liopoproteinaemia are two components of the atherogenic profile seen in DM. Elevated low density lipoprotein-cholesterol (LDL-c) has also been found to be an independent risk factor for the development of cardiovascular disease and is often reported to be the commonest lipid abnormality found in patients with DM (Udawat and Goyal, 2001; Idogun et al., 2007).

3.2 Atherosclerosis

Atherosclerosis or arteriosclerosis is a disease of large and medium size muscular arteries and is characterized by endothelial dysfunction vascular inflammation and build up of lipids, cholesterol, calcium and cellular debris within intima of vessel wall. This build up results in plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities in the blood flow and diminished oxygen supply to the target organ. (Madhumathi et al., 2006). Atherosclerotic disease has been found to be the most common cause of myocardial ischemia. Myocardium is said to be ischaemic when the pumping capability of the heart is impaired as a result of fall in the coronary blood flow which could not meet up with the metabolic need of the heart. In artherosclerotic disease, there is a localised lipid deposits called plaques develop within the arterial walls. In the severe cases of the disease these plaques become calcified and are so large that they physically narrow the lumen of the arteries producing stenosis (Mohrman and Heller, 2006). umerous studies have revealed important risk factors for the development of arthrosclerosis and these

include diseases such as diabetes mellitus, arterial hypertension, and also smoking and elevated blood cholesterol

Current concepts in atherosclerosis suggest that oxidation of LDL-c is involved in its pathogenesis. The critical role of oxidized LDL-c in atherogenesis may be due to its rapid uptake by the foam cells lining the arterial intima, which are thought to have macrophage-like properties. When LDL-c is oxidized chemotactic effect is exerted on monocytes and this increase the uptake of LDL-c leading to the formation of arterial plaque. Lipid oxidation can be inhibited by the use of antioxidants such as vit E which inhibit the formation of lesions in hypercholesterolemic rabbits (Chein and Frishman, 2003).

Hypercholesterolemia has also been implicated in the process of atherogenesis and a curvilinear relationship has been documented between increasing cholesterol and increasing incidence of CVD (Brunzell et al., 2008). The role of LDL-c in the development of CVD cannot be overemphasized as there is documented evidence that high levels of LDL-c not only cause atherosclerosis but pharmacological interventions that reduce LDL-c are associated with stabilization and regression of atherosclerosis in proportion to the cholesterol lowering achieved (O'Keefe et al., 2004). Low levels of HDL-c have been consistently reported in cardiovascular diseases (Idogun et al., 2007; Sani-Bello et al., 2007, Singh et al., 2007). Primary treatment of coronary artery disease (and atherosclerosis in general) should include attempts to lower blood lipid by dietary and pharmacological techniques to prevent and possibly reverse further deposit of plaques.

3.3 Benign Prostatic Hyperplasia (BPH)

Benign Prostatic Hyperplasia (BPH) is a neoplastic enlargement of the prostate gland, and is a common problem among aging men (Ejike and Ezeanyika, 2010; Dharmananda, 2011). The etiology of this disease is still poorly understood, but it has been proposed to have two phases:

One of the phases involves no clinical sign but there maybe some microscopic changes while the other manifests as the disorder of urination caused by the obstruction of the urinary tract by an enlarged prostate gland (Dharmananda, 2011).

Epidemiological studies have demonstrated that many of the risk factors associated with cardiovascular diseases apply also as risk factors for BPH. The problems associated with diabetic may be considered very strong as the risk in non-insulin dependent diabetes (NIDDM); which most often connected with insulin resistance may be a possible direct contributor to the growth of BPH (Dharmananda, 2011). NIDDM which arises from either impairment of insulin utilization or dysfunction on the metabolism of carbohydrates, fats and protein or both culminates in hyperlipidemia- hence elevation in plasma cardiovascular risk factor. BPH is therefore associated with metabolic syndrome (Kasturi et al., 2006; Ozden, 2007).

4. Herbal drugs used to control CRF in the disease states

Herbal medicines may be described as medicines prepared either with a single plant part or combinations of different plant parts either fresh,dried or as extract are now recognized as

potent therapeutic agents. Plants derived medicines commonly referred to as "phytomedicines" have been effectively employed in the management of variety of pathological conditions and are associated with fewer side effects (Nirmala et al., 2011; Ogbonnia et al, 2011). In recent years, they have been found to be effective both as hypoglycaemic and hypolipidemic agents (Ogbonnia et al., 2008c; 2010b) and have also been empirically used by many people from various cultures to lower cholesterol levels (Hamed, et al., 2010). Herbal medicines owe their therapeutic activities to the presence in them of secondary organic compounds or natural products constituents called the 'active constituents'.

4.1 Herbal active constituents

Herbal drugs contain natural products or secondary metabolites as the active constituents responsible for their physiological and pharmacological activities. The physiological and pharmacological activities have been found amongst alkaloids, phenolics and flavonoid compounds, glycosides (steroidal and saponins), and terpenoids, and is brought about through one or combination of two or more of the mechanisms that are the same as in the disease state they are being used. The mechanisms of their antidiabetic and antilipidemic activities which contribute to lowering of plasma lipids are the same mechanisms responsible for lowering of cardiovascular risk factors. These include the following: Glycosidase (Glucosidase) inhibition mechanism; alpha-amylase inhibition mechanism; antioxidant activities mechanism; inhibition of hepatic glucose metabolizing enzymes mechanism and inhibition of glycosylation of haemoglobin mechanism. These different mechanisms of activities are briefly discussed below

4.2 Possible mechanism of actions

The different classes of secondary product active constituents present in different herbal medicines may act through one or different mechanisms to bring about lowering or clearing of cardiovascular risk factors in a patient which may be probably the same mechanism through which they act exert their pharmacological action to control the disease state in question. Notably some of these possible mechanisms of actions may include:

4.2.1 Glycosidase (Glucosidase) inhibitor mechanism

One of the earliest features of type II diabetes and also observed in pre-diabetic phase is the loss of early phase secretion of insulin. Early phase insulin secretion is seen after a meal or after oral or intravenous ingestion of glucose and it is responsible for inhibition of hepatic glucose output and its absence results in postprandial hyperglycemia. (Ogbonnia and Anyakora 2009c). The α-glucosidase inhibitors category of drugs have been found to decrease postprandial glucose level by interfering with carbohydrate digestion and delaying gastrointestinal absorption of glucose . Slowing down digestion and breakdown of starches may have beneficial effects on insulin resistance and glycaemic index control on people suffering from diabetes. In this group some cryptic or water soluble alkaloids especially polyhydroxy alkaloids, have been identified to be potent glucosidase inhibitor (Kameswara et al., 2001). This as a whole comprises of relatively simple monocyclic pyrrolidine and

piperidine alkaloids, necines, amino alcohols which are derivatives bicyclic pyrrolizidine, and are mostly esters of amino alcohols and of aliphatic carboxylic acids.

4.2.2 Inhibition of hepatic glucose metabolizing enzymes mechanism

Synthesis of glucose by the liver and kidney from non carbohydrate precursor such as lactate, glycerol and amino acid constitutes a process known as gluconeogenesis. The liver hydrolytic enzymes glucose-6-phosphatase and fructose-1, 6- diphoshatase have been shown to play a crucial role in gluconeogenesis contributing to hyperglycaemic condition found in diabetes. Herbal drug products may act by binding with the enzymes. Treatment with an herbal drug has been observed to decrease the activities of these liver enzymes significantly with a concomitant decrease in blood sugar level (Lazar, 2006).

4.2.3 Antioxidants effects

Phenolics and polyphenolics are associated with antioxidant properties and have been reported to categorically reduce the oxidation of the LDL-c (Kar, 2007). Flavonoids in hawthorn extract have been found to reduce wall tension in normal and sclerotic blood vessels. These chemicals are also presumed to stimulate beta-2-receptors and thus widen coronary arteries and blood vessels in skeletal muscle . Flavonoids and other antioxidants act to destroy free radicals which are particles that can damage cell membranes, interact with genetic material and possibly develop heart diseases and cancer. They have also been found to decrease two other markers of cardiovascular disease, homocysteine and C-reactive protein. C-reactive protein (CRP) has been reported to be associated with increased risk of cardiovascular disease, myocardial infection (MI) coronary artery disease mortality among individuals with angina pectoris.

Oxidative stress has been reported to increase in diabetic patients and is regarded as common pathway by which many classical cardiovascular disease (CVD) risk factors and postprandial dysmetabolism may initiate and promote atherosclerosis (WHO 1985). Studies have shown that treatment with antioxidant reduces diabetic complications (Negappa et al., 2003). Flavonoids have been shown to scavenge reactive oxygen species (ROS) that are produced under severe stress conditions and protect plant cell and animal cell from oxidative stress and may have important role in human health.

4.2.4 Inhibition of glycosylation of haemoglobin mechanism

It has now become apparent that both fasting and postprandial hyperglycaemia contributes to overall glycaemic burden and therefore total glycosylation of haemoglobin, HbA. Many studies have shown that there is substantial evidence and a very strong correlation between hyperglycaemia and the risk of developing cardiovascular disease and mortality. Postprandial hyperglycemia has been found to occur together with postprandial hyperlipidaemia which is also associated with increased oxidative stress and endothelia dysfunction. However, one could therefore postulate that herbal drug products that are effective in the reduction of postprandial hyperglycaemia may not only play a role in managing type II diabetes but could also offer a tantalizing possibility of reducing cardiovascular risk.

S/no	Plant/Herbal Drugs	Work Done	Reference
1.	Alstonia congensis Engler (Apocynaceae) bark and Xylopia aethiopica (Dunal) A. Rich (Annonaceae) fruits	Evaluation of acute in mice and subchronic toxicity	Ogbonnia et al., 2008[a]
2	Leone Bitters, a Nigerian polyherbal formulation	Antimicrobial evaluation, acute and subchronic toxicity studies	Ogbonnia et al., 2008[a], 2010[a]
3.	Parinari curatellifolia Planch, (Chrysobalanaceae) seeds	Assessing plasma glucose and lipid levels, body weight and acute toxicity following oral administration of an aqueous ethanolic extract.	Ogbonnia et al., 2008[b]
4.	poly-herbal formulation	on alloxan- induced diabetic rats	Ogbonnia et al., 2008[b], 2010[b]
5.	Treculia africana Decne and Bryophyllum pinnatum Lam	Evaluation of Hypoglycaemic and Hypolipidaemic Effects of Aqueous Ethanolic Extracts	Ogbonnia et al., 2008[c]
6.	Stachytarpheta angustifolia	Evaluation of acute and subchronic toxicity in animals and phytochemical profile	Ogbonnia et al., 2009a
7.	Parinari curatellifolia Planch (Chrysobalanaceae) seeds	Evaluation of acute in mice and subchronic toxicity	Ogbonnia et al., 2009b
8.	Parinari curatellifolia and Anthoclista vogelli	Diabetes and cardiovascular factors	Ogbonnia et al., 2011
9.	Azadirachta indica	Diabetes Mellitus and hypolipidemic effects	Dinesh et al., 2011
10.	Holarrhena antidysenterica	Diabetes	Ali et al., 2009
11.	Annona muricata Linn Centratherum anthelmintica	Diabetes Diabetes	Shah et al., 2008
12.	Grape seed extract	cholesterol	http://www.nativeremedies.com/article/cholesterol-education-heart-disease.html
13.	Red yeast rice contains a natural form of lovastatin	cholesterol	
14.	Vilis vinifera extract and Oroxylum indicum	cholesterol	D'Mello et al., 2011
15.	Garlic	Cholesterol, antithrombic Cardiovascular diseases	
16.	Hawthorn leaf and flower		Hoareau and DaSilva,1999

17.	Cinnamomic camphoric aetherolleum	Coronary artery disease (CAD)	
18.	Rosmarini folium (Rosemary leaf)		
19.	Pini aetheroleum(pine neddle)		
20.	Eucalypti folium (Eucalyptus leaf)		
21.	Menthae aetheroleum (menthol)		
22.	Bacopa monnieri Linn	Diabetes	Ghosh et al., 2006
23.	Feronia elephantum Corr	Diabetes	Mishra and Garg, 2011
24.	Achilleamellifolium (yarrow) Convallaria majalis (lilly of the valley)Crategeus laevigata (hawthorn) Cynarascolymus (globeantichoke) Gingko biloba (gingko) Vibumum opulus	Cardiovascular diseases	Hoareau and DaSilva, 1999

Table 2. Some researched plants and plant medicines found to have lowering effects on cardiovascular risk factors.

5. Summary

- The danger and the increasing prevalence of heart diseases world over are now of a great concern
- These diseases could be attributed to the cardiovascular risk factors which also have been identified to be the underlying latent or potent causes of death in heart diseases in particular and also in many other disease states
- Cardiovascular risk factors include triacylglycerols (triglycerides), cholesterol, cholesteryl esters, very low density lipoprotein – cholesterol (VLDL-c), low density lipoprotein-cholesterol (LDL-c), and anti-athrogenic HDL which are collectively referred to as plasma lipids
- Cholesterol is a fat-like substance that is present in cell membranes and is a precursor to steroid hormones and bile acids.
- Coronary atherosclerosis is the deposition of cholesterol and fibrin complexes within the lumen of a coronary artery that narrows the lumen, thereby limiting blood flow.
- Coronary heart disease (CHD) is atherosclerosis of one or more coronary arteries that has resulted in symptomatic disease such as angina pectoris, myocardial infarction, or congestive heart failure, or has required coronary artery surgery or coronary angioplasty.
- Lipoproteins are lipid-containing proteins in the blood that transport cholesterol throughout the body.
- Disease states with underlying cardiovascular risk factors include diabetes, atherosclerosis and benign prostatic hyperplasia.

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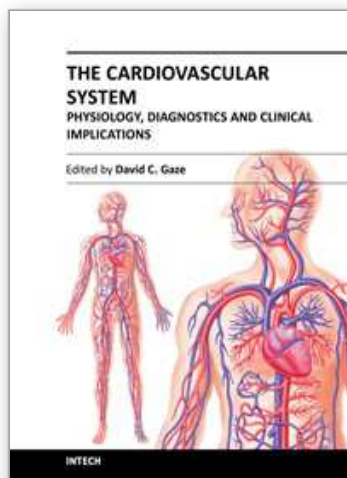
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Edited by Dr. David Gaze

The cardiovascular system includes the heart located centrally in the thorax and the vessels of the body which carry blood. The cardiovascular (or circulatory) system supplies oxygen from inspired air, via the lungs to the tissues around the body. It is also responsible for the removal of the waste product, carbon dioxide via air expired from the lungs. The cardiovascular system also transports nutrients such as electrolytes, amino acids, enzymes, hormones which are integral to cellular respiration, metabolism and immunity. This book is not meant to be an all encompassing text on cardiovascular physiology and pathology rather a selection of chapters from experts in the field who describe recent advances in basic and clinical sciences. As such, the text is divided into three main sections: Cardiovascular Physiology, Cardiovascular Diagnostics and lastly, Clinical Impact of Cardiovascular Physiology and Pathophysiology.

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